ISSN 0973-3930

Volume 39 | Issue 4 | October–December 2019

International Journal of Diabetes in Developing Countries

Official Publication of
Research Society for the
Study of Diabetes in India

Springer

International Journal of Diabetes in Developing Countries
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International Journal of Diabetes in Developing Countries is published 4 times a year. Volume 39 (4 issues) of will be published in 2019.

ISSN 0973-3930 print version
ISSN 1998-3832 electronic version

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International Journal of Diabetes in Developing Countries

Volume 39 · Number 4 · October–December 2019

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):597–599
https://doi.org/10.1007/s13410-019-00781-8

EDITORIAL

Long-term remission of type 2 diabetes—two roads to the elusive goal

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Published online: 24 October 2019

The remission of type 2 diabetes has always been and continues to be the "holy grail" of diabetes management. Considering the gradually progressive chronic nature of the disease and its attendant complications, both researchers as well as patients intensely hope to discover a means of achieving a sustainable, if not permanent, cure. The rising prevalence of diabetes has been linked to increase in obesity in the general population [1]. Although lean type 2 diabetes is increasingly recognized in several parts of the world, especially the Indian subcontinent, the contribution of obesity to the diabetes pandemic cannot be underestimated. In fact, WHO has lowered the cut-offs for defining obesity in certain susceptible populations [2]. In light of this understanding of obesity as an etiological factor, it is logical to pin hopes of diabetes remission on the control or reversal of obesity. The improvement in glycemic status with lifestyle interventions which target weight loss is already well known and forms an important component of the current standard of care for diabetes [3]. However, the reports of acute remission of diabetes after bariatric surgery lead to a revival of interest in this important topic [4].

Bariatric surgery and diabetes remission

Although initially approved only for morbid obesity, the observation of improved glycemic status of operated individuals with diabetes generated considerable interest in the role of this surgery in the management of diabetes. With the increasing number of surgeries performed, a substantial proportion of diabetic obese patients also underwent bariatric surgery. The data obtained from such patients revealed that diabetes improved in a high percentage of type 2 diabetes patients who underwent bariatric surgery [5]. In fact the indications of bariatric surgery were later expanded to obesity with difficult to control comorbidities including diabetes. Short-term follow-up reports showed that 60–90% of patients had remission of diabetes [6, 7]. However, the short-term remission depends upon factors such as age, glycated hemoglobin levels, duration of diabetes, and insulin/oral hypoglycemic agent use. The same factors may be expected to cause reappearance of diabetes post the initial remission, and hence, the durability of remission is a question of paramount importance. In this issue, Minhem et al. have tried to address this question by retrospectively reviewing the data of bariatric surgeries performed at their center in Lebanon. They report a promising 42.3% complete diabetes remission after a mean follow-up of around 5 years with an additional 20% showing a partial remission.

The existing literature on long-term remission from other parts of the world is equally promising. Long-term remission at 15 years was reported at close to 30% in one study [8]. Around 50% complete remission was reported at a median follow-up of 11 years in another study [9]. Around 40–60% remission (depending upon the surgical technique used) at 5 year follow-up was reported in RCT comparing bariatric surgery with conventional treatment. Minhem et al. show that the diabetes remission after bariatric surgery is not limited to Western populations and the benefits can be extended to other areas of the world. The variation in these studies may be attributed to the nature of surgical procedure and the patient factors affecting remission mentioned above. These issues notwithstanding, bariatric surgery does offer a ray of hope for the possible "cure" of diabetes for at least some, if not all patients.

The idea behind very low calorie diets—the less traveled road

An interesting observation regarding diabetes remission was that glycemic improvement appears immediately after

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bariatric surgery and achieves a peak much before clinically apparent weight loss has occurred [10]. This was surprising considering that obesity was believed to be a major driver of insulin resistance and diabetes. Several mechanisms have since been postulated to explain this glycemic improvement and the same have been demonstrated in experimental animals. These include increased GLP-1 secretion, reduction of "anti-incretins" secretion due to bypass of foregut, reduced glucose uptake in small intestine, bile acid absorption, FGF 19 levels, and gut microbiome [11, 12]. However, Lingvay et al. demonstrated a different phenomenon—changes in glycemic status that occur post-bariatric surgery can be observed prior to bariatric surgery in the same patients by exposing them to a diet regimen which usually followed post-surgery [13]. This paper concluded that the remission of diabetes may have very little relation to the actual surgery and anatomical changes it entails.

The statement that obesity causes insulin resistance and type 2 diabetes is a simplistic view of a metabolically complex pathogenesis. Insulin resistance is correlated more with central obesity rather than peripheral obesity—the use of waist hip ratio as a marker of metabolic syndrome reflects this observation. Further, it is understood that liver is a major source of insulin resistance and liver fat dictates the severity of insulin resistance [14]. Similarly an effect of pancreatic fat on beta cell function was also proposed. A major support to these findings came from the CounterPoint Study [15]. The study demonstrated that a 30% reduction in liver fat levels led to a normal fasting glucose in type 2 diabetes patients within a 7-day period. This reduction was achieved by utilizing a very low calorie diet (VLCD). Further, the insulin secretion also improved, albeit gradually—around 8 weeks later. The improvement in insulin secretion correlated with reduction in pancreatic fat. While this study provided a proof-of-concept that VLCD can be used to achieve diabetes remission, the durability of this response was circumspect. A mean weight loss of 15 kg was required to achieve normalization of both beta cell function as well as liver insulin resistance. Whether such a degree of weight loss can be sustained was doubtful. However, the Counterbalance study [16] proved that the weight loss can be sustained up to 6 months and the remission could be maintained up till significant weight regain did not occur. Subsequent to these two proof-of-concept studies, a large-scale trial named DiRect was launched. This trial randomized 306 obese type 2 diabetes mellitus patients in a primary care setting who were randomized to an intervention group who received VLCD for 3–5 months followed by reintroduction of food and a control group. Close to 50% of the subjects in the intervention arm managed to achieve a diabetes remission at the end of 12 months [17]. The 2-year follow-up of this trial was published recently which shows that 36% of patients have diabetes remission [18]. In the RCT published by Mollentze et al. in this edition, VLCD was able to induce diabetes remission at 6 months in one out of nine subjects and was well tolerated. This data shows that the impressive results of DiRECT study can be replicated elsewhere, although the remission rates may be lower.

The choice between two roads

The long-term sustainability of weight loss induced by VLCD has been questioned by several authors [19]. Even the existing data is up till 2 years only. One proposed reason refers to the increase in GLP-1 and PPY with fall in ghrelin noted after bariatric surgery while the reverse occurs after dieting—which may be a proxy for VLCD [20]. A comparison of available data suggests that the remission rates are much higher with bariatric surgery compared with VLCD.

It may be safe to therefore conclude that bariatric surgery is a superior modality in terms of diabetes remission rates. However, bariatric surgery apart from being a major invasive procedure is not without its share of problems. Adverse effects of bariatric surgery include dumping syndromes, malabsorption, vitamin deficiencies, and osteoporosis apart from direct surgical complications [21]. Further, not every patient with diabetes is likely to achieve remission—therefore, undergoing a surgery for the sole purpose of remission may not be a risk worth taking. Even among those who achieve a remission, failure to correct eating behavior after bariatric surgery does indeed lead to regain of the pre-surgery weight as well as reappearance of glycemic abnormalities.

In many such situations VLCD may be a viable alternative. Many patients would voluntarily opt for a nonsurgical alternative as a shot at remission instead of a major surgical intervention. The effects as well as adverse effects of VLCD would be easily reversed as compared with a permanent alteration in bowel anatomy. Further, those who are less likely to achieve a remission after bariatric surgery, as suggested by available scores such as DiaRem and Ad DiaRem [22], may try VLCD to achieve remission. Thus, VLCD may also help in selecting patients for bariatric surgery with a goal of diabetes remission.

Finally, in several resource limited settings such as Asia, the number of diabetes patients is huge and surgical treatments can be offered to only a small fraction of this population—in such settings VLCD can be a good interim as well as long-term option.

In the fight against type 2 diabetes, the elusive goal of remission is now a tangible one. With the two roads of bariatric surgery and VLCD at our disposal, a long-term solution for diabetes may be within reach.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):600–610
https://doi.org/10.1007/s13410-019-00720-7

REVIEW ARTICLE

Pharmacist-led interventional programs for diabetic patients in Arab countries: A systematic review study

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Received: 4 April 2018 / Accepted: 3 February 2019 / Published online: 28 February 2019

Abstract

Introduction Diabetes mellitus (DM) is a highly prevalent metabolic disorder in the Arab world. Uncontrolled DM is associated with serious microvascular and macrovascular complications. Reduction of such complications can be achieved by good glycemic control through utilization of pharmacological and non-pharmacological treatments. Patient education programs can improve treatment outcomes. Thus, the present study reviewed articles that evaluate pharmacist's interventional (educational/care) programs in the management of diabetic patients in Arab countries in order to quantify benefits of such programs.

Methods A careful manual literature search was done in PubMed and Google Scholar for clinical trials that focus on the role of the pharmacist in care, education, or management of all types of DM in Arab countries. Information from these studies was summarized in relation to general study characteristics (study design and area of study); description of study population, sample size, and the type and components of pharmaceutical intervention; follow-up time, frequency, and duration of contact moments during intervention; and assessment criteria, results, and conclusions. The risk of bias in individual studies was assessed using the Cochrane risk of bias tool.

Results Six studies were included in this review. The included studies were conducted in four Arabic countries, two in Jordan and United Arab Emirates, and one each in Sudan and Iraq. Five studies assessed the benefits of implementing pharmaceutical interventions (pharmaceutical-led patient care or education) among type 2 DM patients and only one study assessed such benefits among patients with gestational DM. Follow-up of patients ranged from 15 weeks to 12 months. Only one study had a high risk of bias. All studies showed a significant improvement in patient knowledge, adherence to treatment, and glycemic control.

Conclusion Pharmacists' interventions in the management of DM patients in Arab countries tend to result in positive outcomes such as enhanced patient knowledge, greater adherence to treatment, and eventually better glycemic, lipid, and blood pressure control.

Keywords Pharmacist intervention · Diabetes mellitus · Arab countries

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder. The global prevalence of diabetes has been increasing dramatically over the recent decades. In 2017, approximately 451 million adults were diagnosed to have diabetes worldwide with a prevalence of 8.4% [1]. The highest prevalence (16.17%) for diabetes in the world is in the Arab region [2]. DM is characterized by hyperglycemia due to insulin insufficiency, insulin resistance, or

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both. Long-term uncontrolled hyperglycemia is associated with the development of serious microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (atherosclerosis) complications [3]. These complications pose a substantial economic burden to patients and to healthcare services especially in Arab countries [4–7]. Reduction of DM complications through good glycemic control can successfully reduce health-related costs [8, 9]. In this regard, glycemic control can be achieved by the utilization and total adherence to both pharmacological and non-pharmacological (lifestyle changes) treatments [10]. Patients' good knowledge about DM and its treatment results in greater adherence to DM management and thus eventually leads to better glycemic control [11]. Many studies performed in Arab countries such as Qatar, United Arab Emirates (UAE), Iraq, and Saudi Arabia found poor knowledge about DM management and care among diabetic patients [12–15]. To improve diabetes treatment outcomes, the treatment plan should include effective patient education programs [16] that focus on improving self-care knowledge and behaviors including lifestyle modifications (such as dietary control, regular exercise, and psychosocial coping skills) and medical self-care (medication use and self-monitoring of blood glucose) [17]. Although patient education can be done by different members of the healthcare team such as registered nurses, dieticians, or pharmacists, but DM education by pharmacists was found to be better since pharmacists can play additional role in ensuring patient safety and adherence to the prescribed medications [18]. Although many review studies were conducted to assess the benefits of pharmacist-led interventional (educational/care) programs for DM patients, unfortunately no review study focused to evaluate the benefits of such programs among Arab DM patients and thus, this systematic review study was performed to answer the following question: what are the benefits of applying pharmacist-led interventional programs during treatment of DM patients in Arab countries.

Methods

Search strategy

An extended literature search was conducted during November 2017, using the electronic databases PubMed and Google Scholar with the following keywords: "Pharmacist", "diabetes" and one of the following three words "Care," "intervention," or "education". The Arab world includes 22 countries (12 in Asia and 10 in Africa); therefore, database search was done 22 times by adding each country's name to the above keywords (Table 1).

Table 1 Keywords and keywords combinations

Concept	Keywords	Keywords combination
Pharmacist-led interventional program	Pharmacist; Diabetes; Intervention; Name of each Arab country including: Algeria; Bahrain; Comoros; Djibouti; Egypt; Iraq; Jordan; Kuwait; Lebanon; Libya; Mauritania; Morocco; Oman; Palestine; Qatar; Saudi Arabia; Somalia; Sudan; Syria; Tunisia; United Arab Emirates and Yemen	Pharmacist diabetes intervention (repeated using all countries names)
Pharmacist-led educational program	Pharmacist; Diabetes; education; Name for each Arab country	Pharmacist diabetes education (repeated using all countries names)
Pharmaceutical care	Pharmacist; care; Diabetes; Name for each Arab country	Pharmacist diabetes care (repeated using all countries names)

Inclusion criteria and study selection

All published articles (during any time period), that focus on the role of the pharmacist in care, education, or management of adult (18–99 years) patients with any type (Type 1, type 2, or gestational) of DM who live in Arab countries, were included in this review study. Only clinical trials (randomized, non-randomized, controlled, and non-controlled) were included, whereas observational studies, surveys, and reviews were excluded.

Review method

The main author of this study reviewed manually all articles' titles during database search. For articles with a suitable title, the abstracts were reviewed, and if insufficient information regarding pharmacist role and study area presented in the abstract, the full article was reviewed. Fortunately, all reviewed articles were freely accessed.

Extraction and summarizing methods

Information from these studies was summarized in relation to general study characteristics (study design and area of study); description of study population; sample size; the type and components of pharmaceutical intervention; follow-up time, frequency, and duration of contact moments during intervention; and assessment criteria including both clinical and patient-reported outcomes, results, and conclusions. The risk of bias in individual studies was assessed with the Cochrane Risk of Bias tool [19].

Results

Thirteen studies were found through the search procedure. Of these, six studies fulfilled the inclusion criteria and seven studies were excluded. Four of the excluded studies [20–23] were cross-sectional studies assessing the role of pharmacists in the care and education of diabetic patients by the use of questionnaires that were either directed to the patients or the pharmacists. The fifth study [24] that assessed pharmaceutical intervention in managing diabetic patients was excluded because of its design (qualitative study), while the other study was excluded because pharmacist role was only evaluation of medication adherence and side effects without any intervention [25]. The last study [26] was excluded because it was performed for Arabic patients who lived in Australia. The included studies were heterogeneous in terms of intervention, patients, outcomes, and assessment methods (Table 2).

The included studies were conducted in four Arab countries, one in Iraq [27], two in Jordan [28, 29], one in Sudan [30], and two in United Arab Emirates (UAE) [31, 32]. Five studies assessed the benefits of implementing pharmaceutical interventions among type 2 DM patients and only one study assessed such benefits among patients with gestational DM. Follow-up of patients ranged from 15 weeks to 12 months (Fig. 1).

Risk of bias

The risk of bias within studies was assessed with the Cochrane Risk of Bias tool. All but one (Elnour et al. [32]) study were subjected to some form of bias; however, only two studies were considered to have a high risk of bias (Mahwi and Obied [27], and Wishah et al. [29]) (Table 3).

Iraq

Mahwi and Obied [27] conducted a randomized controlled clinical trial at the DM Center in Sulaimani, Kurdistan region, Iraq. One hundred thirty patients (only 123 completed the study) with uncontrolled type 2 DM (without regard to disease duration and type of anti-diabetic treatment) were enrolled in this study. The patients were allocated into two groups: a usual care group (51 patients) received traditional medical care and the second group (intervention group) (50 patients) received pharmaceutical care with medical care. They were followed-up every 5–6 weeks for a total of three visits (15–18 weeks) through weekly telephone calling. In the intervention group, the pharmacist assessed medication history of each patient to identify and resolve drug-related problems such as partial or complete lack of response to the prescribed medications, dosing errors, and patient non-adherence. However, it is not clear whether the pharmacist resolved drug therapy problems on his own or after negotiation with the endocrinologist. The results of this study revealed that clinical outcomes such as HbA1c (− 2.33% vs − 0.47%; $p < 0.001$) and fasting blood glucose (FBG) (− 53 mg/dl vs − 15.7 mg/dl; $p = 0.001$) were significantly reduced in the intervention arm compared with the control group. Drug therapy–related problems (DTP) were reported in 66.1% of patients prior to the beginning of the study and significantly reduced to 1.6% ($p < 0.001$) in the intervention group at the end of the study. The rate of medication adherence (assessed by pill count and four-item Morisky scale) was increased (from 22.6 to 80.7%; change 58.1%) significantly ($p = 0.000$) after implementation of the care program.

There were many limitations in this study that reduce the reliability of its findings. Firstly, DM patients were included in this study without regard to duration of the disease. Disease duration may be significantly different in the intervention arm compared with the control group, and according to the American Diabetes Association (ADA), patients with long-standing DM were less likely to respond to pharmacological and non-pharmacological treatment and thus were less likely to attain glycemic control [33, 34]. Secondly, a risk of bias was found in assessing benefits of pharmaceutical care program with regard to medication adherence and DTP, since the study measured medication adherence and DTP only for patients in the intervention group.

Jordan

Jarab and colleagues [28] conducted a randomized controlled clinical trial at the DM Center of the Royal Medical Services Hospital, Amman, Jordan, where 171 adult patients (only 156 completed the study) diagnosed with type 2 DM for at least 1 year previously who had uncontrolled hyperglycemia (HbA1c over 7.5%) despite being on anti-diabetic medication(s) were enrolled in this study. Patients were follow up/followed up for 6 months after being divided into two groups; the control group (79 patients) which received usual care provided by the DM clinic and the intervention group (77 patients) received clinical pharmacy services that include baseline assessment to check appropriateness of the prescribed medications (anti-diabetic, anti-hypertensive, and anti-dyslipidemic agents) to each patient, making recommendations (when necessary) to physicians to intensify drug dose and/or simplify drug dosing regimen. After baseline assessment, the clinical pharmacists provided patients with structured education about type 2 DM, risks and types of complications, prescribed medications, proper dosage, possible side effects, and the importance of self-care activities including adopting healthy dietary habits, regular physical activity, and blood glucose monitoring. Additionally, patients in the intervention group received a telephone call (average 20 min) every 8 weeks to discuss and review the prescribed therapy, to

Table 2 Main characteristic of included studies

Authors of the study	Study location	Sample size (patients completed study)	Male/ female ratio	Age of participated patients (mean ± SD)	Type of DM	Baseline HbA1c (mean ± SD)	Follow-up period	Study design	Pharmacist intervention	Measured outcome	Effect of intervention on the measured outcomes
Mahwi and Obied [27]	Diabetes Center in Sulaimani, Iraq	130 (123)	38/85	52 ± 7.86 (intervention) 53.5 ± 10.81 (control)	Type 2	11.53 ± 1.83 (intervention) 9.97 ± 2.75 (control)	15–18 weeks	Randomized controlled clinical trial	Identification and resolving drug-related problems	HbA1c, FBG, medication adherence and drug-related problems.	All are significantly improved
Jarab et al. [28]	Diabetes Center of the Royal Medical Services Hospital, Amman, Jordan	171 (156)	97/74	63.4 ± 10.1 (intervention) 65.3 ± 9.2 (control)	Type 2	8.5%* (intervention) 8.4%* (control)	6 months	Randomized controlled clinical trial	Education about type 2 DM and its treatment, assessing safety and effectiveness of prescribed therapy.	HbA1c, FBG, lipid profile and BMI, Medication adherence, DM knowledge and self-care activities	All are significantly improved activities
Wishah et al. [29]	Diabetes Clinics, Jordan University Hospital, Jordan	106 (101)	46/60	52.9 ± 9.6 (intervention) 53.2 ± 11.2 (control)	Type 2 diabetes	8.9 ± 1.6 (intervention) 8.2 ± 1.3 (control)	6 months	Randomized controlled clinical trial	Structured education about proper medication dosage, side effects, medication adherence, lifestyle change	HBA1c, FBG, BP, lipid profile, BMI, adherence and self-care activities	All are significantly improved
Ahmad et al. [30]	NyalaTeaching Hospital, Sudan	330 (300)	180/120	51.8 ± 4.7 (overall)	Type 2	9.3 ± 1.7 (intervention) 10.4 ± 1.8 (control)	6 months	Randomized controlled (pre-post) interventional clinical trial	Education about DM, SMBG and lifestyle changes	HbA1c, PPBG, BP and patient satisfaction	All are significantly improved
Al Mazroui et al. [31]	Zayed Military Hospital, UAE	240 (234)	166/74	48.7 ± 8.2 (intervention) 49.9 ± 8.3 (control)	Type 2	8.5* (intervention) 8.4* (control)	12 months	Randomized controlled clinical trial	Education on lifestyle change and medical treatment, DRP	HbA1c, FBG, BP, lipid profile, BMI, CHD risks, QOL, DM knowledge, adherence to medication, lifestyle change	All are significantly improved in the intervention group
Elnour et al. [32]	Al-Ain Hospital, Al-Ain, United Arab Emirates	180 (165)	0/180	30.9	Gestational diabetes	6.85* (intervention) 6.87* (control)	Follow-up during pregnancy and 6 months after delivery	Randomized, controlled, longitudinal, prospective clinical trial	Education about self-care of GDM, lifestyle modification, frequency of self-monitoring of blood glucose, and necessary skills to deal with hyper and hypoglycemia	HbA1c, pre-prandial blood glucose, BP, maternal and neonatal complications knowledge of DM, QOL	All are significantly improved

SD = standard deviation; DM = diabetes mellitus; T2DM = type 2 diabetes mellitus HbA1c = glycosylated hemoglobin; PPBG = post-prandial blood glucose; FBG = fasting blood glucose; BMI = body mass index; CHD = coronary heart disease; QOL = quality of life; DRP = drug-related problems; GDM = gestational diabetes mellitus; * = standard deviation was not mentioned in the study

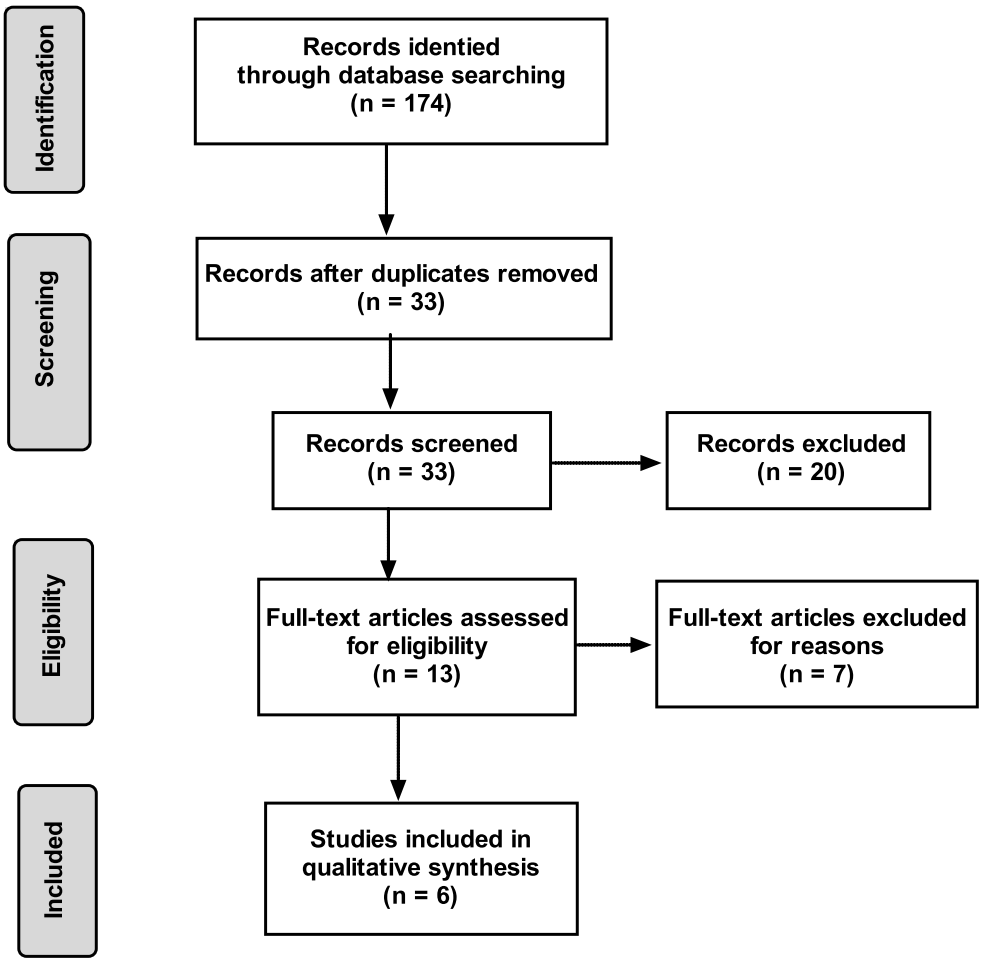

Fig. 1 PRISMA flow chart of reviewed articles

emphasize the importance of adherence to treatment plan, and to answer patient questions and deal with patient concerns.

At the end of the study, clinical outcomes such as glycosylated hemoglobin (HbA1c) (− 0.8% vs + 0.1%; $p = 0.019$); fasting blood glucose (FBG) (− 41 mg/dl vs + 16 mg/dl; $p = 0.014$); systolic blood pressure (BP) (− 5.8 mmHg vs. + 1.1; $p = 0.035$); diastolic BP (− 7.1 mmHg vs + 1.8; $p = 0.026$); total cholesterol (− 27 mg/dl vs. + 3.9; $p = 0.04$); low-density lipoprotein cholesterol (LDL-C) (− 23.2 mg/dl vs. 0 mg/dl; $p = 0.031$); and serum triglycerides (TG) (− 44.3 mg/dl vs. + 17.7 mg/dl; $p = 0.017$) were significantly improved for patients in the intervention group as compared to those in the control group. Although many clinical outcomes (HbA1c and lipid profile) were improved for patients in the intervention group, it is not clear whether these effects are directly linked to the pharmacist educational program or due to initiating of new therapies, where more patients in the intervention group (13.3%) as compared to those in the control group (8.7%) were shifted from oral anti-diabetics to insulin. Additionally, more patients in the intervention group were given statins (19.6%) as compared to only 3.1% in the control group. Body mass index (BMI) was also improved, but not to a statistically significant level, for patients in the intervention group as compared to those in control group (− 0.5 vs + 0.4). At the end of the study, the percentage of patients who were adherent (assessed by the four-item Morisky scale) to their treatment was increased to a greater extent (45.5% vs 6.3%; $p = 0.003$) in the intervention group compared to control group. Additionally, most domains (diet, physical activity, and blood glucose monitoring) of self-care activities (assessed by Summary of Diabetes Self-Care Activities Questionnaire) were significantly ($p < 0.05$) improved in the intervention group compared to the control group.

In a randomized controlled clinical trial study conducted by Wishah and colleagues [29] in the DM clinic of the Jordan University Hospital, Amman, Jordan, 106 (only 101 completed the study) type 2 DM patients either newly diagnosed or already diagnosed with uncontrolled hyperglycemia despite being treated with lifestyle modification and/or oral antidiabetic agents were enrolled in this study. Patients were followed-up every 3 months for a total of 6 months after being divided into two groups: a usual care group (51 patients) (physician and nurse care) and the second group (intervention group) (50 patients) which receive special care by collaboration between pharmacist and physician. In the intervention group, the clinical pharmacist makes recommendations to

Table 3 Risk of bias among included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Mahwi and Obied [27]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk (difference in the baseline HbA1c level; patient informed consent was not obtained)
Jarab et al. [28]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Wishah et al. [29]	Low risk	Low risk	High risk	Unclear	Unclear	Low risk	High risk (difference in the baseline HbA1c level)
Ahmad et al. [30]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	High risk (difference in the baseline HbA1c level)
Al Mazroui et al. [31]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Elnour et al. [32]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

the caring physician regarding the need to initiate oral anti-diabetic agents, titrate drug therapeutic dosage, and change the current medication due to ineffectiveness. Additionally, the clinical pharmacist provided each patient (in 30-min sessions during each visit throughout the study period) with a structured education about type 2 DM, risks of DM complications, prescribed medications, proper dosage, possible side effects, and importance of adherence to DM self-care activities. A printed educational leaflet and brochures containing information about diabetes, diabetes medications, life-style modifications, and self-care activities were also provided to the patients in the intervention group. Furthermore, telephone calls were done to follow-up patients, encourage medication adherence, and to assess safety and effectiveness of the prescribed medications besides resolving any patient concerns.

Clinical outcomes such as glycosylated hemoglobin (− 1.6% vs − 0.3%; $p = 0.01$) and fasting blood glucose (− 53 mg/dl vs − 1.6 mg/dl; $p = 0.01$) were significantly improved in intervention group compared to control group. Patient-reported outcomes such as medication adherence (assessed by the 4-item Morisky scale) (+ 3.1 points vs − 0.7 points; $p = 0.01$), DM knowledge (assessed by Michigen 14-item diabetes knowledge test) (3.9 points, vs 0.7 points; $p = 0.01$) and all self-care activities (diet, exercise, self-monitoring of blood glucose, and foot care) (assessed by the revised summary of diabetes self-care activities scale) were significantly ($p = 0.01$) improved in the intervention group compared to control group. Whereas other outcomes such as the lipid profile components including total cholesterol (− 19.4 mg/dl vs − 11.9 mg/dl; $p = 0.25$), LDL-c (− 13.3 mg/dl vs − 4 mg/dl; $p = 0.32$), HDL-c (+ 3.3 mg/dl vs + 1.1 mg/dl; $p = 0.75$), TG (− 40.3 mg/dl vs − 3.3 mg/dl; $p = 0.37$), and BMI (− 0.5 vs + 0.5; $p = 0.11$) were improved in the intervention arm, but they fail to achieve statistical significance.

Although there was no significant difference in the duration of DM between patients in control and intervention groups, the lack of information regarding the number of newly diagnosed DM patients in each group can be considered as a major limiting factor for reliability of the study results, since it is well known that newly diagnosed type 2 DM is better responding to interventions (drugs or education) than long history DM patients [35].

Sudan

Ahmad and colleagues [30] conducted a prospective randomized controlled clinical trial at Nyala Teaching Hospital, Sudan. Three hundred and thirty patients (only 300 completed the study) with type 2 DM who were already treated with oral anti-diabetic agents (with or without insulin) were enrolled in this study. Patients were followed-up for 6 months after being allocated into two groups; the control group (100 patients) received usual care by medical and nursing staff, while the intervention group (200 patients) received a special care program by a team of physicians, nursing staff, and a clinical pharmacist expert in DM management. The pharmacist role within the DM care team involves education of patients about their disease state, self-monitoring of blood glucose (SMBG), and lifestyle changes. Additionally, he was responsible for optimizing treatment for each patient. At the end of the follow-up period, clinical outcomes such as HbA1c, postprandial blood glucose (PPBG), systolic and diastolic BP (− 1.5%, − 34.2 mg/dl, − 9.9 mmHg and − 5.3 mmHg) respectively, were significantly ($p = 0.001$) improved in the intervention group. Whereas the improvement in the control group for HbA1c, PPBG, and systolic and diastolic blood pressure (− 0.9%, − 5.4 mg/dl, − 0.5 mmHg, + 0.4) respectively, did not reach statistical significance ($p > 0.05$). Most domains (general satisfaction, technical quality, and financial aspects) of patient-reported satisfaction (assessed by Patient Satisfaction Questionnaire — 18) were significantly ($p < 0.05$) improved in the intervention group compared with the control group. The level of satisfaction with DM care (advice about medication adherence and lifestyle modification, besides offering eye

and foot examination) was assessed by DM satisfaction questionnaire. All of these parameters, except advice about medication adherence, were significantly ($p < 0.05$) improved in the intervention group compared with the control group.

The limitation of this study was mainly due to its design that compares the benefits of care program in each group (pre-post care difference) separately rather than comparing the resulted change between patients in control and intervention group. Additionally, many patients in the control group have longer disease duration which may be associated with low response to the intervention [33].

United Arab Emirates (UAE)

Al Mazroui et al. [31] conducted a randomized controlled longitudinal clinical trial at Zayed Military Hospital, UAE, where 240 (only 234 completed the study) type 2 DM adult patients treated (whether controlled or not controlled) by oral anti-diabetics were enrolled in this study.

Patients were followed-up for 12 months after being allocated into two groups; the control group (117 patients), which received usual care by medical and nursing staff; the intervention group (77 patients) received pharmaceutical care by a clinical pharmacist who performs baseline assessment to check the appropriateness of prescribed medications to each patient, making recommendations (when necessary) to physicians to intensify drug treatment and/or simplify drug dosing regimen. Then the pharmacist provided patients with structured education on DM and the risks of its complications, education on medications including proper dosage, side-effects, storage, and importance of medication adherence, besides education on lifestyle change such as healthy diet, physical exercise, and blood glucose monitoring. Additionally, patients in the intervention group were asked about any problems that they had encountered with regard to taking their medication. A printed leaflet was given to each patient to assist with the educational program. The educational advice was reinforced when patients came to the hospital pharmacy to collect their prescribed medicines on their monthly schedule.

The clinical outcomes such as HbA1c (− 1.6% vs − 0.1%; $p < 0.001$); fasting blood glucose (FBG) (− 45 mg/dl vs − 14 mg/dl; $p < 0.001$); systolic blood pressure (BP) (− 4.2 mmHg vs. − 0.5; $p < 0.001$); diastolic BP (− 8.9 mmHg vs. + 0.2; $p < 0.001$); total cholesterol (− 30.5 mg/dl vs. + 1.9 mg/dl; $p < 0.001$); HDLc (+ 4.6 mg/dl vs + 0.4; $p < 0.01$); LDL-C (− 19.7 mg/dl vs. + 5 mg/dl; $p < 0.001$); serum triglycerides (− 31 mg/dl vs. + 16.8 mg/dl; $p < 0.001$); BMI (− 1.05 vs + 0.01; $p = 0.004$), and 10 years coronary heart disease (CHD) risk (measured by Framingham scoring system) (− 2.86% vs 0.0%; $p < 0.001$) were significantly improved for patients in the intervention group as compared to those in the control group. Additionally, most of the patient-reported outcomes such as medication knowledge (assessed by checking if patients can name their prescribed medicines, the daily dosage, the strength and purpose of each medicine, and any significant adverse effects of that medicines) (+ 13.8% increase in patient proportion who have good knowledge vs + 0.1; $p < 0.05$), rate of medication adherence (assessed by self-reported information from the patient regarding forgetting doses, intentionally missing, or taking extra doses) (26.9% vs 16.6%; $p < 0.05$), adherence to lifestyle modification and patient quality of life [assessed by self-reported questionnaire of health-related quality of life (Short Form 36)] were improved significantly for patients in intervention group as compared to those in the control group.

One of the major limitations in this study was the scanty information regarding the extent and frequency (just at baseline or whenever necessary) of treatment modification and whether it was done just for antihypertensive medications or also for anti-diabetic medications.

Elnour and colleagues [32] conducted a randomized, controlled, longitudinal, prospective clinical trial to evaluate the benefits of pharmaceutical care to patients with gestational diabetes (GDM). The study was performed at Al-Ain Hospital, Al-Ain, United Arab Emirates, and involved 180 (only 165 completed the study) patients with GDM aged 20–39 years.

All patients were followed-up during pregnancy and for an additional 6 months after delivery. They were divided into two groups; the control group (66 patients) which received traditional care while the intervention group (99 patients) received pharmaceutical care by a clinical pharmacist who discusses with each patient the treatment option that best fits her daily routine. The clinical pharmacist also provided each patient with structured education (in 10–30-min sessions) about GDM, diet, exercise, recommended timing and frequency of self-monitoring of plasma glucose, and skills to deal with plasma glucose results if they were outside the desired range besides educating patients about insulin administration and storage. An educational booklet was given to each patient in the intervention group to assist with this educational program.

The results showed a statistically significant ($p < 0.05$) improvement in clinical outcomes such as HbA1c (− 0.47% vs − 0.32%), maternal complications [e.g., decreased incidence of pre-eclampsia (5.1% vs. 16.7%), eclampsia (1.0% vs. 7.6%), episodes of severe hyperglycemia (3.0% vs. 19.7%) and need for cesarean section (7.1% vs. 18.2%)], and neonatal complications [e.g., decreased incidence of neonatal hypoglycemia (2.0% vs. 10.6%), respiratory distress at birth (4.0% vs. 15.2%), and hyperbilirubinemia (1.0% vs. 12.1%)] were reported for patients in the intervention group compared to the control group. Patient-reported outcomes such as diabetes knowledge (assessed by a brief diabetes knowledge questionnaire) (general knowledge + 50 points vs 46 points; insulin knowledge + 18 vs + 15 points) and health-related quality of

life (assessed by SF 36) were improved to a statistically significant ($p < 0.05$) level for patients in the intervention group, while the improvement in the pre-prandial plasma glucose and blood pressure failed to achieve statistical significance. No limitations were found in the methods and results of this study.

Discussion

This review showed that all pharmacist interventions, whether it involved patient education and/or resolving drug-related problems, were effective in improving glycemic control as measured by reduction in HbA1c (− 0.8% to − 2.33%) and FBG (− 43 mg/dl to − 53 mg/dl) for type 2 DM patient in Arab countries. These results were in tune with other studies conducted in developed and developing countries, which indicates that pharmacist intervention can significantly improve glycemic control in type 2 DM patients [36]. The role of pharmacist intervention in improving glycemic control was found significant during all follow-up periods. However, short-term interventions (15 weeks–6 months) produced greater benefits (2.33% vs 1.6% for HbA1c; 53 mg/dl vs 45 mg/dl for FBG) compared with long-term studies (12 months). Similarly, a better glycemic control can be achieved with short- to moderate-period follow-up studies (3–6 months) that include DM patient education by nurse or dietician [37]. Three of pharmacist interventional studies [28–30] had similar periods of follow-up (6 months), the greater glycemic control (1.6% decrease in HbA1c vs 0.8–1.5%) was achieved in a Jordanian study [29] that enrolled both newly and previously diagnosed diabetic patients. This finding is reasonable since newly diagnosed type 2 DM patients respond better to interventions (drugs or education) than patients with long history of DM [35]. The greatest reduction in HbA1c was achieved when the pharmacist-led patient education was accompanied by using educational booklets rather than using telephone calls. Similarly, Suppapitiporn and colleagues reported that combining patient education with the administration of diabetes booklet results in greater glycemic control [38]. On the other hand, pharmaceutical interventional program [32] for patients with gestational diabetes also produced a significant improvement in glycemic control (HbA1c reduced by 0.47%); however, this improvement is smaller than that achieved by pharmacist intervention in type 2 DM patients. The short duration of education sessions (10–30 min) in this study compared to studies conducted for type 2 DM patients may be the main cause of such difference, since the improvement in glycemic control is directly related to the duration of the educational session [39].

Three studies [29–31] examined the benefits of pharmacist intervention on blood pressure among type 2 DM patients. All showed a significant reduction in systolic (− 4.2 to − 9.8 mmHg) and diastolic (− 5.3 to − 8.9 mmHg) blood pressure, which was in tune with similar finding that assessed benefits of pharmaceutical care programs among type 2 DM patients in non-Arab countries [36]. The heterogeneous design, varying follow-up periods, and diverse methods of statistical analysis among these three studies make it difficult to know the best intervention to improve systolic and diastolic blood pressure. However, the greater reduction in blood pressure was found in interventions that involve pharmacists' recommendations to intensify antihypertensive drug dose when necessary. Pharmacist intervention among patients with gestational DM was not associated with any benefit to improve blood pressure, perhaps due to the fact that most included patients had normal blood pressure [40]. The outcome of pharmacist intervention on the lipid profile was assessed in three studies [28, 29, 31]. All of them revealed improvement in total cholesterol levels (− 19.4 mg/dl to − 30.5 mg/dl), LDL-c levels (− 13.3 mg/dl to − 23.2 mg/dl), HDL-c levels (+ 3.3 mg/dl to + 4.6 mg/dl), and TG levels (− 31 mg/dl to − 44.3 mg/dl). This finding was in agreement with similar findings by Pousinho and colleagues which showed that most pharmacist intervention studies were effective in improving lipid profile among type 2 DM patients [41]. The best improvement achieved in the lipid profile was reported in studies that involved both patient education (importance of adherence to prescribed medications and lifestyle modification) and dose adjustment of the anti-dyslipidemic drugs when necessary. The reviewed articles demonstrated well-recognized improvement in BMI (− 0.5 to − 1.05) of type 2 DM patients due to pharmacist interventions that focus on patient education of lifestyle changes. This finding was consistent with the findings reported by others, which showed the role of pharmacist intervention in the management of type 2 DM patients [41]. The improvement in BMI was greater in studies with a longer period of follow-up (12 months vs 6 months). This finding is reasonable since weight loss by lifestyle modification can be achieved slowly [42].

The benefits of pharmacist interventions on patient-reported outcomes such as medication adherence, patient knowledge, self-care activities, quality of life and/or patient satisfaction were assessed in most of the reviewed studies. Medication adherence was evaluated as a secondary outcome in four studies [27–29, 31], and mostly based on self-reported approach. The tools used for evaluation of this parameter varied slightly among the reviewed studies, where some of them utilized self-reports of forgetfulness or negligence, while others utilized general questionnaire such as short Morisky scale. Additionally, there was a slight variation between studies in the method for reporting medication adherence results at which three studies reported results in terms of adherence rate while the last one reported the result in terms of Morisky points. Despite the variability of methods used to measure and report data on adherence, it was clear that pharmacist intervention resulted in significant improvement of

medication adherence rate (increased by 26.9 to 58.1%). A similar finding was found in many other studies that evaluate pharmacist intervention among DM patients [43, 44]. This improvement may be related to the pharmacist's role in educating and encouraging patients to adhere to their prescribed therapy. Because drug-related problems are considered as a major factor for patient non-adherence [45] so it is not uncommon to find the highest improvement in adherence rate (58.1%) in the Iraqi study which was designed solely on solving drug-related problems. The short duration of follow-up in Iraqi study may be an additional factor in getting such very high adherence rate [46].

Although it is difficult to know the exact benefit of pharmacist intervention on patient knowledge because of diversity of the used assessment tools, it was clear that pharmacist educational interventions significantly improved DM patient knowledge, and this finding was in tune with other reports that declared improved patient knowledge through pharmacist interventions in Jordanian patients with other chronic diseases [47]. Self-care activities were assessed using Summary of Diabetes Self-Care Activities Questionnaire in two Jordanian studies. In both studies, the pharmacist educational intervention was effective to significantly improve most domains (diet, physical activity, and blood glucose monitoring) of patient self-care activities. Similar findings were reported by other studies conducted in Middle East countries [48, 49]. Moreover, two of the reviewed studies [31, 32] assessed the quality of life as a secondary outcome. Both indicated a marked improvement in the quality of life for diabetic patients (type 2 DM and GDM). This was in tune with findings reported by others [50], which focus on the benefits of pharmacist intervention programs in the management of type 2 DM patients. Such improvement may be directly related to solving drug- and disease-related problems and indirectly related to pharmacist care/educational role in improving glycemic control. Meanwhile, it is difficult to quantify the improvement in the quality of life because of heterogeneous study design, follow-up period, type of anti-diabetic medication, and age of included patients. Additionally, patient satisfaction was assessed in one study. That study showed that most domains of patient-reported satisfaction were significantly ($p < 0.05$) improved for patients in the intervention group, and a similar finding was obtained in studies conducted in other developing countries [51]. Two studies [31, 32] assessed the benefits of pharmacist intervention to reduce the risk of diabetes complications such as CHD and gestational diabetes complications. The studies reviewed here indicate a direct relationship between pharmacist intervention and risk reduction of CHD. They clearly showed significant reduction of this risk factor in the intervention arm, corresponding with similar data reported by others [52], which found that pharmacist intervention reduces CHD risk through improvement in glycemic control, blood pressure, lipid profile, and body weight. However, it was not clear whether such risk reduction is translated into real life and this can be solved only by doing studies with a very long period of follow-up. Pharmacist intervention in GDM patients reduces both maternal and neonatal DM-related complications. Although there was no similar study done until recently to compare such results, its result appears to be acceptable and reasonable since it is well known that controlling blood glucose level reduces both maternal and neonatal complications for patients with GDM [53].

Conclusion and recommendations

Pharmacists' interventions in DM management performed in Arab countries tend to result in enhanced patient knowledge; greater adherence to both pharmacological and non-pharmacological treatments; and eventually better glycemic, lipid, and blood pressure control. Further, precisely designed long-term studies are highly recommended to confirm the benefits of the interventions by pharmacists in the management of DM.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):611–617
https://doi.org/10.1007/s13410-019-00723-4

ORIGINAL ARTICLE

Long-term outcomes of diabetes after laparoscopic Roux-en-Y gastric bypass in a Lebanese bariatric practice

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Received: 4 June 2018 / Accepted: 10 February 2019 / Published online: 15 April 2019

Abstract

Introduction Roux-Y-gastric bypass (RYGB) is highly effective in treating obesity related type II diabetes mellitus (DM). There are a few studies from the Middle East and North Africa (MENA) on the impact of RYGB on DM.

Objective The aim of our study was to evaluate the impact of RYGB on DM in our patient population.

Methods We retrospectively reviewed our database and selected obese patients with type II DM who underwent primary laparoscopic RYGB from 2005 to 2015. Complete remission (CR) of DM was defined as HbA1c < 5.7%, FBG < 100 mg/dL without medications. Partial remission (PR) was defined as HbA1c 5.7–6.4%, FBG 100–125 mg/dL without medications. Improvement was defined by a significant reduction in HbA1c (> 1%) or FBG (> 25 mg/dL) or reduction in HbA1c and FBG accompanied by discontinuing insulin.

Results Out of 245 RYGB patients, 107 had DM. In comparison, diabetic patients were older and had more hypertension and dyslipidemia. At 5 years with a follow-up (F/U) of 56%, total weight loss in diabetics (24.7%) was lower than non-diabetics (27.7%). At a mean F/U of 5.6 ± 2.7 years, range (1.4 to 10.7), there was a significant reduction in HbA1C (7.9 to 6.1%), FBG (158 to 111 mg/dL), intake of oral hypoglycemic (73.6 to 29.7%), as well as insulin therapy (15.4 to 2.2%). The rate of DM CR was 42.3%, PR 20.5%, improvement 23.1%, and no change 14.1%.

Conclusion This is the first report from the MENA region on the long-term outcomes of RYGB in the treatment of type II DM. The results are similar to those in the international literature.

Keywords Gastric bypass · Diabetes · Remission · Long-term · Lebanon

Introduction

Diabetes mellitus (DM) has been considered a worldwide epidemic with estimated worldwide population of 382 million in 2013 that is expected to rise to 592 million by 2035 [1]. When compared to medical management, bariatric surgery is superior in the long-term treatment of DM and other obesity related comorbidities [2, 3]. Bariatric surgery also results in the long-term decrease in macrovascular and microvascular complications of DM [4]. Roux-en-Y gastric bypass (RYGB) is a well-established procedure for morbidly obese patients with DM [5]. DM remission post RYGB has been frequently studied with long-term remission rates ranging around 49–58% with the vast majority of such reports coming from Europe, North America, and Southeast Asia [6–10]. In the Middle East and North Africa (MENA), DM is also an important cause of morbidity and mortality with the highest worldwide comparative prevalence at 10.9% [1]. In Lebanon, the prevalence of DM is estimated to be 8.5% [11]. Other countries such as Saudi Arabia have higher prevalence rates around 24% [12]. Despite the significance of high DM prevalence in MENA region, there is a paucity of long-term data on the impact of RYGB on DM [13–15]. Therefore, our objective is to study the long-term glycemic outcomes of RYGB in our morbidly obese patient population.

Presented at the 23rd World Congress of International Federation for the Surgery of Obesity & Metabolic Disorders (IFSO), September 2018

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Methods

Study setting

The study was based on our retrospective review of the medical records and our prospectively collected bariatric database at the Metabolic and Bariatric Surgery Unit, American University of Beirut Medical Center, Beirut, Lebanon.

Inclusion/exclusion criteria

Obese patients (BMI ≥ 30 kg/m^2) who underwent laparoscopic RYGB over the years 2005–2015 were selected for analysis. Patients with previous history of bariatric surgery were excluded. One type I DM patient was excluded from the analysis as we are particularly interested in reporting type II DM outcomes.

Exposure

Patients were then categorized according to DM. Baseline patient characteristics, demographics, anthropometric measures, and comorbidities were compared between diabetic and non-diabetic patients.

Outcomes

Percent total weight loss (TWL) was reported at years 1 through 5 consecutively, and last follow-up beyond 5 years (6 to 11). Then, TWL was compared between diabetic and non-diabetic patients. Among diabetic patients, changes in medication intake and cardiometabolic parameters such as hemoglobin A1c (HBA1c), fasting blood glucose (FBG), total cholesterol, low-density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides were reported. Glycemic outcomes post RYGB, namely, overall remission, complete remission (CR), partial remission (PR), improvement, and unchanged were adapted from the American Diabetes Association (ADA), the American Society for Metabolic and Bariatric Surgery (ASMBS), and previous literature [16–18]. Detailed definitions on glycemic outcomes are presented in Table 1.

Surgical procedure

All procedures were done under general anesthesia with the patient supine in lithotomy position. Four laparoscopic ports were used in addition to a Nathanson liver retractor to retract the left lateral segment of the liver. The gastric pouch measuring 30 ml was fashioned in most cases using 60-mm blue or purple Endo GIA reloads (Covidien, Boulder, CO). The biliopancreatic limb measured 50 to 100 cm. The Roux limb measured 150 cm and was placed in an ante-colic ante-gastric orientation. The gastrojejunal anastomosis was performed in a hand-sewn fashion using two layers of 2–0 PDS over a 36French orogastric tube. The jejunojejunostomy (JJ) was performed using a single Endo GIA stapler 60-mm white cartridge. The common enterotomy was closed by a single-layer 2-0 PDS suture. The mesenteric defect at the JJ anastomosis was closed with 2-0 Prolene sutures in a running fashion in all patients. The Petersen defect was closed in around 70% of patients, typically over the latter part of the experience.

Statistical analysis

Continuous variables were presented by means and standard deviations, while categorical variables were presented as frequencies and percentages. Student *t* test, paired *t* test, or Wilcoxon signed rank test were used for the comparison of continuous variables, and Pearson's $\chi 2$ test, Fisher's exact test, or McNemar's test were used for categorical variables. A multivariate linear regression was performed using stepwise method to adjust the effect of confounders on TWL. Statistical significance was set at the 5% level. Statistical analysis was performed using IBM SPSS, version 24 (IBM Corp., Armonk, NY, USA).

Table 1 Definitions of glycemic outcomes after LRYGB

Outcome	Definition
Overall remission	Sub-diabetic/normal glucose metabolism (HbA1c < 6.5%, FBG < 126 mg/dL) in the absence of antidiabetic medications. Equivalent to achieving either CR or PR.
Complete remission (CR)	Normal measures of glucose metabolism (HbA1c < 5.7%, FBG < 100 mg/dL) in the absence of antidiabetic medications.
Partial remission (PR)	Sub-diabetic hyperglycemia (HbA1c 5.7–6.4%, FBG 100–125 mg/dL) in the absence of antidiabetic medications.
Improvement	Significant reduction in HbA1c (by > 1%) or FBG (by > 25 mg/dL) or reduction in HbA1c and FBG accompanied by discontinuing insulin.
Unchanged	The absence of remission or improvement as described above.

Criteria adapted from the following references [16–18]. *HbA1c* hemoglobin A1c, *FBG* fasting blood glucose

Table 2 Baseline demographic characteristics in diabetic and non-diabetic RYGB patients

	Non-diabetics	Diabetics	All patients	*p* value*
Frequency (%)	138 (55.9)	107 (43.7)	245 (100)	
Age (years)	38.3 ± 9.9	48.6 ± 8.2	42.8 ± 10.5	*< 0.001*
Male	75 (54.3)	59 (55.1)	134 (54.7)	0.90
Weight (kg)	131.2 ± 26.8	125.6 ± 23.7	128.7 ± 25.6	0.09
Height (cm)	169.3 ± 9.9	169 ± 9.7	169.2 ± 9.8	0.79
BMI (kg/m^2)	45.5 ± 7.1	44.0 ± 7.2	44.8 ± 7.2	0.09
< 50	111 (80.4)	90 (84.1)	201 (82.0)	0.46
≥ 50	27 (19.6)	17 (15.9)	44 (18.0)	
Hypertension	57 (41.3)	79 (73.8)	136 (55.5)	*< 0.001*
On medication	27 (19.6)	57 (53.3)	84 (34.3)	*< 0.001*
Dyslipidemia	99 (71.7)	94 (87.9)	193 (78.7)	*0.002*
On medication	11 (8.0)	44 (41.1)	55 (22.4)	*< 0.001*
GERD	75 (54.3)	61 (57.0)	137 (55.9)	0.76
On PPI	20 (14.5)	16 (15.0)	36 (14.7)	0.92
Depression	23 (16.7)	19 (17.8)	42 (17.1)	0.82
On medication	17 (12.3)	13 (12.1)	30 (12.2)	0.97
Smoker	55 (39.9)	45 (42.1)	100 (40.8)	0.73
Alcohol (> once/week)	13 (9.4)	7 (6.5)	20 (8.2)	0.41

Mean ± SD for continuous variables. Frequency (%) for categorical variables. *Non-diabetics vs. diabetics. *BMI* body mass index, *GERD* gastroesophageal reflux disease, *PPI* proton pump inhibitor. Significant *p* values are in italics

Results

Our cohort includes 245 morbidly obese patients who underwent primary laparoscopic RYGB. Type II DM was present in 107 patients (43.7%). Diabetic patients were older (48.6 ± 8.2 vs. 38.3 ± 9.9 years, $p < 0.001$), had similar male gender (55.1% vs 54.3%) and BMI (44.0 ± 7.2 vs. 45.5 ± 7.1 kg/m^2). They were more likely to have hypertension treated with medications (53.3% vs. 19.6%, $p < 0.001$), as well as dyslipidemia treated with medications (41.1% vs. 8.0%, $p < 0.001$). Other baseline variables are presented in Table 2.

Diabetic patients had worse percent TWL at all yearly points (years 1 through 5) in comparison to non-diabetic patients (Table 3). At first postoperative year with follow-up rate 87%, percent TWL in diabetic patients was 26.9 ± 6.0 vs. 30.5 ± 7.6 in non-diabetic patients, $p < 0.001$. At fifth postoperative year with follow-up rate of 56%, percent TWL in diabetic patients was 24.7 ± 8.1 vs. 27.7 ± 7.8 in non-diabetic patients, $p = 0.038$. A multivariate analysis on 5-year TWL was done to adjust for confounders such as age, gender, BMI, DM, hypertension, and dyslipidemia. After adjustment, DM was still

Table 3 Percent total weight loss (%TWL) and follow-up in diabetic and non-diabetic RYGB patients

	Non-diabetics		Diabetics		All patients		*p* value*
	Follow-up (%)	% TWL	Follow-up (%)	% TWL	Follow-up (%)	% TWL	
Year 1	121/138 (87.7)	30.5 ± 7.6	93/107 (86.9)	26.9 ± 6.0	214/245 (87.3)	29.0 ± 7.2	< 0.001
Year 2	98/138 (71.0)	31.6 ± 7.9	77/107 (72.0)	27.4 ± 7.2	175/245 (71.4)	29.7 ± 7.9	< 0.001
Year 3	79/138 (57.2)	30.0 ± 7.4	70/107 (65.4)	26.6 ± 7.9	149/245 (60.8)	28.4 ± 7.8	0.007
Year 4	73/137 (53.3)	29.8 ± 7.5	58/100 (58.0)	26.3 ± 7.3	131/237 (55.3)	28.3 ± 7.6	0.009
Year 5	72/127 (56.7)	27.7 ± 7.8	51/92 (55.4)	24.7 ± 8.1	123/219 (56.2)	26.5 ± 8.1	0.038
Year 6–11	66/124 (53.2)	27.0 ± 8.0	52/87 (59.8)	23.1 ± 7.8	118/211 (55.9)	25.3 ± 8.1	0.009

Mean ± SD for continuous variables. *TWL (non-diabetics vs. diabetics). Follow-up is presented as number of follow-ups/number of eligible subjects (% follow-up rate)

Table 4 Early and late postoperative complications of RYGB categorized by diabetes

	Non-diabetics $N = 138$	Diabetics $N = 107$	All patients $N = 245$	p value*
Early (≤ 30 days)	11 (8)	9 (8.4)	20 (8.2)	0.90
Major	5 (3.6)	6 (5.6)	11 (4.5)	0.46
Leak	3 (2.2)	1 (0.9)	4 (1.6)	
Bleeding	2 (1.4)	4 (3.7)	6 (2.4)	
Small bowel obstruction	1 (0.7)	1 (0.9)	2 (0.8)	
Minor	8 (5.8)	5 (4.7)	13 (5.3)	0.70
Readmission	5 (3.6)	4 (3.7)	9 (3.7)	
Wound infection	2 (1.4)	1 (0.9)	3 (1.2)	
UTI	1 (0.7)	0 (0)	1 (0.4)	
Pneumonia	2 (1.4)	2 (1.9)	4 (1.6)	
Fluid/electrolyte disturbance	1 (0.7)	0 (0)	1 (0.4)	
Late (> 30 days)	41 (29.7)	29 (27.1)	70 (28.6)	0.65
Major	12 (8.7)	8 (7.5)	20 (8.2)	0.73
PE	1 (0.7)	0 (0)	1 (0.4)	
MI	1 (0.7)	1 (0.9)	2 (0.8)	
Bleeding	2 (1.4)	0 (0)	2 (0.8)	
Small bowel obstruction				
Peterson hernia	3 (2.2)	3 (2.8)	6 (2.4)	
Jejunojejunostomy hernia	3 (2.2)	1 (0.9)	4 (1.6)	
Other	3 (2.2)	3 (2.8)	6 (2.4)	
Duodenal ulcer	0 (0)	1 (0.9)	1 (0.4)	
Minor	33 (23.9)	25 (23.4)	58 (23.7)	0.92
Gallstone disease	15 (10.9)	10 (9.3)	25 (10.2)	
Hiatal hernia	0 (0)	1 (0.9)	1 (0.4)	
Incisional hernia	0 (0)	2 (1.9)	2 (0.8)	
Anemia requiring IV iron	24 (17.4)	16 (15)	40 (16.3)	
Fluid/electrolyte disturbance	1 (0.7)	0 (0)	1 (0.4)	
Admission for depression	1 (0.7)	0 (0)	1 (0.4)	

Frequency (%) for categorical variables. *Diabetics vs. non-diabetics. Mean postoperative follow-up duration of all patients = 5.5 ± 2.5 years, range (1.4, 11.5) years

negatively associated with TWL at 5 years ($p = 0.038$). Early (≤ 30-day) complications and late (> 30-day) complications were similar in diabetic and non-diabetic patients. Table 4 gives a detailed presentation of complications categorized based on DM status.

Table 5 summarized some of the cardiometabolic parameters and medications intake that we studied, and which showed significant postoperative improvement in diabetic patients. Mean HbA1c in diabetic patients decreased from 7.9 ± 2.0% preoperatively to 6.1 ± 1.0% postoperatively ($p < 0.001$). Mean FBG decreased from 158 ± 61 mg/dL to 111 ± 38 mg/dL ($p < 0.001$). Oral hypoglycemic medications intake decreased from 73.6 to 29.7% ($p < 0.001$). Also, dependence on insulin therapy decreased from 15.4 to 2.2% ($p = 0.002$). Other parameters such as total cholesterol, HDL, and triglycerides also showed significant improvement.

Out of the 107 diabetic patients, 78 patients had follow-up beyond 1 year to allow assessment of DM resolution. Mean follow-up duration of diabetic patients was 5.6 ± 2.7 years, range (1.4, 10.7). CR was achieved in 33 patients (42.3%), PR in 16 patients (20.5%), improvement in 18 patients (23.1%), and unchanged status in 11 patients (14.1%). Overall remission represented by achieving either CR or PR did occur in 49 diabetic patients (62.8%). A subgroup analysis showed that patients who had remission of DM had statistically higher TWL in comparison to patients who had persistent DM particularly at years 1, 2, 3, and 4, but similar weight loss at year 5. At year 1, TWL ($n = 72$) in patients with DM remission was 28.2 ± 6.5 vs. 23.3 ± 3.8 in patients with persistent DM, $p < 0.001$. At year 5, TWL ($n = 47$) in patients with DM remission was 26.2 ± 9.4 vs. 22.0 ± 5.4 in patients with persistent DM, $p = 0.1$.

Table 5 Change in cardiometabolic parameters of diabetics after RYGB

Diabetics	N	Preoperative (1)	Postoperative (2)	Decrease (1)–(2)	*p* value*
HbA1c	67	7.9 ± 2.0	6.1 ± 1.0	1.8 ± 1.8	*< 0.001*
FBG	68	158 ± 61	111 ± 38	46 ± 56	*< 0.001*
Total cholesterol	66	188 ± 42	177 ± 36	11 ± 34	*0.010*
LDL	62	111 ± 35	106 ± 32	5 ± 29	0.17
HDL	64	43 ± 12	54 ± 14	− 11 ± 10	*< 0.001*
Triglyceride	65	212 ± 144	115 ± 54	97 ± 140	*< 0.001*
Oral hypoglycemics	91	67 (73.6)	27 (29.7)	40 (44.0)	*< 0.001*
Insulin therapy	91	14 (15.4)	2 (2.2)	12 (13.2)	*0.002*

Mean ± SD for continuous variables. Frequency (%) for categorical variables. *Decrease (preoperative-postoperative). Significant *p* values are in italics. Mean postoperative follow-up duration of diabetics = 5.6 ± 2.7 years, range (1.4, 10.7) years

Discussion

DM is a widely prevalent disease in the MENA region with prevalence ranging from 8 to 24% [1]. Several long-term complications arise from poor control of DM such as cardiovascular disease, neuronal injury, renal dysfunction, and amputations [19]. As a result, metabolic surgery to treat DM has gained the interest of researchers, general practitioners, endocrinologists, and bariatric surgeons. RYGB is a well-established procedure that has been in practice for several decades [20]. Benefits of this procedure related to weight loss and DM remission have been frequently studied [6–8]. However, outcomes from the MENA region are scant.

We studied laparoscopic RYGB weight loss and glycemic outcomes in selected Lebanese population. Our results show that diabetic patients had worse weight loss outcomes at years 1 through 5 post RYGB. Nevertheless, 5-year TWL at 24.7% is still considered to be successful (> 20%). Since diabetic patients were also older, had more hypertension, and dyslipidemia, we did multivariate analysis to adjust for confounders that affect weight loss. Following multivariate analysis, DM remained a negative predictor of TWL at 5 years, which is in accordance with results from previous bariatric literature [21, 22].

On further subgroup analysis within diabetic patients, TWL at years 1 through 4 was significantly higher in individuals who had DM remission in comparison to those who had persistent DM. Our results failed to show statistical difference in TWL at 5 years probably due to the small size of the sample ($n = 47$). Kadera et al. reported similar findings with higher weight loss 2 years postoperatively in patients with DM remission [23].

In our diabetic patient population, 62.8% had overall remission of DM. This figure is similar to international studies on DM remission after gastric bypass (GB), some of which are presented in Table 6 [6–8, 13, 14, 24]. From the MENA region, we found only two articles discussing DM remission following GB [13, 14]. Abusnana et al. from UAE reported 43% CR at one-year post RYGB but was limited by small sample size [13]. Taha et al. from Egypt reported 91% overall remission at 3 years post one-anastomosis GB (OAGB) [14]. Other international reports on GB range between these points. For example, Aminian et al. reported 49% overall remission rate 7 years post RYGB [7]. Moreover, the benefits of RYGB on DM are not limited to patients with BMI ≥ 35 kg/m^2. The American Society of Metabolic and Bariatric Surgery (ASMBS) endorses the presence of high-quality evidence supporting bariatric surgery including RYGB in class I obesity patients (BMI 30–34.9 kg/m^2) with DM [25].

Table 6 Studies on diabetes mellitus remission after gastric bypass

First author	Year of publication	Country	Procedure	Number of diabetics	HbA1c criteria (%)	FBG criteria (mg/dL)	F/U duration (years)	Overall remission (%)
Chen [24]	2018	Taiwan	RYGB/OAGB	245	< 6.5	< 126	5	74
Adams [6]	2017	USA	RYGB	84	< 6.5	< 126	12	51
Aminian [7]	2017	USA	RYGB	511	< 6.5	< 126	7	49
Obeid [8]	2015	USA	RYGB	66	< 6.5	< 126	10	58
Middle East and North Africa								
Taha [14]	2017	Egypt	OAGB	361	< 6.5	–	3	91
Abusnana [13]	2015	UAE	RYGB	14	< 5.7	< 100	1	43
Our study		Lebanon	RYGB	78	< 6.5	< 126	5.6	63

HbA1c hemoglobin A1c, *FBG* fasting blood glucose, *F/U* follow-up, *RYGB* Roux-en-Y gastric bypass, *OAGB* one-anastomosis gastric bypass

Some literature on bariatric surgery suggests that RYGB is superior to sleeve gastrectomy (SG), but inferior to OAGB in weight loss and remission of DM [7, 10, 24, 26]. Almalki et al. reported significantly higher DM remission post OAGB (70.5%) in comparison to RYGB (39.4%) [10]. A recent systematic review had the same conclusion [26]. As for SG, which is currently the most commonly performed bariatric procedure, rates reported on DM remission range from 28 to 66% [7, 15, 24]. Aminian et al. studied predictors of DM remission post bariatric surgery and formulated the Individualized Metabolic Surgery (IMS) score which is based on preoperative duration of DM, preoperative number of DM medications, insulin use, and glycemic control (HbA1C < 7%) [7]. For diabetic patients with high IMS scores, remission rates were similarly low for both RYGB and SG. This could be explained by depleted functional beta cell reserve in these patients. For intermediate range scores, RYGB was more effective in achieving DM remission than SG. Age, BMI, C-peptide level, and duration of DM (ABCD) score is another scoring system that was reported to better predict DM remission in comparison to IMS [24]. Benefits of bariatric surgery are not only limited to remission of DM but also apply to the prevention of DM in obese patients [27].

Limitations

The limitations of this study are related to its retrospective nature. We were able to report DM remission rates at last follow-up rather than at specific time points postoperatively; however, our mean follow-up duration was excellent and exceeded 5 years. We did not report relapse rates after short-term remission.

Conclusion

This is the first report from the MENA region on the long-term outcomes of RYGB in the treatment of type II DM. Our results are similar to those in the international literature highlighting the effectiveness of RYGB in the treatment of DM. Through our literature review, we noticed the lack of enough studies in the field of bariatric surgery in the MENA region. Therefore, we recommend researchers from this region to conduct larger prospective studies. We also recommend future studies to compare bariatric outcomes including DM remission between middle eastern and other populations and ethnicities as this could explore outcome differences between these populations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):618–625
https://doi.org/10.1007/s13410-019-00734-1

ORIGINAL ARTICLE

The safety and efficacy of a low-energy diet to induce weight loss, improve metabolic health, and induce diabetes remission in insulin-treated obese men with type 2 diabetes: a pilot RCT

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Received: 12 June 2018 / Accepted: 27 February 2019 / Published online: 22 March 2019

Abstract

Background Data are sparse on the safety and efficacy of commercially available energy-restricted meal plans in obese subjects with type 2 diabetes mellitus (T2DM). This study examined the safety and efficacy of a commercially available low-energy diet in insulin-treated obese men with type 2 diabetes.

Methods Eighteen men ≥ 35 years old who had class III obesity, had received insulin treatment for ≥ 1 year for type 2 diabetes, and had glycated hemoglobin (Hb) ≥ 6.5% were randomized to receive either a low-energy diet ($N = 9$) or standard medical nutrition intervention ($N = 9$) for 6 months.

Results Compared with 1.5% (± 3.55) in the control group, the mean percentage weight loss in the intervention group at 6 months was 9.6% (±4.91) ($p < 0.01$). Complete and partial diabetes remission occurred in one subject each in the intervention group and no subjects in the control group. Mean glycated Hb levels were 8.9% (± 2.76) and 9.1% (± 1.53) (p = NS) at baseline and 6.5% (± 0.64) and 7.4% (± 1.12) ($p = 0.0606$) at 6 months for the intervention and control groups, respectively. Compared with 0.85 mmol/L at baseline, the mean high-density lipoprotein cholesterol (HDL-C) level in the intervention group at 6 months increased to 0.96 mmol/L ($p < 0.01$) while it remained unchanged in the control group.

Conclusions Among obese men with insulin-treated type 2 diabetes, compared with standard medical nutrition, 6 months of a low-energy diet resulted in complete diabetes remission in one subject and partial remission in another while improving diabetes control and decreasing the median daily dose of insulin in the remainder.

Keywords Type 2 diabetes mellitus · Obesity · Low-energy diet · Diabetes remission · Coronary heart disease risk · HDL cholesterol

Abbreviations

BMI	body mass index
BP	blood pressure
BW	body weight
CHD	coronary heart disease
FPG	fasting plasma glucose
FFQ	food frequency questionnaire
HBGM	home blood glucose monitoring

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HDL-C	high-density lipoprotein cholesterol
Hb	hemoglobin
hs-CRP	highly-sensitive C-reactive protein
IL-6	interleukin-6
IWQoL	Duke University 32-item Impact of Weight on Quality of Life Questionnaire
kJ	kilojoules
LDL-C	low-density lipoprotein cholesterol
NC	neck circumference
OHA	oral hypoglycemic agents
SA	South Africa
SEMDSA	The Society for Endocrinology, Metabolism and Diabetes of South Africa
T2DM	type 2 diabetes mellitus
TC	total serum cholesterol
TG	triglyceride
VLCD	very low-calorie diet
WC	waist circumference
UKPDS	United Kingdom Prospective Diabetes Study
6MWT	6-Minute Walk Test
16-PF	16 Personality Factors test

Background

The prevalence of diabetes in South Africa (SA) in subjects 15 years and older in 2014 was 9.5% [1]. Obesity and physical inactivity are strong predictors of type 2 diabetes (T2DM) with obesity the more powerful of the two [2]. Weight loss of 5–10% in subjects with T2DM who were overweight or obese resulted in a clinically meaningful reduction in fasting plasma glucose (FPG), glycated hemoglobin (Hb), and total cholesterol (TC) [3].

Current guidelines advocate very low-calorie diets (VLCD) in obese subjects with T2DM to achieve weight loss greater than 5% in 3 months only under close medical supervision [4]. The data supporting these recommendations are limited [5, 6]. A VLCD consumed daily by obese subjects with T2DM resulted in remission of diabetes in 40% of subjects after 8 weeks [6]. After 6 months, the responders lost 15.4% of their body weight and were still in remission indicating that T2DM is potentially reversible by substantial weight loss.

Obese subjects with T2DM often resort to commercially available low-energy weight-loss programs in an attempt to lose weight and to improve glycemic control. Few studies, however, reported on the safety and efficacy of commercially available energy-restricted meal plans to reduce weight and improve glycemic control in obese subjects with T2DM [7–11]. Meal plans in these trials provided 1200–2000 kcal per day [7–9, 11]. Subjects in intervention groups achieved weight loss of 4.3–21 kg over 4–52 weeks [7–11]. Diabetes remission was not reported in any of these trials while serious hypoglycemia remains a concern [10, 11]. It has also been well-documented that initiation and intensification of insulin therapy contribute to weight gain in subjects with T2DM [12].

The main objectives of this study were to investigate the safety and efficacy of a low-energy commercially available weight loss program in SA to induce weight loss, improve metabolic health, and induce diabetes remission in insulin-treated obese men with T2DM.

Methods

Study design

This was a single-center, prospective, open-label, randomized pilot study conducted over a period of 6 months comparing the effect of a commercial weight loss program with a standard nutrition intervention in insulin-treated men with T2DM and class III obesity.

Subjects

The study population consisted of 18 male subjects. Women were not included in this pilot study of a small number of subjects since men and women may respond differently to rapid weight loss [13]. Subjects were recruited by newspaper advertisement and from private practices in the catchment area of the research unit. Inclusion criteria were age 35–65 years, BMI ≥ 35 kg/m^2, weight < 185 kg, T2DM diagnosed at least 4 years previously, currently managed on insulin for more than 12 months with or without oral hypoglycemic agents (OHA), and a glycated Hb level of $\geq 6.5\%$. Exclusion criteria were diabetes secondary to a specific disease or glucocorticoid therapy, previous bariatric surgery, advanced renal disease, a history of a previous positive HIV test, known malignancies or chemotherapy within the past 12 months, symptoms of heart failure greater than New York Heart Association functional class 2, unstable angina, and untreated major depressive disorder. Subjects continued their usual treatment, including lipid-lowering and anti-hypertensive agents. Insulin use was titrated according to capillary home blood glucose monitoring (HBGM) and carefully recorded.

Randomization

Subjects were assigned to one of two treatment arms by block randomization according to age (35–49.9 and 50–65 years) and BMI (35–45.9 and ≥ 46 kg/m^2).

Anthropometric data, 6-min walk test (6-MWT), and blood pressure (BP) measurement

Anthropometric data including weight were collected, and the 6-MWT and BP measurements were performed according to

standardized methods described in detail in Appendix 1. Body composition was determined by dual energy X-ray absorbtiometry.

Quality of life and psychometric testing

A registered counseling psychologist (AP) evaluated each patient by administering the Duke University 32-item Impact of Weight Quality of Life Questionnaire (IWQoL) and the 16 Personality Factors (16-PF) psychometric test after obtaining the permission of the license holders.

Dietary intake and food diaries

A registered dietician (SvdL) interviewed each subject and administered a food frequency questionnaire (FFQ) before and after completion of the trial to determine each subject's usual daily kilojoule intake. Subjects were also instructed to complete a food diary for a specific day during the preceding week. Subjects were encouraged to pursue physical activity within their individual physical capabilities.

Clinical assessment and laboratory analyses

Each subject was evaluated at the start of the trial by a single endocrinologist (WFM) to establish the presence of obesity-related comorbidities as well as the presence and extent of macro- and microvascular complications of diabetes.

The intervention group

The intervention group followed a commercially available low-fat energy-restricted diet primarily consisting of vegetables supplemented with a vegetable soup-based meal plan (CSN weight loss program - in this trial without aloe-containing drink, barley grass, or green powder). Subjects were booked into a holiday lodge for the first 9 days for close observation. A counseling psychologist provided a structured 2-h daily interactive training program during group sessions spread out over eight sessions followed by an additional one-on-one consultation with each subject.

The intervention entailed a 60-day eating plan consisting of six phases of 10 days each and is described in more detail in Appendix 1. After discharge from the lodge, subjects visited the research facility on a weekly basis to be weighed and to have their capillary blood glucose measurements and BP checked, their food diaries collected, and their insulin dose adjusted. Subjects were also encouraged to see the counseling psychologist individually at least once a month.

Control group

A dietician (SvdL) provided each of the subjects in the control group with a balanced personalized energy-restricted meal plan aimed at weight reduction of 0.5–1.0 kg per week. The control group received the same interactive training program as the intervention group and subjects also visited the research facility weekly for assessment and adjustment of insulin dose.

Outcomes

The primary outcome of the study was remission of diabetes defined as FPG < 5.6 mmol/L and a glycated Hb value of ≤ 6.5% at the end of the study without taking any hypoglycemic agents including insulin. Partial remission was defined as FPG ≥ 5.6 and ≤ 6.9 mmol/L and a glycated Hb value ≤ 6.5% at the end of the study on metformin only. Secondary outcomes were changes from baseline in levels of FPG, total insulin dose, glycated Hb level, body weight (BW), waist circumference (WC) and neck circumference (NC), arterial BP, resting pulse rate, 6-min walking distance, percentage body fat, levels of serum total cholesterol (TC), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), triglyceride (TG), highly sensitive C-reactive protein (hs-CRP), s-interleukin 6 (IL-6), s-leptin, and 10-year risk of coronary heart disease (CHD) based on the UKPDS risk calculator at baseline, 3 and 6 months [14]. Changes from baseline to month 6 in the IWQoL were also determined.

Laboratory tests

All laboratory tests were performed by a private South African National Accreditation System accredited chemical pathology laboratory (van Rensburg Pathologists, Bloemfontein, South Africa).

Statistical methods

Numerical variables were summarized by means and standard deviations or percentiles (depending on data distributions). The two groups were compared using *t* tests or Mann-Whitney tests. Within-group comparisons were made using paired *t* tests or signed rank tests.

Results

Subjects

Nine subjects were randomized to each arm of the study. Two subjects left the control group after 3 months for personal reasons. The two most common comorbidities present at baseline were dyslipidemia (eight subjects in each of the groups)

and systemic hypertension (seven subjects in each group) (Table 1).

Anthropometric variables

At 3 and 6 months, subjects in the intervention group achieved a mean reduction in BW from baseline of 9.0% (± 3.55) (11.6 kg) and 9.6% (± 4.91) (12.6 kg) respectively, compared to 1.9% (± 2.25) (2.6 kg) and 1.5% (± 3.55) (0.6 kg) in control subjects at corresponding time points ($p < 0.01$ for both between-group comparisons) (Table 2).

Glycemic control

The mean glycated Hb level in the intervention group decreased from 8.9% (± 1.74) at baseline to 6.8% (± 0.65) at 3 months ($p < 0.05$) and to 6.5% (± 0.64) at 6 months ($p < 0.01$). The median total daily dose of insulin in the intervention group at 3 months (0.14 (0; 0.22) U/kg) and at 6 months (0.19 (0; 0.22) U/kg) was less than at baseline ($p < 0.01$ for both comparisons).

Insulin was discontinued in three subjects in the intervention group during the trial compared to none of the subjects in the control group. All subjects in the intervention group, except the one who went into remission (see below), were taking metformin at baseline and continued with metformin until the end of the trial. Diabetes remission was achieved in one subject in the intervention group. Compared with 11.7% at baseline, this subject's mean glycated Hb was 6.0% after 6 months. This subject's mean fasting serum TG level decreased from 9.9 mmol/L at baseline to 2.4 mmol/L after 6 months. In this subject, insulin was completely discontinued after 6 weeks. The duration of diabetes in this subject was 5 years, and he had been using insulin since diabetes was diagnosed. One more subject in the intervention group went into partial remission with FPG and a glycated Hb level of 5.5 mmol/L and 6.1%, respectively, while still on metformin, which was discontinued at the end of the trial. He had diabetes for 9 years and used insulin for 7 years. The subjects who achieved either complete or partial remission of diabetes at the end of the trial reduced their BW by 15.2% and 16.5%, respectively.

Table 1 Most commonly occurring comorbidities at baseline for both groups

Comorbid condition	Intervention group ($n = 9$)	Control group ($n = 9$)
Dyslipidemia	8	8
Hypertriglyceridemia	2	2
Systemic hypertension	7	7
Ischemic heart disease	2	2
Chronic atrial fibrillation	2	0
Smoking tobacco	3	3
History of gout	3	4
Osteoarthritis	3	5
One or more abnormal liver enzymes at baseline	4	3
Obesity-associated sleep disorder*	3	1
Depression**	0	3

*Using continuous positive airway pressure breathing at night

**Stable and well-controlled on medication before the onset of trial

Cardiovascular-related measurements

At 6 months, in the intervention group, mean HDL-C levels increased from baseline ($p < 0.01$), WC and NC decreased ($p < 0.01$), the mean distance covered during the 6MWT increased ($p < 0.01$), and the mean IWQoL improved ($p < 0.01$) (Table 2). The median 10-year risk of CHD decreased over 6 months in both the intervention ($p < 0.01$) and the control group ($p < 0.05$).

Adverse events

Compared to 22 episodes in 6 subjects in the control group, 7 episodes of mild to moderate hypoglycemia were recorded in 6 subjects in the intervention group. This may reflect the more aggressive use of insulin in the control group to try and achieve normoglycemia. One subject in the intervention group developed symptomatic orthostatic hypotension and the dose of BP-lowering medication had to be decreased. Five subjects in each group complained about constipation at some stage, and this complaint featured more prominently in the intervention group. Additional adverse events considered to be study unrelated included the development of an ischiorectal abscess and subclinical hypothyroidism (one subject each in the intervention group) and unstable angina in one subject in the control group (unrelated to hypoglycemia).

Discussion

To the best of our knowledge, this is the first study to investigate the effect of an intensive nutrition intervention in men with class III obesity and poorly controlled T2DM and on insulin therapy. Furthermore, the effect of MNT intervention on insulin dose was not described in any detail in previous studies of this nature [7–11].

The weight loss at 6 months reported in this trial is very similar to that previously reported in two other commercial weight loss trials [7, 8]. The decrease in leptin levels in the intervention group was in keeping with increased leptin sensitivity associated with weight loss [15].

Complete and partial remission of diabetes occurred in one subject each in the intervention group compared to none in the control group. None of the clinical trials investigating the

Table 2 Clinical and biochemical variables of subjects at baseline, 3 months and 6 months (mean ± SD)

	Intervention group			Control group		
Variable	Baseline ($N = 9$)	3 months ($N = 9$)	6 months ($N = 9$)	Baseline ($N = 9$)	3 months ($N = 9$)	6 months ($N = 7$)
Age (years)	55.64 (± 7.72)			54.53(± 6.48)		
Mean weight (kg)	131.7 (± 20.51)	120.1 (± 20.08) **	119.1 (± 19.39) **	125.4 (± 26.04)	122.8 (± 24.26) *	124.8 (± 24.69)
% weight change from baseline	–	−9.0 (± 3.55)$^{\Delta\Delta}$	−9.6 (± 4.91)$^{\Delta\Delta}$	–	−1.9 (± 2.25)	−1.5 (± 3.55)
BMI (kg/m^2)	41.3 (± 4.41)	37.6(± 4.70) **	37.3(± 4.62) **	40.1 (± 6.46)	39.3 (± 5.91) *	39.6 (± 6.56)
Daily kJ intake[a]	10,110 (7200; 12,311) ($N = 8$)		8749 (7685; 10,838) ($N = 6$)	10,843 (9051; 16,466) ($N = 7$)		10,365 (6928; 13,182) ($N = 7$)
WC (cm)	137.0 (± 13.85)	123.6(± 14.09)**	125.0 (± 13.98)**	130.5(± 17.67)	127.1(± 17.61)**	130.3(± 17.48)
NC (cm)	49.9(± 2.88)	44.8(± 3.19)**	46.2(± 2.7)**	49.7(± 4.7)	46.9(± 4.46) **	48.4(± 4.91)
Total body fat (%)	44.7(± 4.58)	42.7 (± 5.00) *	39.5 (± 4.99) **	44.5 (± 5.82)	44.5(± 5.41)	44.8 (± 5.84)
S-leptin (pg/ml)[a]	30,027 (24,562; 35,629)	18,336 (14,091; 28,064)**	22,885 (14,839; 34,376)* ($N = 8$)	30,712 (18,120;43,300)	20,322 (19,469;53,715) ($N = 7$)	42,566 (19,110;55,434) ($N = 7$)
Impact of weight quality of life (%)	48.1 (± 15.06)	–	72.1 (17.91)**	56.1 (16.85)		65.7 (17.76)
FPG (mmol/L)	8.9 (± 2.76)$^{\Delta}$	6.7 (± 1.14)	6.4 (± 1.56) $^{\Delta}$	13.1 (± 3.83)	8.0 (± 2.11)**	9.6 (± 2.64)**
Glycated Hb (%)	8.9 (± 1.74)	6.8 (± 0.65)*	6.5 (± 0.64)**	9.1 (± 1.53)	7.4 (± 0.67)**	7.4 (± 1.12)**
Units of insulin per day[a]	50 (46; 67)$^{\Delta}$	20 (0; 28)$^{\Delta\Delta}$**	22 (0; 30)$^{\Delta\Delta}$ **	100 (76; 109)	74 (59; 95)	120 (60; 130)
Units of insulin per kg/day[a]	0.45 (0.31; 0.66)$^{\Delta}$	0.14 (0; 0.22)$^{\Delta\Delta}$**	0.19 (0; 0.22)$^{\Delta\Delta}$**	0.73 (0.67; 0.91)	0.65 (0.51; 0.84)	0.93 (0.43; 1.12)
Resting pulse rate (bpm)	78 (± 15.0)	72 (± 14.8)*	66 (± 12.1)*	75 (± 8.7)	69 (± 11.3)	71 (± 8.6)
Systolic BP (mmHg)	133.6 (± 12.5)	132.2 (± 18.5)	131.3 (± 18.1)	136.4 (± 15.7)	132.1 (± 19.1)	130.1 (± 17.5)
Diastolic BP (mmHg)	84.3 (± 8.7)	81.7 (± 9.8)	78.8 (± 6.5)	82.2 (± 6.9)	77.4 (± 7.9)	74.9 (± 7.3)
TC (mmol/L)	4.6 (± 1.03)	4.1 (± 0.94)	4.4 (± 1.28)	4.9 (± 1.51)	4.5 (± 1.30)	4.3 (± 0.77)
TG[a] (mmol/L)	1.80 (1.7; 3.5)	1.7 (1.4; 2.4)	1.5 (1.3; 2.4)	2.1 (1.5; 3.7)	1.9 (1.2; 2.4)	1.7 (1; 2.4)
HDL-C (mmol/L)	0.85 (± 0.18)	0.83 (± 0.144)	0.96 (± 0.161)**	1.00 (± 0.24)	0.97 (± 0.217)	1.01 (± 0.256)
LDL-C (mmol/L)	2.59 (± 0.79)	2.42 (± 0.93)	2.69 (± 1.33)	2.51 (± 0.76)	2.31(± 0.78)	2.47 (± 0.55)
6-MWT (distance) (m)	373.6 (± 45.4)	403.9 (± 40.9)*	415.3 (± 46.2)**	395.2 (± 69.2)	397.7 (± 87.0)	403.8 (± 86.0)
hs-CRP[a] (mg/L)	7.1 (3.1; 17.5)	4.7 (3.6; 18.1)	6.3 (2; 7.4)	5.4 (2.2; 5.6)	3.6 (2.4; 3.8)	3.3 (2.8; 4.3)
ESR[a] (mm 1st hour)	12.0 (10; 30)	17.0 (7; 30)	15.0 (12; 32)	10.0 (5; 20)	12.0 (6; 14)	15.0 (2; 25)
IL-6[a] (pg/mL)	7.4 (4.5; 7.7)$^{\Delta}$	4.5 (3; 6)	4.7 (2.8; 4.9)	2.5 (2.2; 3.7)	2.1 (1.5; 3.4)	5.5 (2.9; 5.5)
UKPDS 10-year CHD risk (%)[a]	28.1 (13.7; 31.7)	13.6 (10.8; 21.4)*	11.3 (9.6; 18.7)**	23.2 (16.7; 35.2)	19.3 (13.9; 28.6)*	20.6 (9.7; 28.4)*

Comparison between groups at corresponding time points: $^{\Delta}p$ value < 0.05; $^{\Delta\Delta}p$ value < 0.01. Within group changes from baseline to 3 and to 6 months: *p value <0.05 from baseline; **p value from baseline <0.01.

ESR erythrocyte sedimentation rate

[a] Median (interquartile range)

efficacy of commercial weight loss programs reported remission of diabetes [7–11]. A number of recent studies has shown that T2DM may be a reversible condition following non-surgical intensive lifestyle intervention [6, 16–19]. In our study, the median daily energy intake by subjects in the intervention group during the first 8 days of the intervention was 3674 kJ (2948; 3897) (data not shown). It is tempting to hypothesize that moderate-severe energy restriction during the first 10 days, which is the hallmark of the intervention described in this study, may have contributed to complete and partial diabetes remission in our subjects. This notion is supported by the results of two VLCD studies [5, 19].

The mean glycated Hb level of 6.5% (± 0.64) at 6 months in the intervention group was within the target range for good glycemic control [20] and was similar to that reported in two other commercial weight loss trials [7, 8]. Compared to baseline, the median daily dose of insulin in the intervention group was more than halved at 3 and at 6 months.

The decrease in mean resting pulse rate at 3 and at 6 months in the intervention group is in keeping with the expected decrease in resting sympathetic nervous activity following weight loss [21] and may in part be mediated by a decrease in circulating leptin levels [22]. The 6-MWT is regarded as a measure of cardio-respiratory fitness and disability in obese subjects [23]. The increase in distance covered by the intervention group in the 6-MWT in our study is most likely a direct consequence of weight loss [24]. The reduction in 10-year risk of CHD in the intervention group was mainly driven by a decrease in glycated Hb and an increase in HDL-C, while the risk reduction in the intervention group was mainly due to improved glycemic control. The effect of weight loss on systemic inflammation, as measured by IL-6 and hs-CRP levels, is complex [25]. Weight loss studies yielded inconsistent results concerning markers of systemic inflammation [7–10]. The lack of response of markers of systemic inflammation to weight loss in our study may also be attributed to the small number of subjects.

This study is limited by the small sample size, the relatively short duration of 6 months, the enrollment of men only, and the drop-out of two subjects from the control group after 3 months. In addition, subjects were not homogenized at baseline in terms of metabolic variables. However, mean glycated Hb levels at baseline in our study were very similar to that reported by Distiller et al. (8.8%) for a large group of subjects with T2DM in SA before enrolment into a specialized Diabetes Management Program [26]. The strengths of this study are that it was multidisciplinary, all subjects received insulin at baseline, subjects were assessed on a weekly basis, and subjects in the intervention group were under direct supervision for the first 9 days of the intervention. Insulin titration and usage were carefully documented. Adverse effects including hypoglycemia were also carefully monitored and recorded.

Conclusions

The nutrition intervention described in this study and implemented under close medical supervision was safe and effective. The findings of this study should be confirmed by larger studies enrolling subjects of both sexes and conducted over a longer period. Data generated by this study add to the growing body of evidence that diabetes remission is an attainable goal in some subjects with T2DM.

Authors' contributions WFM, GM, and GJ were responsible for the conception and development of the trial protocol. WM, KT, SvdL, and AP conducted the research. WFM and KT compiled the data set, and GJ performed statistical analyses. WM drafted the manuscript, and GJ, AP, SvdL, GM, and KT critically revised the manuscript. All authors read and approved the final manuscript.

Funding This study was funded by an unrestricted educational grant by Mr. Christo Strydom, Bloemfontein, South Africa. The authors had complete autonomy to develop the protocol, conduct the research, analyze data, and write the manuscript.

Availability of data and material Professor G Joubert is the curator of the data set, which is available on request.

Compliance with ethical standards

Conflict of interest Author WF Mollentze was the manager of the Christo Strydom Metabolic Research Unit, University of the Free State, at the time research was conducted. The University of the Free State received partial funding for the Christo Strydom Metabolic Research Unit from CSN, the company that manufactures and distributes CSN products in South Africa. Author WF Mollentze received a speaker honorarium from Novartis within the last 3 years. Author G Joubert declares that she has no conflict of interest. Author S van der Linde declares that she has no conflict of interest. Author A Prins declares she has no conflict of interest. Author GM Marx declares she has no conflict of interest. Author KG Tsie declares that she has no conflict of interest.

Ethical approval All procedures performed involving human subjects in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval to conduct the study was obtained from the Health Sciences Research Ethics Committee, University of the Free State, Bloemfontein, South Africa. (Ethics Committee approval no: ECUFS 158/2015 (registered 16 September 2015))

Informed consent Informed consent was obtained from all individual subjects included in the study. Consent to publish was also obtained from all subjects in the study.

Appendix 1

Anthropometric data, 6-min walk test (6-MWT), and blood pressure measurement

Patients were weighed to the nearest 0.1 kg on a low-profile platform Detecto stand-on scale with handrails (DET

6854KGEUDHR) without wearing shoes and dressed in light indoor clothing after emptying the bladder. Height was determined to the nearest cm with an electronic Detecto measuring rod attached to the wall. Waist circumference (WC) was measured to the nearest cm in the standing position at the end of expiration with a tape measure wrapped horizontally around the waist half-way between the inferior rib cage and the iliac crest. Neck circumference (NC) was measured in the standing position with a measuring tape to the nearest cm. Body composition was determined by a single trained radiographer using a Hologic Horizon W Bone Densitometer. The 6-MWT was performed on a flat surface at the research facility according to American Thoracic Society Guidelines.[1] BP was measured with a Welch Allyn Spot Vital Signs monitor three times in the right arm, which was supported at the level of the heart with a 32–43-cm cuff and with the patient in the sitting position after 5-min rest. The set of measurements with the lowest diastolic reading was used for analysis.

Clinical assessment and laboratory analyses

Each participant was fully evaluated at the start of the trial by a single endocrinologist (WFM) to establish the presence of obesity-related comorbidities as well as the presence and extent of macro- and microvascular complications of diabetes. A resting 12-lead ECG was also obtained. For safety evaluation, the following investigations were performed at baseline, monthly, and at the end of the trial: full blood count, erythrocyte sedimentation rate, serum-urea and electrolytes, s-creatinine, s-magnesium, total and conjugated s-bilirubin, liver enzymes, s-albumin, and s-urate. The 10-year risk for CHD without any additional intervention was calculated with the UKPDS online risk engine.[2]

The intervention

The intervention group followed a commercially available low-fat energy-restricted diet primarily consisting of vegetables supplemented with a vegetable soup-based meal plan, the CSN Weight Loss Programme (in this trial without aloe-containing drink, barley grass, or green powder).[3]

The intervention entailed a 60-day eating plan consisting of 6 phases of 10 days each. Briefly, the meal plan during phase 1 consisted of the following: Day 1, 200 ml soup 6–10 times daily along with fruit in the form of plain fruit salad or fresh fruit; day 2, soup, fresh vegetables and one medium-sized baked potato; day 3, fruit, vegetables and soup; day 4, six bananas and one glass of skimmed milk; day 5, soup, 2 raw tomatoes with each meal and 150 g roasted beef at dinner; and day 6, soup, tomatoes, and vegetables. The soup was reconstituted with hot water from desiccated vegetables in powder form. The day 1–4 menus were repeated on days 7–10. The meal plan for the second 10-day phase consisted of half a glass of grapefruit juice one-half hour before each meal, 2–4 boiled eggs and 1–2 raw tomatoes for breakfast, while the lunch and dinner menu allowed a small portion of beef, fish (without butter) or skinless chicken, along with 6–10 glasses of soup mix each day for 6 days, followed by the menu of days 1–4 from phase 1. Phases 3–6 were various permutations of phases 1 and 2. No alcohol was allowed during phase 1. After completion of the first 60 days, participants were allowed to repeat any of phases 2–6 at their own discretion and to avoid or limit the intake of carbohydrates in the form of bread, pasta, and rice.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):626–632
https://doi.org/10.1007/s13410-019-00726-1

ORIGINAL ARTICLE

Effectiveness of sexual counseling using PLISSIT model on sexual function of women with type 2 diabetes mellitus: results from a randomized controlled trial

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Received: 28 July 2018 / Accepted: 11 February 2019 / Published online: 18 March 2019

Abstract

Background Sexual problems are very common in patients with type 2 diabetes mellitus and due to its chronic nature may affect women's sexual quality of life.

Objectives To study the effect of permission, limited information, specific suggestions, intensive therapy (PLISSIT) model sexual counseling on sexual function of women with type 2 diabetes.

Methods This study is a randomized clinical trial that was conducted on 100 married women aged 35-55 year old with type 2 diabetes referred to endocrinology clinic. The subjects were randomly assigned to the intervention and control groups. In the intervention group, individual counseling was designed based on PLISSIT model, in at least three sessions. The control group received a general health training pamphlet at the end of the study. Before the first session and then 4 and 8 weeks after the intervention, questionnaires of demographic information, Brief Sexual symptom checklist for women (BSSC-W), and Female sexual Function Index (FSFI) were completed for two groups.

Results Total FSFI score of the patients improved after sexual counseling ($p < 0.001$) and in subscales; sexual desire ($p = 0.009$), lubrication ($p = 0.004$), orgasm ($p < 0.001$), and sexual satisfaction ($p < 0.001$). Also sexual function in all subscales except for arousal ($p = 0.181$) and pain ($p = 0.783$) were increased significantly. Although pain was decreased significantly in intervention group over the time, no difference was seen between two groups ($p = 0.783$). The effect size of intervention to promote FSFI was determined 0.42.

Conclusion Considering the effectiveness of a PLISSIT model sexual counseling on sexual function of women with type 2 diabetes, the results of the present study, can be used to promote sexual health of diabetic patients.

Keywords Diabetes mellitus · Women's sexual function · PLISSIT · Sexual counseling

Background

Chronic diseases, especially type 2 diabetes, which have a high prevalence in Iran, have a significant effect on women's sexual life [1, 2]. Although sexual dysfunction is very prevalent, patients with type 2 diabetes are more likely to have sexual dysfunction, pain, and reduced sexual arousal [3, 4]. The total prevalence of sexual dysfunction in type 2 diabetic women in Iran has been reported 78% [5]. In women with type 2 diabetes mellitus, sexual dysfunction and vaginal lubrication problems have been reported 46–82% and 37–70%, respectively. Prevalence of arousal disorder has been 68%, orgasm disorder 38–84%, and painful sex 43–46% [6].

The quality of sexual life and sexual health of diabetic women was reported significantly lower than that of women without this disorder [7, 8]. Sexual disorder is more common in women than men and it has not been related to age, duration of diabetes, and hypertension [9]. Another study also confirmed this result [2].

In the country's healthcare system, despite high capacity, there is still no place to screen sexual problems. The World Health Organization (WHO), emphasizing the integration of sexual health in primary health services, considers sexual issues' training of people and health workers as essential for the

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promotion of sexual health [10]. Regarding the high prevalence of diabetic patients' sexual problems, it seems that diagnosis of sexual problems and counseling about these problems with patients should be more carefully planned in the healthcare system. In some other countries also, health services often are not organized for the needs of diabetic patients, and health workers lack the knowledge and skills to manage such diseases [11].

Regarding high prevalence of sexual dysfunction in type 2 diabetic patients and the effect on the quality of life, it seems very necessary to have sexual counseling. PLISSIT model is the most commonly used tool for studying and evaluating sexual function and can be used by all people. This model was developed by psychologist Jack Annon (1974) to be used by healthcare providers in visits to assess the patients' sexual health needs [12]. The sexual counseling model has a four-stage framework, including a patient permission to start talking about sexual problems, providing limited information, specific suggestions, and intensive care to resolve the sexual problems of the patients. This counseling model has been studied in patients with stoma, breast cancer, multiple sclerosis, uterine, and vaginal cancer, as well as in patients undergoing surgeries such as hysterectomy or cardiac surgery and in all of these patients, it has been proven useful in solving and managing patients' sexual problems [13–16]. Due to scarce evidence about this counseling model in diabetic patients, this study aimed to assess the effect of sexual counseling using PLISSIT model on sexual function of type 2 diabetic women.

Methods

Design

The present study was a parallel randomized clinical trial that was conducted on 100 middle-aged diabetic women (50 in the intervention group and 50 in the control group) referred to endocrinology clinic of Imam Ali hospital in Karaj. The study protocol was reviewed and verified by a sexologist of the research team. Eligible patients randomly assigned to the control and intervention groups after providing consent to participate in the study. Randomization took place by a colleague outside of the research.

Study participants

Diabetic women aged 35 to 55 years participated in this study and the inclusion criteria were as follows: Iranian women with type 2 diabetes, ages 35–55, women with at least one sex problem based on Brief Sexual symptom checklist for women (BSSC-W), reading literacy in Persian to fill in questionnaires, and no medical conditions other than diabetes that affects sexual function. Participating in similar training counseling sessions, pregnancy, and/or lactation, as well as sexual dysfunction in men, were the study exclusion criteria. Assuming the equality of variance in two groups and the mean difference of 0.7 between the two groups, using the following formula with the 0.05 probability error of type 1, and the power of 80%, 50 samples were calculated. In addition, we accounted for a 10% dropout. A total of 55 patients in each group were needed [17].

$$n = \frac{2 \times \left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 S^2}{(d)^2}$$

Simple randomization (card/envelops shuffling) was the method for randomization in this study. The participants were selected randomly (3 days per week every other day) among patients who had the study inclusion criteria referred to endocrinology clinic of Imam Ali hospital. Random allocation was performed by 110 cards that were encoded and placed in a container from 1 to 110, so that 55 envelopes for the intervention group and 55 envelopes for the control group could be extracted. Then, the envelopes were randomly pulled out. Two separate containers were considered for the intervention and control. According to the previous process, the first envelope was placed for the control group and the one for the intervention group, and this was done until the allocation process was complete. To conceal the randomization, the envelopes were sealed as well as we asked an assistant outside the study team to assign the envelopes. The study flowchart based on CONSORT 2010 was illustrated in Fig. 1.

Intervention

At least three sessions of 45 min of individual sexual counseling were designed and developed to improve sexual function based on PLISSIT model in the intervention group. Educational pamphlet for the control group included general care in diabetes and related therapies, nutrition, physical activity, and sexual health. Sexual function questionnaire was completed for both groups before the first session and then 4 and 8 weeks after the intervention.

Permission The researcher asks the patient for permission to enter the sexual discussion and allows him to ask questions in a comfortable and private environment. A sample question asked is "I ask all diabetics about their sexual problems, is it okay to ask you such questions?" or for example "do you have questions about sexual problems to ask me?" [18].

The second stage is to provide *limited information*. The researcher provided brief information to the patient about the effect of diabetes and its side effects on sexual function. The third stage is *specific suggestions* for the given problem. After taking a thorough history and discovering patients' problems, strategies such as administering lubricant and/or introducing a special position for sex and changes in lifestyle can help the person to

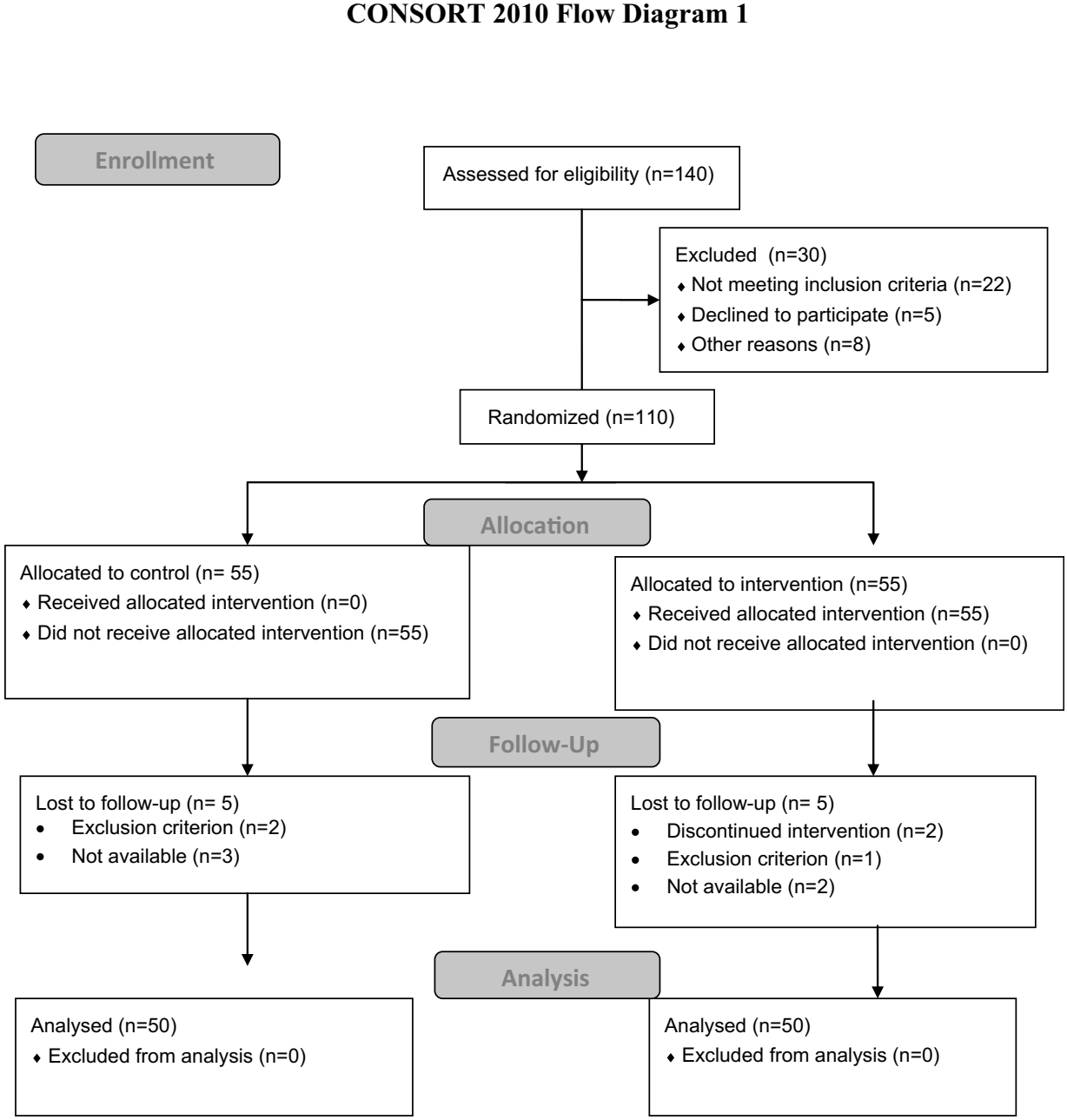

Fig. 1 CONSORT 2010 flow diagram 1

resolve the problem. Exercises can be used such as sensate focus, Kegel exercise, and others, depending on the type of problem and patient's need. The fourth stage is *intensive care*, which identifies any difficulty and sometimes requires referral to other professionals such as a psychiatrist or family consultant.

The first session started with permission, introduction, providing an intimate and comfortable environment for the patient, and asking questions about the onset of the disease and how it was treated. The second session provided limited information on genital anatomy and physiology with images and models, sexual response cycle and changes in life cycle, and the effect of diabetes on the sexual function and life of a person. At this stage, we attempt to correct the information about the changes that may occur sexually in a diabetic person, and/or the mutual effect of a healthy sexual relationship on a diabetic person life, as well as her sexual misconceptions.

The third session offered specific suggestions for the patient's problem, including regular daily walks, recommendations for taking lubricant, Kegel regular exercise, hormonal medications such as Premarin (if necessary under a doctor's control), sensate focus, and changes in sex position [18]. The first author as a female midwife-counselor has conducted sessions and gathered data. Study duration lasted 18 weeks from the first counseling

session of the first participant and the last counseling session of the last participant.

Measures

In this study, data collection tool was a questionnaire that was completed as self-administered. The questionnaire consisted of three parts as below:

Demographic characteristics

Demographic characteristics include marital status, age, education, occupation of the patient and her spouse, duration of the patient's diabetes and type of treatment, level of HbA1c, family income, and body mass index.

Brief Sexual symptom checklist for women

BSSC-W with forward-backward procedure was applied to translate the questionnaire from English to Persian with the author's permission. It consists of six questions; the first question begins with the question of the degree of satisfaction with sexual function, which, if negative, the next question is asked.

Female Sexual Function Index

Female Sexual Function Index (FSFI) questionnaire by Rosen et al. evaluates sexual function of women in six independent fields of sexual desire, sexual stimulation (arousal), lubrication (vaginal wetness), orgasm, satisfaction, and sexual pain with 19 questions [19]. A higher score indicates better sexual function. This tool evaluates women's sexual function over the past 4 weeks. For scoring, the scores of each field are obtained by summing the scores of questions in each field and multiplying them in the factor number. A zero score indicates that the person did not have sexual activity during the last 4 weeks. The maximum score for each domain is 6 and for the whole scale is 36. Validity and reliability of this tool were confirmed in Iranian studies and Cronbach's alpha coefficient for each of the fields and the whole scale was 0.70 and higher [20].

Data analysis

To compare the quantitative variables between the two groups, we used *t* test and for comparing the qualitative variables in two groups, chi-square or Fisher's tests were used. The mean scores of sexual function between the intervention and control groups before 4 and 8 weeks after the intervention were compared using repeated measure ANOVA. *p* value less than 0.05 was considered significant. Cohen *d* was used to determine effect size. Data analysis of this study was done using software SPSS version 19.

Results

The mean age of women was 47.88 ± 5.44 and 48.02 ± 6.03 in the intervention and control groups respectively ($p = 0.903$). Husbands' age mean was 54.46 ± 6.75 in the intervention and 55.36 ± 8.24 for the control group ($p = 0.552$). The highest number in both groups (56%) was for junior and high school without significant difference between the two groups ($p = 0.061$) about income. The duration of the disease in the intervention group was 7.62 ± 5.270 and 7.35 ± 3.995 in the control group ($p = 0.773$). The mean of HbA1C in the intervention group was 8.23 ± 1.52 and 8.170 ± 1.24 in the control group ($p = 0.813$). Eleven women (22%) of the intervention group were in menopausal situation and four of them (18%) needed hormone therapy. Other variables are shown in Table 1.

Repeated measures ANOVA showed that the sexual function mean score had a significant change over time ($p = 0.000$) and a significant difference was observed between the two groups ($p = 0.000$). All subscales of sexual function in the intervention group improved except for pain and arousal (Table 2). Figure 2 shows the trend of the total mean scores of the FSFI in participants of intervention and control groups.

Discussion and conclusion

The present study is a randomized controlled clinical trial that was conducted on type 2 diabetic women and showed that

Table 1 Demographic characteristic of the participants

Variable	Intervention group $N = 50$, N (%)	Control group $N = 50$, N (%)	p value
Kind of therapy			
Insulin	6 (12)	4 (8)	$p = 0.542$
Tablet	33 (66)	38 (76)	
Both	11 (22)	8 (16)	
Number of children			
1–2	10 (20)	9 (18)	$p = 0.101$
3–5	38 (79)	29 (65)	
6 and more	2 (4)	2 (4)	
Body mass index (BMI)			
18.5–24.9	3 (6)	6 (120	$p = 0.421$
25–29.9	29 (58)	31 (62)	
30 and more	18 (36)	13 (42)	
Menopause			
Yes	11 (22)	14 (28)	$p = 0.424$
No	39 (78)	36 (22)	

Table 2 Total FSFI scores in different points of evaluation in the intervention group and control group

FSFI and subscales	Group	Before intervention	4 weeks after intervention	8 weeks after intervention	Test statistics p value	
					Within group	Between group*
Desire	Intervention	3.300 ± 0.019	3.276 ± 0.019	3.708 ± 0.007	$F = 3.04$, $p < 0.05$	$F = 4.861$, $p < 0.01$
	Control	3.336 ± 0.018	3.318 ± 0.018	3.300 ± 0.018		
Arousal	Intervention	4.160 ± 0.013	4.164 ± 0.013	4.226 ± 0.010	$F = 0.75$, $p = 0.928$	$F = 1.723$, $p = 0.181$
	Control	4.242 ± 0.013	4.218 ± 0.013	4.158 ± 0.012		
Lubrication	Intervention	3.852 ± 0.025	3.786 ± 0.025	4.380 ± 0.012	$F = 7.766$, $p < 0.01$	$F = 5.81$, $p < 0.01$
	Control	3.936 ± 0.025	3.876 ± 0.025	3.942 ± 0.024		
Orgasm	Intervention	3.344 ± 0.017	3.464 ± 0.018	4.488 ± 0.018	$F = 33.714$, $p < 0.001$	$F = 23.16$, $p < 0.001$
	Control	3.400 ± 0.017	3.472 ± 0.018	3.536 ± 0.018		
Satisfaction	Intervention	3.152 ± 0.014	3.200 ± 0.015	4.632 ± 0.015	$F = 85.85$, $p < 0.001$	$F = 40.160$, $p < 0.001$
	Control	3.088 ± 0.014	3.104 ± 0.014	3.368 ± 0.018		
Pain	Intervention	5.120 ± 0.018	5.408 ± 0.014	5.656 ± 0.008	$F = 19.908$, $p < 0.001$	$F = 0.285$, $p = 0.783$
	Control	5.064 ± 0.020	5.400 ± 0.014	5.528 ± 0.012		
FSFI (total score)	Intervention	22.932 ± 0.045	23.298 ± 0.050	27.130 ± 0.035	$F = 3.47$, $p < 0.01$	$F = 4.86$, $p < 0.001$
	Control	23.066 ± 0.043	23.438 ± 0.048	23.832 ± 0.050		

Data are presented as mean ± SE

*According to two-way repeated measure ANOVA test

sexual counseling with PLISSIT approach increased the sexual function score and most of its field (except arousal and pain) in women with type 2 diabetes 8 weeks after the intervention significantly. This was the first study conducted based on PLISSIT model for women with type 2 diabetes in Iran.

Although sexual counseling can be done in a variety of ways, PLISSIT model can be very useful, given the potential for its application by doctors and midwives to its third stage. Consistent with the results of the present study, this model of sexual counseling has been performed in various groups of patients including patients with breast cancer, cardiovascular, hysterectomy, and multiple sclerosis, which have been shown to be effective in all cases [13–16]. The results of a study showed that PLISSIT based sexual counseling was effective in improving sexual function of women after hysterectomy and oophorectomy surgery [15]. Other studies conducted in Iran showed that counseling with this model reduced women sexual problems [21, 22].

PLISSIT model-based sexual counseling in the present study increased all domains of sexual function, except for sexual excitement and pain. In the study of Khakbazan et al., also PLISSIT model-based sexual counseling did not have a significant effect on the sexual excitement of women with multiple sclerosis during three 1-h sessions [13]. Diabetic neuropathy, in addition to affecting the sense of pleasure in sex, also affects the sexual excitement [23]. Regarding high prevalence of diabetic sexual problems and the effect on quality of life, it seems that this disorder should be identified more accurately in the healthcare system [5].

In a study examining the effect of sexual counseling in six 1-h sessions based on PLISSIT model on women with sexual problems in Tehran, sexual function and distress of women reduced in the intervention group 7 months after the intervention [22]. But in a systematic and meta-analytic study aimed to study the effectiveness of therapeutic interventions on women's sexual dysfunction, it was found that there is still

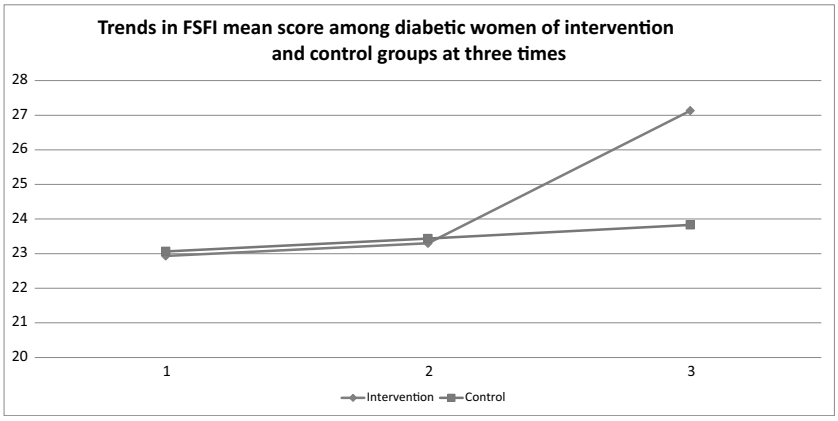

Fig. 2 Trends in FSFI mean score among diabetic women of the intervention and control groups. Axis X shows different times; time 1 is related to before intervention, time 2 and 3 are related to 4 and 8 weeks after intervention respectively. Axis Y shows mean score of FSFI

no reliable evidence to suggest the effectiveness of the various types of interventions [24].

Consistent with the results of the present study, which showed that PLISSIT model-based sexual counseling has increased lubrication, in a study that used this approach to study sexual function of married women with sexual problems, the results showed a significant difference in terms of lubrication [21].

The present study showed that sexual counseling could affect the orgasm of diabetic women, which is consistent with the results of a study that was conducted based on PLISSIT model, in which during three weekly sessions, women sexual function and orgasm increased [25]. Also, Almedia et al. considered sexual counseling based on PLISSIT model as effective on marital intimacy and sexual intimacy and orgasm in mastectomized women [26].

A significant difference was found in the satisfaction domain in the intervention group over time, and also observed between two groups. A study was conducted on sexual satisfaction of 60 women with stoma with PLISSIT model and showed that sexual counseling based on this model can reduce the sexual problems of women and increase their sexual satisfaction [27]. Sexual counseling in the present study in addition to providing appropriate strategies that could lead to better control of blood glucose in women and prevent or control sexual dysfunction, sexual desire, and lubrication improved with techniques, and pain reduced which showed an effect on orgasm improvement as well as satisfaction with sex. Good sex can be a powerful motivation for controlling diabetes and maintaining health [26].

A significant different was found in the variable pain over time, but no significant difference was observed between the intervention and control groups. Consistent with the results of this study, Khakbazan et al. showed that PLISSIT model-based sexual counseling was effective on sexual function of women with multiple sclerosis in three sessions immediately after the intervention and 2–3 months after the intervention but failed to reduce pain in women with multiple sclerosis [13]. A study had evaluated the effect of PLISSIT model-based sexual counseling on sexual function of women with cancers; all of sexual function subscales improved except for arousal and pain that is in line with our study [28]. Pain score was a domain that did not increase in a sexual education program that was conducted in the four 60-min sessions with 1-week interval in another study [29]. In our study, husbands of the participants were not included in intervention; maybe, the presence of them could impact on sexual function of women especially on pain reduction that was showed in a study [30].

One of the limitations of the present study, like other studies focusing on sexual problems, is the multifactorial nature of sexual problems, as well as the effect of mental and emotional conditions on sexuality. This study would be a good guide for the midwifery counseling group and physicians to address the sexual problems of diabetic patients.

Acknowledgements The researchers appreciate the collaboration of the participants in this study.

Funding This study was funded by Alborz University of Medical Sciences.

Compliance with ethical standards

Ethical approval The present study was approved by Abzums.Rec.1396.6 code at the Ethics Committee of Alborz University of Medical Sciences, as well as the registration number of IRCT2017070231662N4 in Iranian Clinical Trial System.

Conflict of interest The authors declare that there is no conflict of interest.

Informed consent Informed consent was obtained from all individual participants.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):633–640
https://doi.org/10.1007/s13410-019-00722-5

ORIGINAL ARTICLE

Prevalence and patterns of cardiac autonomic dysfunction in male patients with type 2 diabetes mellitus and chronic Charcot's neuroarthropathy: a cross-sectional study from South India

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Received: 7 February 2018 / Accepted: 10 February 2019 / Published online: 19 March 2019

Abstract

Aims Our study aimed to look at the prevalence and patterns of cardiac autonomic neuropathy related dysfunction in male patients of type 2 diabetes mellitus with chronic Charcot's foot.

Methods A total of 74 male patients with type 2 diabetes mellitus were included in this study. Three groups of patients were selected: Group 1 included patients with chronic Charcot's foot ($n = 24$), group 2 included patients with diabetic peripheral neuropathy without chronic Charcot's foot ($n = 22$) and group 3 included patients without peripheral neuropathy or chronic Charcot's foot ($n = 28$). The autonomic functions were tested using a personal computer-based cardiac autonomic neuropathy (CANS-504) analyser.

Results The combined sympathetic (SNS) and parasympathetic autonomic function (PNS) abnormalities were detected in about 70.8% in the chronic Charcot's group, 55.6% in the peripheral neuropathy group and 35.7% in the non-neuropathic group. In patients with chronic Charcot's foot ($n = 24$), 29.2% had normal, 20.8% had borderline and 50% had abnormal PNS functions, while 4.2% had normal, 16.7% had borderline and 79.2% had abnormal SNS functions. The Meary's angle (183.18 ± 73.83 vs 157.98 ± 14.11; $p < 0.196$) and Calcaneal pitch (7.07 ± 3.30 vs 8.5 ± 1.88; $p < 0.219$) were greater in the subjects with combined autonomic neuropathy, suggesting more structural deformity in them.

Conclusion Cardiac autonomic neuropathy-related dysfunction was found to be more common in type 2 diabetes patients with chronic Charcot's foot. This study has highlighted that patients with diabetic mellitus and chronic Charcot's foot should be screened comprehensively in order to prevent complications related to cardiac autonomic dysfunction.

Keywords Charcot's foot · Autonomic · Dysfunction · Cardiac autonomic · Neuropathy

Introduction

Chronic Charcot's foot (CF), a potentially disabling yet under-recognized complication of diabetes [1, 2], is characterized by marked swelling of the foot with varying degrees of bony destruction, joint subluxation and a rocker bottom foot deformity [3, 4]. The overall prevalence of chronic Charcot's foot varies between 0.16 and 13% from a general diabetic clinic to a special diabetic foot clinic at either end of the spectrum [5, 6]. The major causes of morbidity in Charcot's foot are secondary to non-healing foot ulcers, osteomyelitis and amputation [7, 8]. The exact pathogenesis of Charcot's foot is still elusive. The mechanisms include complex interactions of poor glycemic control, peripheral neuropathy, autonomic dysfunction, repetitive unrecognized trauma, activation of the inflammatory cascade and osteoclasts, and production of inflammatory markers (interleukins, RANK-L, NF-κB) which lead to osteolysis, bone resorption and bone destruction, joint destruction and deformities [9, 10]. Autonomic dysfunction also plays an important role in the pathogenesis of CF by a localized increase in blood flow through arteriovenous shunting and thereby stimulating the pathogenic mechanisms of Charcot's foot [11, 12]. However, autonomic neuropathy-related functional abnormalities in patients with chronic Charcot's foot (CF) have not been investigated adequately.

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Hence, this present study is aimed at assessing the prevalence and pattern of autonomic neuropathy-related dysfunction in patients with chronic Charcot's foot.

Materials and methods

This is a cross-sectional study on cardiac autonomic neuropathy in patients with chronic Charcot's foot. The study subjects were selected from the Integrated Diabetes Foot Clinic and Diabetes Outpatient services at the Endocrinology Department of Christian Medical College, Vellore, from January 2015 to December 2016. The study included three groups of patients with diabetes mellitus: Group 1 included patients with chronic Charcot's foot, group 2 included patients with diabetic peripheral neuropathy without Charcot's foot and group 3 included patients without Charcot's foot or peripheral neuropathy. The sample size was calculated with an 80% power and a 5% error based on a prior study on Charcot's foot [13]. The minimum adequate sample size to detect the difference in autonomic function testing in the 3 groups was 20 subjects for each arm. The baseline demographic parameters such as age, sex, BMI and duration of diabetes were assessed. A detailed foot examination including a neurological examination with a 10-g Semmes Weinstein monofilament and vibratory sensation with a 128-Hz tuning fork and vibration perception threshold (VPT) by biothesiometry was performed to determine the underlying peripheral neuropathy [14]. An X-ray of the affected foot was taken with two views, which included a lateral anterior oblique and a standing lateral to establish the diagnosis of the Charcot's foot. Meary's angle was calculated by measuring the angle between the line originating from the centre of the body of the talus, bisecting the talar neck and head, and the line through the longitudinal axis of first metatarsal. In addition, the calcaneal pitch was calculated by measuring the angle created by a line drawn from the calcaneal tuberosity to the plantar aspect of the distal part of the calcaneus and a horizontal line drawn from the plantar calcaneal tuberosity to the fifth metatarsal head. The biochemical investigations included hemoglobin, glycosylated hemoglobin (HbA1c), serum creatinine, fasting lipid profile and urinary microalbumin. Diagnosis of diabetic retinopathy was determined by an ophthalmologist, and diabetic nephropathy was defined as urinary microalbumin > 30 mg/g of creatinine [15].

The study subjects included 74 male patients who were divided into three groups: Group 1 ($n = 24$) included patients with chronic Charcot's foot, group 2 ($n = 22$) included patients with peripheral neuropathy without chronic Charcot's foot and group 3 ($n = 28$) included patients with no peripheral neuropathy or chronic Charcot's foot. Group 1 was taken as cases, while group 2 and group 3 were taken as controls. This study included only male patients to avoid gender-related differences in autonomic function [16].

Selection of study subjects

Group 1: Chronic Charcot's foot: Patients with diabetes mellitus with clinical evidence of swelling and deformity of one or both feet with radiological evidence of joint destruction and loss of joint alignment characteristic of chronic Charcot's foot.

Group 2: Diabetic peripheral neuropathy without chronic Charcot's foot: Patients who were unable to feel a 5.07 Semmes-Weinstein monofilament of < 10 g at 4 or more locations out of 10 sites on the feet and were unable to perceive a vibration threshold of less than 25 V with the use of a biothesiometer. The X-ray of both feet showed no evidence of Charcot's feet.

Group 3: No diabetic peripheral neuropathy and no chronic Charcot's foot: Patients who were able to perceive a 2-g 5.07 Semmes-Weinstein monofilament at six or more out of the 10 standard locations of the foot and preserved vibration perception threshold (VPT) with a biothesiometer.

Patients with underlying coronary heart disease, proliferative retinopathy, and other advance respiratory, renal or neurological illnesses or on medication such as beta-adrenergic antagonists, anticholinergic drugs and calcium channel blockers that could alter the autonomic function tests were excluded, and an informed written consent was obtained from all the subjects prior to inclusion in the study.

The tests for autonomic functions were carried out in the morning. The patients were instructed not to smoke or drink caffeine 3 h prior to testing. The assessment of CAN was done using an automated Cardiac Autonomic Neuropathy System Analyzer (CANS 504) (Diabetik Foot Care, Chennai, India), a personal computer-based analyser which analysed both the sympathetic and parasympathetic autonomic nervous system response. The system used an ECG Cardio-Tachogram (R-R interval) and an advanced automatic NIBP (non-invasive blood pressure) module to conduct a battery of tests. Being fully automatic, it eliminated the need for manual recordings, readings and calculations. The tests for autonomic dysfunction were performed with the CANS 504 as per standard protocols [17, 18]. The tests for parasympathetic system dysfunction were inclusive of heart rate variability (RR interval ratio), between the longest RR interval and shortest RR interval on response to deep breathing, standing and Valsalva on an automated continuous ECG recoding. The tests were performed as follows:

1. The heart rate response to deep breathing (E: I ratio) was calculated based on the ratio of the RR interval during deep breathing at six breaths per minute (5 s as inspiration and 5 s as expiration).
2. The heart rate response to standing was calculated between the RR interval at around the 30th beat and the 15th beat from a continuous ECG recording of heart rate for a period 2 min from supine to standing position.
3. The heart rate response to Valsalva (Valsalva ratio): the heart rate was recorded at 1 min before the Valsalva manoeuvre, during the manoeuvre and 1 min following the manoeuvre. The Valsalva ratio is calculated from the longest RR interval during the phase of relaxation and shortest RR interval during the phase of manoeuvre.

The tests that were performed for sympathetic system dysfunction included tests to assess the maximum increase in blood pressure on sustained hand grip and a postural drop in blood pressure on standing. These tests were performed as follows:

1. In the sustained hand grip test, the patient had to squeeze a handgrip dynamometer at 30% maximum for a period of 5 min and automatic NIBP (non-invasive blood pressure) was measured in the contra-lateral arm. The difference in diastolic blood pressure measured in the contra-lateral arm before the release of contraction and before the beginning of a handgrip procedure was taken as measure of response.
2. In order to test for a postural drop in blood pressure after standing, the blood pressure was recorded 2 min after patient was supine, and then patient was made to stand and blood pressure was again checked 2 min after patient was standing. The difference in the systolic blood pressures between supine and standing posture was taken as a measure of response.

Interpretation of autonomic function tests

The criteria for normal test for heart rate variations were defined as *E/I* ratio of > 1.21 on deep breathing, 30:15 ratio of > 1.04 on standing and Valsalva ratio > 1.21 with Valsalva manoeuvre. BP response to standing of < 10 mmHg and BP response to sustained handgrip of ≥ 16 mmHg were considered normal. Abnormal tests were defined as *E/I* ratio of < 1.1, 30:50 ratio of < 1.0, Valsalva ratio of < 1.21 and BP response of < 30 mmHg and < 10 mmHg, respectively. Each of these tests was categorized as normal (score − 0), borderline (score 1) and abnormal (score 2) according to Ewing's criteria [17, 19].

Autonomic function testing in the study subjects was further classified into parasympathetic, sympathetic and combined abnormality in cardiac autonomic functions based on the original studies by Ewing and colleagues [17]. While changes in heart rate during Valsalva manoeuvre reflect parasympathetic modulation and BP response to Valsalva reflect sympathetic activity, the CANS analysis we used was done based on Ewings criteria [17] which has specified only Valsalva ratio based on heart rate variability as a measure of sympathetic function. Thus, the Valsalva ratio described in our study was a part of only the sympathetic function assessment as described previously. The patients were defined to have a parasympathetic nervous system (PNS) abnormality if more than or equal to 1 of the before mentioned three tests on heart rate variability were found to be abnormal. The patients were defined to have a sympathetic nervous system (SNS) abnormality if more than equal to 1 of the before mentioned two tests on blood pressure changes were found to be abnormal. The patients were defined to have combined dysfunction in both systems (PNS and SNS) if any of the following combinations were present: (i) Any test of PNS was abnormal, and any test of SNS was borderline; (ii) any test of PNS was borderline, and any test of SNS was abnormal; and (iii) any test of PNS was abnormal, and any test of SNS was abnormal [20].

Statistical analysis

All continuous variables (age, BMI, blood glucose, etc.) were summarized using the mean with the standard deviation, if the data was normally distributed. The variables with a skewed distribution were described with a median and range. All other categorical variables were described using frequencies and a percentage. The statistical analysis was performed with the commercially available software package (SPSS for Windows, version 17.0, SPSS, Inc., Chicago, IL).The various clinical and biochemical parameters of patients with normal, abnormal and borderline PNS and SNS dysfunction were compared using a one-way analysis of variance (ANOVA). The difference was considered significant at a two-tailed p value of ≤ 0.05.

Results

The demographic and biochemical profiles of the study subjects are shown in Table 1. The age of the patients ranged from 43 to 77 years with a mean age of 59.77 ± 8.89 years. The mean duration of diabetes was 47.36 ± 9.02 years. The mean HbA1c was 8.16 ± 1.81%. The mean age, duration of diabetes, glycemic control (HbA1c) and other parameters were comparable among the three groups.

The individual test abnormalities in all the study subjects are shown in Fig. 1. The pattern of individual test abnormalities for each group is shown in Fig. 2. Thirty-nine percent (39%) of patients were detected to have both

Table 1 Demographic and biochemical parameters of study subjects

Variables	Diabetes mellitus with chronic Charcot's foot (group 1; $n = 24$)	Diabetes mellitus with peripheral neuropathy (group 2; $n = 22$)	Diabetes mellitus without neuropathy or Charcot's foot (group 3; $n = 28$)	p value Group 1 vs group 2	p value Group 1 vs group 3
Age (years)	58.12 ± 9.0	59.14 ± 9.38	61.68 ± 8.36	0.712	0.149
Duration of diabetes (months)	43 ± 7.09	48.47 ± 9.80	49.48 ± 8.88	0.059	0.010*
BMI(kg/m^2)	27.77 ± 5.42	24.79 ± 3.52	25.64 ± 6.81	0.034*	0.220
Haemoglobin (g/dL)	12.07 ± 1.90	12.39 ± 1.87	13.78 ± 1.68	0.589	0.002**
HbA1c (%)	8.14 ± 1.79	8.90 ± 2.02	7.63 ± 1.50	0.193	0.280
Serum creatinine (mg/dL)	1.08 ± 0.48	0.97 ± 0.24	0.96 ± 0.22	0.323	0.265
Total cholesterol (mg/dL)	149.09 ± 33.76	166.44 ± 28.32	147.8 ± 40.43	0.091	0.904
Triglycerides (mg/dL)	78.57 ± 14.01	136.44 ± 60.02	135.38 ± 61.06	0.209	0.182
HDL-C (mg/dL)	35.91 ± 10.75	37.06 ± 8.37	38.69 ± 10.19	0.710	0.360
LDL-C (mg/dL)	87.04 ± 35.39	106.45 ± 19.44	86.42 ± 30.02	0.030*	0.948
Urinary microalbuminuria	171.63 ± 24.11	104.22 ± 11.82	83.84 ± 18.20	0.282	0.04
Systolic BP (mmHg)	126.67 ± 19.03	129.52 ± 14.65	119.63 ± 10.18	0.573	0.115
Diastolic BP (mmHg)	77.08 ± 8.06	78.48 ± 6.53	78.52 ± 5.33	0.526	0.464
Retinopathy	18(75%)	6 (27.2%)	5 (17.85%)	0.04	0.03
Nephropathy	14 (58.33%)	11 (50%)	10 (35.71%)	0.455	0.232
Peripheral neuropathy*	19(82%)	22(100%)	–	0.162	–

*As per inclusion criteria, group 2 had patients with only peripheral neuropathy and group 3 had patients with no peripheral neuropathy

parasympathetic and sympathetic abnormality. The 30:15 RR ratio on standing was found to be the most common abnormal parasympathetic function test across all the groups, and diastolic BP change with hand grip was found

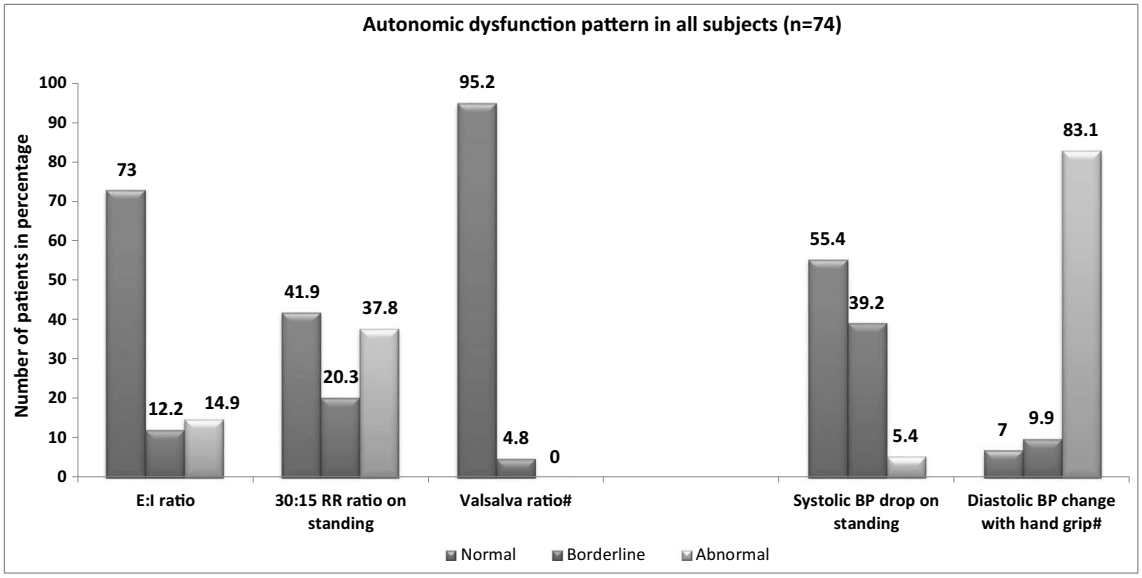

Fig. 1 Overall autonomic function pattern in all 74 study subjects. The *E*/*I* ratio on deep breathing was abnormal in 15 (14.9%) and 30:15 beat ratio was abnormal in 28 (37.8%). Valsalva ratio was found to be normal in 60 (95.2%) out of 63 patients who had completed the test successfully. Seventy-one subjects were able to complete sustained handgrip test of which 83.1% had abnormal response to diastolic blood pressure. Postural drop in blood pressure on standing was found to be abnormal in 4 (5.4%)

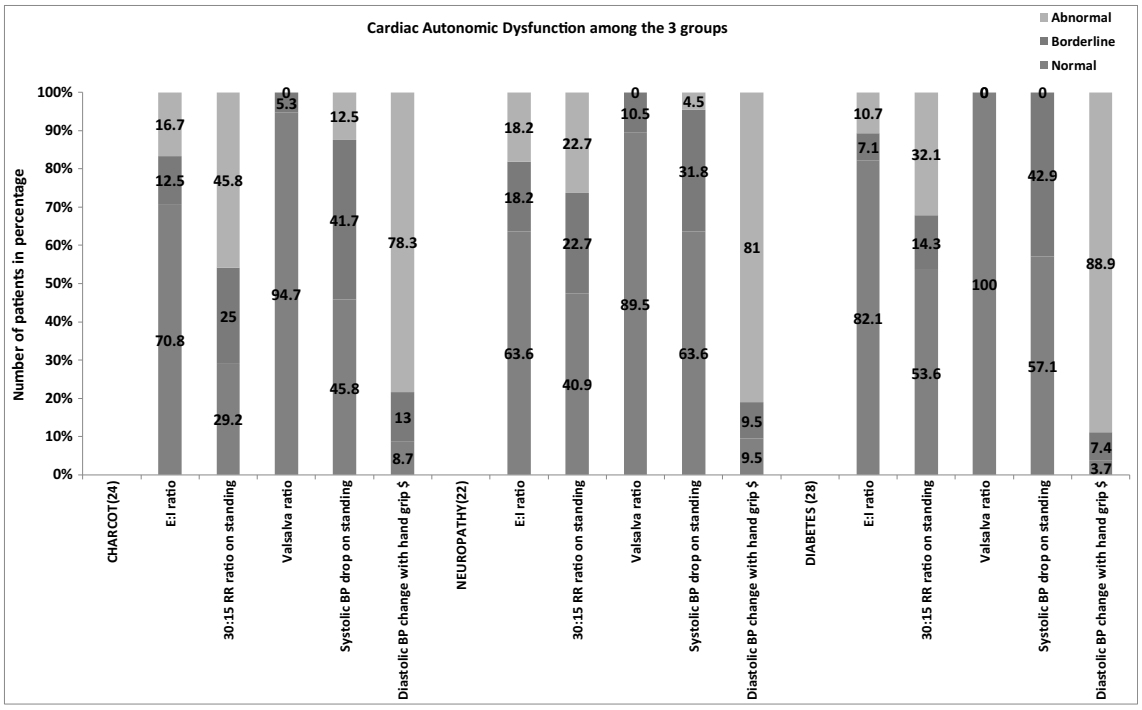

Fig. 2 Abnormality of individual test in each group of patients. The *E*/*I* ratio was abnormal in 4 (16.7%) in Charcot's group, 4 (18.2%) in neuropathic group and 3 (10.7%) in non-neuropathic diabetes mellitus group. The 30:50 RR ration on standing was abnormal in 11 (45.85%), 8 (22.7%) and 9 (32.1%) in Charcot's group, neuropathic and non-neuropathic diabetes mellitus groups, respectively. Valsalva ratio was normal in majority of the patients across all groups. Systolic drop in BP abnormality was detected in 3 (12.5%) in Charcot's group and 1 (4.5%) in neuropathic group. Abnormality in diastolic change in BP with hand grip was demonstrated in 18 (78.3%) Charcot group, 17 (81%) in neuropathic group and 24 (88.9%) in non-neuropathic diabetes mellitus group

to be the most common abnormal sympathetic function test. The pattern of parasympathetic and sympathetic functional abnormalities is shown in Table 2. The parasympathetic function abnormalities were detected in 50% in both Charcot's foot (group 1) and peripheral neuropathy group (group 2) and 35.7% in non-neuropathic group (group 3). The sympathetic function abnormalities were detected in 79.2% in the Charcot's group (group 1), 81.9% in the peripheral neuropathy group (group 2) and 85.7% in the non-neuropathic group (group 3). The combined sympathetic and parasympathetic nervous system abnormalities were detected in 70.8% of patients with chronic Charcot's foot (group 1), 55.6% of patients with peripheral neuropathy (group 2) and 37.5% of patients in the non-neuropathic group (group 3).

In patients with chronic Charcot's foot ($n = 24$), the Meary's angle was 175.99 ± 62.98 degrees (95%CI; 149.4°–202.6°) and the Calcaneal pitch was 7.23 ± 3.14° (95%CI; 5.9°–8.5°). The Meary's angle (183.18 ± 73.83 vs 157.98 ± 14.11; $p < 0.196$) and Calcaneal pitch (7.07 ± 3.30 vs 8.5 ± 1.88; $p < 0.219$) were greater though not statistically significant in subjects with combined autonomic neuropathy ($n = 17$) than subjects with isolated sympathetic neuropathy ($n = 6$) subjects.

Discussion

The primary objective of this study was to assess the prevalence and patterns of cardiac autonomic dysfunctions in patients with type 2 diabetes and chronic Charcot's foot (CF). In our study, the mean age of patients with chronic Charcot's foot was 58 years (range 51–67 years) which was comparable with previous studies [6, 21]. The duration of diabetes in CF group in this study was 4.1 years (49.48 ± 8.88 months) which was much shorter when compared to previous studies. The duration of diabetes at the time of diagnosis of CF was more than 10 years in previous Western studies [8, 22]. However, studies by Petrova showed that at the time of onset of Charcot's osteoarthropathy, patients with type 2 diabetes had much shorter duration of diabetes than the patients with type 1 diabetes [23]. Recently, a lower duration of 7.16 ± 6.28 years has been reported in a study conducted on diabetes mellitus patients with Charcot's foot from Pakistan [24]. Though our study was not powered enough to elicit the possible mechanisms, the early onset of Charcot's foot in our population is an intriguing finding. Given the paucity of Indian data on the epidemiology of Charcot's foot and underreporting of cases, larger longitudinal studies can provide insights into a possible dichotomy of age of presentation of Charcot's foot, with

Table 2 Cardiac autonomic function abnormalities among study subjects

Particulars	Charcot's group, *N* (%)	Neuropathic group, *N* (%)	Non-neuropathic group, *N* (%)
Parasympathetic function abnormalities			
Normal	7 (29.2%)	6 (27.3%)	12 (42.9%)
Borderline	5 (20.8%)	5 (22.7%)	6 (21.4%)
Abnormal	12 (50%)	11 (50%)	10 (35.7%)
Sympathetic function abnormalities			
Normal	1 (4.16%)	2 (9.1%)	1 (3.5%)
Borderline	4 (16.66%)	2 (9.1%)	3 (10.71%)
Abnormal	19 (79.16%)	18 (81.82%)	24 (85.71%)

diabetic patients of the subcontinent having an earlier onset. Our study has also shown an earlier onset of cardiac autonomic dysfunction in patients with chronic Charcot's foot.

Though the duration of diabetes has been documented as an independent risk factor for development of cardiac autonomic neuropathy [25], there are numerous studies that have shown that cardiac autonomic dysfunction can be detected at time of diagnosis of diabetes in patients with either T1DM or T2DM irrespective of age, suggesting that cardiac autonomic dysfunction presentation is not limited by age or type of diabetes and can even occur before or within a few years of diabetes mellitus being evident clinically [26, 27]. Further, cardiac autonomic dysfunction through the sympathetic denervation of the lower limb vasculature can induce lower extremity hyperemia, increase inflammation and erosion into the joints/bones and therefore contribute in Charcot's neuroarthropathy [28]. Thus, our finding, though in a smaller population, can provide the way for larger studies looking into the pathogenetic associations of Charcot's foot with cardiac autonomic dysfunction even with a shorter duration of diabetes.

In our study, patients with CF had a relatively higher BMI (27.77 ± 5.42 kg/m^2) when compared to those with peripheral neuropathy without Charcot's foot (25.64 ± 6.81) ($p = 0.22$). Previous studies have reported that obesity is an important risk factor for the evolution of Charcot's neuroarthropathy, foot ulcer and increased risk of amputation [29, 30].

In our study, a significantly higher prevalence of combined sympathetic and parasympathetic dysfunctions was observed (70.8%) in the chronic Charcot group (group 1), compared to that (55.6%) in the peripheral neuropathy group (group 2) and that (37.5%) in the non-neuropathic group (group 3). Several studies in the past have used different criteria for the diagnosis of autonomic neuropathy and have shown a variable prevalence of autonomic dysfunction in patients with chronic Charcot's foot [13, 23, 24]. In a study by Young et al. [13], the autonomic function was assessed in 17 patients with Charcot's foot and was compared with 17 patients with peripheral neuropathy. Three cardiovascular autonomic tests—*E* to *I* ratio, Valsalva ratio and RR ratio—were used. Autonomic function abnormalities were detected in all patients with Charcot's foot and in 59% with neuropathy [13]. In another study by Stevens et al., the heart rate response to breathing, Valsalva ratio and postural fall in systolic blood pressure were abnormal in both Charcot's patients ($n = 12$) and the ulcerated neuropathy group ($n = 12$), without any significant differences seen between the two groups [30]. A study by Jirkovska et al. compared the Ewing heart rate variability tests (HRV) with power spectral analysis (PSA) in 17 patients of acute Charcot's foot. Autonomic function abnormalities were detected in 82% by Ewing's test and 94% by PSA. The results between Ewing test and PSA were comparable without any significant difference [31].

In the present study, we did not find any statistically significant associations of the fasting plasma glucose, 2 h postprandial plasma glucose, HbA1c and duration of diabetes with cardiac autonomic dysfunction in patients with chronic Charcot's foot (group 1). The prevalence of diabetic retinopathy and urinary microalbuminuria was significantly higher in the diabetic patients with chronic Charcot's foot.

In our study, isolated sympathetic dysfunction was detected in 25% patients in the Charcot's group (group 1), 22.2% in the peripheral neuropathy group (group 2) and 39.2% in the non-neuropathic group (group 3), while isolated parasympathetic dysfunction was not detected in any of the groups. Selective sympathetic damage is an important cause of Charcot's foot [32]. Sympathetic nerve damage is associated with increased blood flow and arteriovenous shunting in Charcot's foot [33]. In the study by Stevens et al. [30], the peak skin blood flow was greater in patients with Charcot's foot as compared to those with only peripheral neuropathy. In our study, the other important finding was the greater derangement in the Meary's angle and the Calcaneal pitch in Charcot's foot patients with combined autonomic neuropathy as compared to patients in whom isolated sympathetic and parasympathetic functions were involved. This association has not been evaluated in any of the previous studies.

Our study highlights the significant prevalence (71%) of cardiac autonomic dysfunction in patients with chronic Charcot's foot. In our study, there was an earlier age of onset

of chronic Charcot's foot during the course of the disease than reported in western literature. Our patients with Charcot's foot have a relatively higher BMI when compared to the patients with peripheral neuropathy and those with no neuropathy. However, the smaller number of cases is a limitation of our study. Further, our study has not evaluated the adrenergic responses to hypoglycemia which would have provided further clinical insights into the association between cardiac autonomic dysfunction and Charcot's foot in type 2 diabetes.

Conclusions

Cardiac autonomic function-related abnormalities are common among patients with chronic Charcot's foot. Indian patients with type 2 diabetes mellitus developed features of chronic Charcot's neuroarthropathy much earlier than their western counter parts, with patients having a higher body mass index being more prone for chronic Charcot's neuroarthropathy. Patients with combined autonomic neuropathy had more bone and joint deformity. This study has highlighted that male patients with type 2 diabetes and chronic Charcot's neuroarthropathy should be screened for cardiac autonomic neuropathy-related abnormalities and should be advised proper foot wear and foot care in order to prevent foot deformities, foot ulceration and lower limb amputations.

Funding There was no external funding for this study.

Compliance with ethical standards

The study was approved by the Institutional Review Board of the Christian Medical College Vellore, India (IRB MIN NO.9353; dated March 3, 2015).

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study. No animals were used in this study

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):641–646
https://doi.org/10.1007/s13410-019-00717-2

ORIGINAL ARTICLE

Irisin level in type 2 diabetic patients and its relation to glycemic control and diabetic complications

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Received: 5 March 2018 / Accepted: 19 January 2019 / Published online: 6 February 2019

Abstract

Background Irisin is a new myokin and adipokine related to human obesity and insulin resistance status.

Aims To investigate whether serum irisin is related to glycemic indicators and micro and macrvascular complications in patients with T2DM.

Methods The study included 60 T2DM patients and 30 healthy controls. Anthropometric measures, neurological assessment, and fundus examination were done to all patients. Correlations of serum irisin and blood glucose, glycosylated hemoglobin (HbA_{1C}), urinary albumin, estimated glomerular filtration rat (eGFR), C-reactive protein (CRP), and carotid intima media thickness (CIMT) were analyzed using Spearman's correlation coefficient.

Results In diabetic patients, there was negative correlation between irisin level and duration of diabetes($r = -0.302$, $p = 0.023$), body mass index (BMI) ($r = -0.663$, $p < 0.001$), HbA_{1C} ($r = -0.528$, $p < 0.001$), urinary albumin ($r = -0.439$, $p < 0.001$), CRP ($r = -0.692$, $p < 0.001$), and CIMT ($r = -0.807$, $p < 0.001$). Levels of irisin were significantly lower in patients with peripheral diabetic neuropathy (PDN) compared to those without PDN (0.11 ± 0.05 vs. 0.22 ± 0.11 ng/ml, $p < 0.001$). Levels of irisin were not significantly different between patients with diabetic retinopathy and those with normal fundi.

Conclusions In T2DM patients, negative correlations between irisin and $HbA_{1C,}$ urinary albumin, and CIMT were found. Moreover, patients with diabetic neuropathy had lower irisin levels.

Keywords Type 2 diabetes · Irisin · Carotid intima media thickness · Nephropathy · Neuropathy

Introduction

Diabetes has a worldwide prevalence and it is expected to affect about 366 million people by 2030 [1]. Diabetes is associated with different microvascular and macrovascular complications which are related to increased morbidity and mortality in diabetic patients. Characterizing molecular markers of these complications could have diagnostic and therapeutic implications.

Irisin is a new peptide that performs significant functions in human health and disease. It is a myokin as well as adipokine that is secreted by muscles and subcutaneous fat and influenced by physical activity and nutritional status. Irisin has been linked to human obesity and insulin resistance status [2].

Fibronectin type III domain-containing protein 5(FNDC5), the precursor of irisin, is a membrane protein that is encoded by the *FNDC5* gene. Irisin is formed by connecting N-terminal fibronectin III (FNIII)-like domain to a flexible C-terminal. Exercise induces *FNDC5* expression by increasing levels of proliferator-activated receptor-γ coactivator-1α in the muscle [3].

Irisin produces browning of white adipose tissue and increases energy expenditure by increasing uncoupling protein 1 levels that decrease body weight and improve insulin resistance [4]. Previous studies reported that lower serum irisin was linked to metabolic syndrome, diabetes [5], chronic kidney disease [6], and fatty liver disease [7].

Data about the relationship between irisin and glycemic indices in diabetes are controversial. While some studies reported negative correlation between irisin and blood glucose level [5], other studies found positive correlation [8].

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Moreover, few studies have been conducted on the association between serum irisin and diabetic complications.

Most of previous studies in non-diabetic population suggested that low irisin level might be related to chronic kidney disease [6, 9]. However, recent study found no correlation between serum irisin and renal function tests in diabetic patients [5]. In addition, some studies reported that serum irisin was independent predictor for macrovascular diseases in diabetic and non-diabetic patients [10, 11]. To our knowledge, no study to date has assessed the relationship between irisin and diabetic neuropathy.

The aims of the present study were (1) to assess irisin level in T2DM patients compared to healthy subjects and (2) to investigate the potential association between serum irisin and (i) glycosylated hemoglobin (HbA_{1C}) as an indicator of glycemic control; (ii) CRP as a marker of inflammation; (iii) microvascular complications (nephropathy, retinopathy, and neuropathy); and (iv) CIMT as a surrogate marker of atherosclerosis.

Methods

The study included 60 patients with T2DM recruited from internal medicine department and clinic of tertiary care hospital. The patients were included if (i) they were between 35 and 70 years old and (ii) they had diagnosis of T2DM based on the American Diabetes Association criteria [12]. Patients with anemia, eGFR less than 30 ml/min/1.73m^2, liver cirrhosis, and congestive heart failure were excluded.

Thirty control subjects (healthy volunteers among the family members of patients) were enrolled as controls. The inclusion criteria were (i) age between 35 and 70 years, (ii) absence of diabetes or impaired glucose tolerance, and (iii) absence of chronic liver or renal diseases.

In all patients, thorough clinical evaluation was performed including body mass index (BMI) and waist circumference measurement. Duration and type of treatment of diabetes were noted. Diabetic peripheral neuropathy (DPN) was diagnosed based on a standardized clinical examination which included Semmes-Weinstein monofilament examination and 128 Hz tuning fork. Diagnosis of DPN in our study was done based on clinical examination which included Semmes-Weinstein monofilament examination and 128 Hz tuning fork. DPN was diagnosed if symmetric distal neuropathy (i.e., hypoactive deep tendon reflexes, reduced tactile, and/or vibration sensation) with at least moderate severity of one or more of the typical symptoms (pain, burning, paresthesia, numbness or cramps) in the lower extremities. Fundus examination was done to determine the presence and class of diabetic retinopathy (DR). The international severity scale of DR, i.e., no apparent retinopathy; mild, moderate, and severe nonproliferative diabetic retinopathy (NPDR); and PDR was used for identification of DR grade. The patients were divided into two groups according to the presence or absence of DPN. B-mode duplex ultrasound was performed by an experienced doctor using a high frequency 7.5-MHz linear probe of ATL-HDL 5000 machine for measurement of CIMT.

Blood samples were collected for measurement of serum irisin, fasting, and post prandial blood glucose, HbA_{1C}, total cholesterol, triglycerides (TG), C-reactive protein (CRP), urinary albumin, serum creatinine, and estimated glomerular filtration rat (eGFR) calculated by the Modification of Diet in Renal Disease (MDRD) equation.

Irisin sample collection and assay principle

Samples were collected in serum separator tubes and were allowed to clot for 30 min. Centrifugation was done for 15 min at approximately 1000×*g* and stored at − 80 °C. Irisin ELISA Kit (Wuhan ElAab science Co., Ltd., CHINA) was used to quantify serum irisin level in ng/ml that employs the quantitative sandwich enzyme immunoassay technique using monoclonal antibody specific for irisin. The test was performed according to manufacturers' instructions.

Statistical analyses

Data was entered on the Statistical Package of Social Science Software program, version 23 (SPSS) to be statistically analyzed. (IBM Corp. Released 2015 Version 23.0.). Data was summarized using range, mean, and standard deviation for quantitative variables or frequency and percentage for qualitative ones. Comparison between groups was performed using independent sample *t* test and one-way ANOVA (if parametric variables) or Mann-Whitney test and Kruskal-Wallis if (non-parametric variables) for quantitative variables while comparison for qualitative variables was performed through chi-square test. Spearman's correlation coefficients were calculated to signify the association between different quantitative variables. *p* values less than 0.05 were considered statistically significant.

Results

Demographic, clinical, and laboratory characteristics of participants

The mean age of diabetic patients was 47.39 ± 8.42 years, which was not significantly different between patients and control group. The mean duration of diabetes was 4.2 ± 2.6 years. Among 60 diabetic patients there were 41 (68.3%) using oral hypoglycemic agents and 19 (31.6%) receiving

insulin. Gender, weight, and BMI were not significantly different in subjects with diabetes compared to controls (Table 1). DPN was found in 19 patients (31.6%). Twenty four patients (40%) had DR which included 15 patients with non-proliferative retinopathy (NPDR), 6 patients with proliferative retinopathy (PDR), and 3 patients with maculopathy. Mean HbA1c in diabetic patients was (8.8 ± 1.0%). Serum creatinine was normal and albuminuria ranged from 15.0 to 510.0 mg/l in diabetic subjects (Table 2).

Irisin level in patients with T2DM compared to controls

Mean irisin level in diabetic patients (0.18 ± 0.10 ng/mL) was not significantly different from its level in control group (0.16 ± 0.05 ng/mL) ($p = 0.940$) (Table 1).

Correlations between serum irisin and metabolic parameters in diabetic patients

Negative correlations between serum irisin and fasting blood glucose ($r = -0.419$, $p = 0.001$), HbA_{1C} ($r = -0.528$, $p < 0.001$), cholesterol ($r = -0.446$, $p = 0.001$), TG ($r = -0.491$, $p < 0.001$) were found. CRP was indicator of inflammation and insulin resistance was negatively correlated with serum irisin ($r = -0.692$, $p < 0.001$) (Table 3).

Relationship between irisin level and CIMT in diabetic patients

A significant negative correlation between serum irisin and CIMT in diabetic patients ($r = -0.807$, $p < 0.001$) was detected.

Table 1 Characteristics of diabetic patients compared to controls

Variables	Diabetic group ($n = 60$)	Control group ($n = 30$)	p value
Age (years)	47.39 ± 8.42	47.56 ± 8.52	0.957
Sex n (%)			
Male	26 (43.3)	14 (46.6%)	0.949
female	34 (56.6)	16 (53.3%)	
Weight (kg)	86.16 ± 10.76	87.50 ± 7.44	0.524
Height (cm)	170.02 ± 4.09	174.06 ± 5.41	*0.016*
BMI (kg/m^2)	29.73 ± 2.89	28.85 ± 1.66	0.233
Duration of DM (years)	4.2 ± 2.6	–	
Diabetes medications			
Oral hypoglycemics n (%)	41 (68.3%)	–	
Insulin n (%)	19 (31.6%)		
FBG (mg/dl)	189.1 ± 46.6	83.93 ± 7.98	< *0.001*
Irisin (ng/ml)	0.18 ± 0.10	0.16 ± 0.05	0.940
CIMT (mm)	1.00 ± 0.18	0.83 ± 0.06	< *0.001*

CIMT carotid intima media thickness

Correlation between serum irisin and urinary albumin, eGFR, and serum creatinine in diabetic patients

Spearman's correlation analysis was performed to evaluate the relationship between irisin level and different indices of diabetic nephropathy. There was only significant negative correlation between irisin level and urinary albumin ($r = -0.439$, $p = 0.001$), but no significant correlation was found between serum irisin and eGFR ($r = -0.256$, $p = 0.057$), or serum creatinine ($r = 0.141$, $p = 0.299$).

The association between serum irisin and diabetic neuropathy and retinopathy

Mean irisin level was found to be significantly lower in patients with PDN than in those without PDN (0.11 ± 0.05 vs 0.22 ± 0.11 ng/ml, $p < 0.001$). However, mean irisin level in patients with DR (0.13 ± 0.02 ng/ml) and normal fundi (0.21 ± 0.11 ng/ml) was not statistically different ($p = 0.069$).

Discussion

The current study showed that irisin level was not significantly different between diabetic and healthy subjects**.** Many previous studies reported lower levels of irisin in diabetic patients [13–15]. Other researchers found either no relationship between irisin and diabetic status [4, 16], or unexpectedly higher levels of irisin in diabetic subjects [17]. This conflicting data could be explained by an initial rise of serum irisin in prediabetic state as a compensatory mechanism aiming at regulation of energy expenditure and glucose metabolism [18] and after the development of diabetes; there might be exhaustion or habituation in this mechanism leading to lower irisin expression and activity. The negative correlation we found between irisin level and diabetes duration might support this assumption.

Moreover, most of our patients were receiving oral treatment only, and the mean duration of diabetes was around 4 years which may indicate that they still have insulin reserve and it could partially explain the non-significant difference of serum irisin level between diabetic and healthy subjects.

Although the underlying mechanism by which irisin affects glucose metabolism is not entirely recognized, it has been found that irisin increases glucose uptake by muscle, inhibits gluconeogenesis [19], promotes white adipocyte browning [2], and enhances the expression of glucose transporter 4 and mitochondrial biogenesis [2, 8, 20].

Serum irisin and glycemic indices

The results of this study demonstrated negative correlations between serum irisin and glycemic indices. This coincides

Table 2 Laboratory data and carotid intima media thickness (CIMT) measurements in diabetic group

	Range			Mean	±	SD	Median	IQR		
Age (years)	35.0	–	69.0	47.4	±	8.4	44.5	40.5	–	52.0
Duration of DM (years)	0.7	–	10.0	4.2	±	2.6	4.0	2.0	–	6.0
Weight (kg)	65.0	–	105.0	86.2	±	10.8	84.0	79.5	–	96.5
Height (cm)	162.0	–	179.0	170.0	±	4.1	170.0	166.0	–	173.0
BMI (kg/m^2)	24.7	–	35.9	29.7	±	2.9	29.4	27.7	–	31.6
Waist circumference (cm)	88.0	–	111.0	102.1	±	4.6	101.0	99.5	–	105.5
Micro albumin (mg/L)	15.0	–	510.0	125.7	±	122.2	90.0	31.5	–	155.0
FBG (mg/dL)	126.0	–	315.0	189.1	±	46.6	179.0	155.0	–	213.0
HbA_{1c} %	7.1	–	11.0	8.8	±	1.0	9.0	8.0	–	9.5
Creatinine (mg/dL)	0.5	–	1.3	0.9	±	0.2	0.9	0.8	–	1.0
eGFR (ml/min/1.73m^2)	149	–	60	96	±	16.3	96	114	–	83
C-reactive protein (mg/dL)	0.1	–	4.0	1.1	±	0.7	1.0	0.6	–	1.5
Cholesterol (mg/dL)	170.0	–	356.0	258.3	±	51.7	252.5	210.0	–	302.5
triglycerides (mg/dL)	90.0	–	320.0	177.4	±	55.6	173.5	150.0	–	201.5
Irisin (ng/mL)	0.0	–	0.50	0.18	±	0.10	0.2	0.12	–	0.24
CIMT (mm)	0.7	–	1.43	1.00	±	0.18	1.0	0.84	–	1.10

IQR, interquartile range (25th–75th percentiles); *HbA1c*, glycosylated hemoglobin; *eGFR*, estimated glomerular filtration rate; *CIMT*, carotid intima media thickness

with the findings of previous studies. Serum irisin was negatively correlated with blood glucose, fasting insulin, and HbA_{1C} in patients with T2DM [17, 21]. Furthermore, recent study showed significant reduction of fasting blood glucose and fasting serum insulin in diabetic mice with irisin treatment [19]. These results differ from some published studies. Hee et al. [22] found positive association between serum irisin and fasting glucose and insulin resistance in patients with metabolic syndrome. Liu et al. [15] reported that irisin level had positive association with blood glucose in non-diabetic patients but not in diabetics. Moreover, no association was found between irisin and blood glucose in one study [23]. Different populations studied may partially explain these contradictory results.

Table 3 Correlation between serum irisin and different variables in diabetic patients

Variable	Serum irisin (ng/mL)	
	r	*p* value
Age (years)	$r = -0.262$	0.051
Duration of DM (years)	$r = -0.302$	*0.023*
Weight (kg)	$r = -0.620$	*< 0.001*
Height (cm)	$r = -0.256$	0.057
BMI (kg/m^2)	$r = -0.663$	*< 0.001*
Waist circumference (cm)	$r = -0.460$	*< 0.001*
Fasting blood glucose (mg/dL)	$r = -0.419$	*0.001*
HbA_{1c} (%)	$r = -0.528$	*< 0.001*
Cholesterol (mg/dL)	$r = -0.446$	*0.001*
Triglycerides (mg/dL)	$r = -0.491$	*< 0.001*
Urinary micro albumin (mg/L)	$r = -0.439$	*0.001*
Creatinine (mg/dL)	$r = 0.141$	0.299
eGFR (ml/min/1.73m^2)	$r = 0.231$	0.331
C-reactive protein (mg/dL)	$r = -0.692$	*< 0.001*
CIMT (mm)	$r = -0.807$	*< 0.001*

BMI, body mass index; *HbA1c*, glycosylated hemoglobin; *eGFR*, estimated glomerular filtration rat; *CIMT* carotid intima media thickness

Significant of italic value is $p < 0.05$

Irisin level and CIMT

The current study revealed negative correlation between serum irisin and CIMT. Irisin has been linked to the occurrence of atherosclerosis [24]. It was negatively associated with CIMT in peritoneal dialysis patients [25]. Furthermore, low serum irisin was independent risk factor of atherosclerosis in patients with Behçet's disease [26], and it was associated with the development of macrovascular complications in T2DM [11]. Yet, positive association between irisin and CIMT in healthy non diabetic subjects was previously reported [27].

The exact mechanism by which irisin is related to atherosclerosis is unclear. Our study demonstrated negative association between irisin level and the atherogenic lipid. Oelmann et al. [28] reported significant association between serum irisin and a favorable lipid profile in general population. Additionally, irisin treatment significantly reduced the serum levels of triglyceride and cholesterol in diabetic mice [19]. The mechanism by which irisin reduces plasma lipid could be related to adenosine monophosphate-activated protein kinase

(AMPK) signaling pathway and enhancing fatty acid oxidation [19]. Inflammation is considered an important contributing factor in the pathogenesis of atherosclerosis. CRP which is one of the most important indicators of inflammation and insulin resistance has emerged as predictor of atherosclerosis [29]. We found negative correlation between serum irisin level and CRP. Accordingly, irisin may promote atherosclerosis development in T2DM patients through its effect on lipid metabolism, inflammation, and insulin resistance.

Correlation of irisin level and indicators of diabetic nephropathy

In diabetes, albuminuria is an early indicator of progression of diabetic nephropathy. In our study, serum irisin had negative correlation with urinary albumin. Previous studies in diabetic patients found that low circulating levels of irisin were associated with the degree of albuminuria [30, 31] and higher serum irisin may reduce the progression of albuminuria by improving metabolic indices [9].

On the other hand, there was no significant correlation between irisin level and eGFR or s. creatinine in our study. This finding is inconsistent with previous studies. One study found that lower levels of serum irisin were associated with the presence of nephropathy in diabetic patients [32]. Also, it was reported that reduction of irisin level was associated with the progression of chronic kidney disease (CKD) stage [33]. However, no significant correlation was found between circulating irisin level and renal function indices in a cohort of T2DM patients [5].

One of the suggested mechanisms of low irisin level in CKD is that the rise in serum creatinine causes negative feedback inhibition on irisin secretion by the muscles [6]. This might explain the absence of significant association between irisin and serum creatinine in our study as our patients had normal serum creatinine.

Irisin level and diabetic retinopathy and nephropathy

The association between serum irisin and diabetic retinopathy is unclear. Serum irisin level was not different between diabetic patients with NPDR and those without DR [34]. Although, another study found that T2DM patients with PDR had significantly low serum and vitreous irisin concentrations compared with T2DM patients without DR [30]. In our study, irisin level was not significantly different between patients with DR and those with normal fundi.

We found that patients with peripheral neuropathy had significantly lower irisin level than those without. To our knowledge, there is no previous data about the relationship between irisin level and diabetic neuropathy. The link between irisin and retinopathy and neuropathy in diabetics could be related to the effect of irisin on endothelial dysfunction and inflammation which are important risk factors for microvascular complications [34, 35]. It is worth to mention that our study has several limitations; first, this cross-sectional study with small sample size could not determine the causal relationship between serum irisin and micro and macrovascular complications. Further large, prospective, and interventional studies are needed to confirm our results. Second, patients with severe renal impairment had been excluded from the study which prevents proper assessment of the relationship between irisin and the stage of CKD. Lastly, we did not use any of measurements of the insulin resistance in this study; however, we used CRP as indirect indicator of the degree of inflammation and insulin resistance. In conclusion, serum irisin correlates significantly with glycemic indices in patients with T2DM. Low serum irisin levels were associated with the presence of diabetic macrovascular and microvascular complications.

Acknowledgments All authors acknowledge their gratitude to the staff members of inpatient and clinics of internal medicine department for their help and support.

Compliance with ethical standards

Ethical approval This cross-sectional study was conducted from April 2014 till April 2015 after approval of the institutional ethical committee. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Informed consent Informed consent was obtained from all patients for being included in the study.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):647–653
https://doi.org/10.1007/s13410-019-00728-z

ORIGINAL ARTICLE

Serum level of orexin A and its correlation with metabolic risk factors in type 2 diabetes mellitus patients

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Received: 11 September 2018 / Accepted: 11 February 2019 / Published online: 20 March 2019

Abstract

Aim The present study was aimed to assess the role of the peptides (orexin A, leptin, and insulin) in type 2 diabetes mellitus patients (T2DM) and metabolic syndrome (MetS) patients.

Methods One hundred patients of either sex, at least 18 years of age and fulfilling the American Diabetes Association (ADA) criteria for type 2 diabetes mellitus (T2DM, $n = 100$) and 100 patients fulfilling the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III) criteria for metabolic syndrome (MetS, $n = 100$) were included. For comparison, 38 healthy controls (healthy control, $n = 38$) were included in the study. The peptide levels (orexin A, leptin and insulin) and inflammatory biomarkers (hsCRP and TNF-α) were estimated using quantitative enzyme-linked immunosorbent assay.

Results Serum levels of orexin A (OXA) were significantly lower while leptin, insulin, hsCRP and TNF-α levels were significantly higher in group III as compared to group II and group I. Waist circumference (WC), homeostatic model assessment insulin resistance (HOMA-IR), triglycerides (TG), HDL, leptin, and TNF-α were found to be the independent predictor of OXA, while WC, FPI, HOMA-IR, SBP and TG were found to be the independent predictor of leptin in group III, i.e., T2DM patients with MetS. Furthermore, in group II, i.e., T2DM patients without MetS, none of the metabolic variable was found to be the independent predictor of OXA and leptin.

Conclusion The serum levels of OXA and leptin are altered and significantly correlate to increase in the number of metabolic determinants in type 2 diabetes mellitus patients.

Keywords Type 2 diabetes mellitus · Metabolic syndrome · Insulin resistance · Orexin

Introduction

Metabolic syndrome (MetS) is the term allied to various associated pathologies of metabolic dysregulations such as obesity, hypertension, insulin resistance, and dyslipidemia which, along with the pro-inflammatory and prothrombotic cytokines, alleviates the risk of developing cardiovascular disorders (CVD), thus also termed as cardiometabolic syndrome or insulin resistance syndrome. The worldwide as well as Indian prevalence of MetS ranges from about 10% to as much as 84%, depending upon the region (urban or rural), composition of the population (sex, age, race, and ethnicity), and the definition of the syndrome used [1–4].

Orexins (A and B), derived from a common precursor pre-pro-orexin, are also known as hypocretins due to their hypothalamic origin. Apart from the central regulation of appetite and sleep/wakefulness cycle, orexins are also involved in the regulation of metabolic homeostasis [5–8]. In addition to the central role, the detection of orexins in human plasma and peripheral organs such as the pancreas and adipocytes has led to the confirmation of their peripheral role also [9, 10]. Various studies have reported the reduced circulating level of orexin A (OXA) in obese patients [11, 12] which further have shown positive association with improved glucose and lipid profile [13], thus reporting the contribution of orexins in metabolic and endocrine homeostasis.

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The central regulatory link between orexin and leptin has been supported by the fact that the orexin-containing neuron expresses the leptin receptors [14]. In contrast to OXA, leptin mainly inhibits appetite, increases energy expenditure, regulates glucose utilization, and improves insulin sensitivity [15–17], dysregulation of which potently contributes to the development of MetS [18]. The altered blood levels of these peptides in obese patients have been assessed and correlated to the metabolic risk profile [12, 19] but as such insights into the present relationship of these peptides (OXA, leptin, and insulin) in type 2 diabetes mellitus (T2DM) and MetS patients are not clear.

Considering the above facts, the present study was aimed to assess the serum level of peptides (orexin A, leptin, and insulin) and inflammatory biomarkers (hsCRP and TNF-α) and to further find out their correlation with metabolic risk factors in T2DM patients with and without MetS.

Methods

Study population

After medical evaluation by the physician (including assessment of medical history and physical examination), 100 patients of either sex, at least 18 years of age, and fulfilling the American Diabetes Association (ADA) criteria for T2DM ($n = 100$) and 100 patients fulfilling the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III) criteria for MetS ($n = 100$) were included as per the study protocol. For comparison, 38 healthy controls (healthy control, $n = 38$) were included in the study. T2DM patients of either sex were screened as per the ADA criteria, i.e., fasting blood glucose (FBG) ≥ 126 mg/dl. MetS patients were diagnosed as having at least three components out of these five components as per the NCEP-ATP-III criteria: waist circumference (WC), men > 102 cm (40 in.)/women > 88 cm (35 in.); triglycerides (TG) $\geq$ 150 mg/dl; high-density lipoprotein (HDL) cholesterol, men < 40 mg/dl/women < 50 mg/dl; blood pressure, systolic blood pressure (SBP) ≥ 130 mmHg/diastolic blood pressure (DBP) ≥ 85 mmHg; and fasting glucose $\geq$ 110 mg/dl [20]. A healthy control population was considered as individuals who were not suffering from any metabolic disorders (T2DM, obesity, dyslipidemia, and thyroid) and cardiovascular diseases. Patients with less than 18 years of age, patients with diabetes complications (nephropathy, neuropathy, and retinopathy), patients with thyroid dysfunction, and pregnant/lactating women were excluded from the study.

Statistical analysis

Descriptive and inferential statistical analyses were performed using SigmaStat software version 3.5. One-way analysis of variance (ANOVA) followed by the Bonferroni t test was performed to assess the differences between all the three groups in terms of metabolic variables and biochemical parameters. To find the association of serum level of peptides (OXA, leptin, and insulin) with the metabolic variables and inflammatory biomarkers (hsCRP and TNF-α), Pearson correlation and further multiple regression analyses were carried out. All the data were expressed as mean ± SEM. $p \leq 0.05$ was accepted as statistically significant.

Assessment of clinical biomarkers

Anthropometric indices were measured (waist circumference, weight, height, and BMI), and other metabolic variables were assessed in the study groups at the baseline. Blood pressure was measured using a standard mercury sphygmomanometer. Blood samples were collected in the morning after12-h fasting from all the patients for measuring the serum level of metabolic and biochemical markers.

The serum concentration of OXA was assessed using an orexin-A/hypocretin human enzyme-linked immunosorbent assay (ELISA) kit (Fine Test Pharmaceuticals Inc., catalog-EH3487), according to the manufacturer's protocol. The serum leptin estimation was carried out with a leptin ELISA kit (Diagnostic Biochem Canada Pharmaceuticals Inc., catalog-CAN-L-4260), and plasma insulin estimation was carried out with an insulin ELISA kit (DRG International, Pharmaceuticals Inc., catalog-EIA-2935) according to the manufacturer's protocol. The serum concentration of hsCRP estimation was also carried out using the ELISA kit (Diagnostic Biochem Canada (DBC) Pharmaceuticals Inc., catalog-CAN-CRP-4360), and TNF-alpha levels were estimated using a human TNF-alpha, ELISA kit (Krishgen Biosystems, USA-India Inc., catalog-KB1145), according to the manufacturer's protocol. Insulin resistance was calculated using the homeostatic model assessment (HOMA), with the equation: HOMA − IR = (fasting plasma glucose in mg/l × fasting plasma insulin)/405 [21].

Results

Clinical and biochemical characteristics of patients

The metabolic profile and biochemical profile of the study population are shown in Table 1. The MetS was

found to be more prevalent in females (59%), while T2DM was found to be more prevalent in males (62%). In T2DM patients with MetS, hypertension (40%) and dyslipidemia (28%) were found to be the major co-morbid conditions. Moreover, 32% of the patients were found to have both hypertension and dyslipidemia. The age difference between the study groups and the healthy control group was not found to be significant. Furthermore, the metabolic parameters such as WC, BMI, SBP, DBP, TG, and FBG were found to be significantly higher in group III, i.e., T2DM patients with MetS, as compared to group II, i.e., T2DM patients without MetS, and group I, i.e., healthy control, while HDL levels were found to be significantly lower in group III as compared to group II and group I.

Among peptides, fasting plasma insulin (FPI) was found to be significantly higher in group III as compared to group II and group I. Also, the differences between group II and group I in terms of FBG and FPI were found to be significant ($p \leq 0.05$). Furthermore, a significant difference was observed for serum levels of OXA, leptin, hsCRP, and TNF-α in all the three groups ($p \leq 0.05$). Serum OXA levels were found to be significantly lower in group III, i.e., T2DM patients with MetS, as compared to group II and group I, while the serum levels of leptin, hsCRP, and TNF-α were found to be significantly higher in group III as compared to group II and group I ($p \leq 0.05$).

The association between various variables in the study groups was carried out using the Pearson correlation analysis, as presented in Table 2. In group III, i.e., T2DM patients with MetS, the correlation coefficient (r) showed a significantly inverse relationship of OXA with WC, BMI, FBG, FPI, HOMA-IR, SBP, TG, leptin, hsCRP, and TNF-α ($p \leq 0.05$), while a significant positive association was observed with HDL ($p \leq 0.05$). On the contrary, serum leptin levels showed a significant positive correlation with WC, BMI, FBG, FPI, HOMA-IR, SBP, DBP, TG, hsCRP, and TNF-α ($p \leq 0.05$), and an inverse relationship was observed with HDL ($p \leq 0.05$). Furthermore, hsCRP showed a significant positive correlation with WC, BMI, FBG, FPI, HOMA-IR, TG, SBP, and DBP ($p \leq 0.05$) and an inverse relationship was observed with HDL ($p \leq 0.05$). Similarly, serum TNF-α levels showed a significant positive correlation with WC, BMI, FBG, FPI, HOMA-IR, and TG ($p \leq 0.05$), while an inverse relationship was observed with HDL ($p \leq 0.05$). The corresponding correlation graph of OXA with leptin and HOMA-IR is specified in Fig. 1 and Fig. 2 respectively.

The metabolic variables which were found to be significantly correlated with biochemical parameters (orexin,

Table 1 Demographic, metabolic, and biochemical profiles of the study population

Metabolic variables	Healthy control, group I ($n = 38$)	T2DM patients without MetS, group II ($n = 100$)	T2DM patients with MetS, group III ($n = 100$)
Age (years)	48.12 ± 0.26	52.12 ± 1.78	55.71 ± 1.90
Gender (F/M)	12/26	38/62	59/41
WC (in.)	28.55 ± 0.52	31.18 ± 0.81*	34.05 ± 0.24*#
Weight (kg)	56.28 ± 1.67	59.07 ± 1.81*	72.53 ± 1.49*#
Height (cm)	155.86 ± 0.98	156.03 ± 0.77	154.23 ± 0.76
BMI (kg/m^2)	22.55 ± 1.86	23.78 ± 1.27*	28.60 ± 1.53*#
SBP (mmHg)	119.35 ± 0.74	124.67 ± 1.80*	142.56 ± 1.85*#
DBP (mmHg)	78.64 ± 1.45	82.09 ± 0.09*	94.07 ± 1.04*#
FBG (mg/dl)	94.21 ± 0.39	137.9 ± 2.56*	156.64 ± 2.44*#
TG (mg/dl)	109.64 ± 1.82	134.81 ± 1.59*	180.19 ± 1.87*#
HDL (mg/dl)	48.92 ± 0.18	43.20 ± 0.69*	38.60 ± 0.81*#
Orexin A (pg/ml)	46.09 ± 0.29	33.21 ± 0.80*	23.67 ± 1.74*#
Leptin (ng/ml)	12.78 ± 0.23	19.08 ± 0.34*	28.14 ± 0.48*#
FPI (μIU/ml)	15.33 ± 0.57	28.56 ± 0.22*	37.98 ± 0.89*#
HOMA-IR	2.04 ± 0.06	3.95 ± 0.13*	5.07 ± 0.48*#
hsCRP (mg/l)	0.76 ± 0.33	1.13 ± 0.12*	3.24 ± 0.34*#
TNF-α (pg/ml)	15.21 ± 0.28	41.34 ± 0.07*	82.21 ± 0.12*#

Data are expressed as mean ± SEM. $p \leq 0.05$ was considered as statistically significant

*$p \leq 0.05$ vs. healthy control (group I)

#$p \leq 0.05$ vs. T2DM patients without MetS (group II)

Table 2 Pearson correlation matrix of various metabolic variables in group III (T2DM patients with MetS)

Metabolic variables	T2DM patients with MetS (group III, $n = 100$)			
	OXA	Leptin	hsCRP	TNF-α
WC (cm)	− 0.30 0.002	0.29 0.002	0.31 0.001	0.26 0.007
BMI (kg/m^2)	− 0.28 0.004	0.27 0.006	0.30 0.001	0.28 0.003
FBG (mg/dl)	− 0.27 0.004	0.33 < 0.001	0.30 0.002	0.29 0.002
FPI (μIU/ml)	− 0.31 0.001	0.32 < 0.001	0.24 0.01	0.28 0.004
HOMA-IR	− 0.26 0.008	0.28 0.003	0.34 0.001	0.27 0.004
SBP (mmHg)	− 0.21 0.02	0.35 < 0.001	0.30 0.001	0.29 0.002
DBP (mmHg)	− 0.09 0.92	0.28 0.004	0.20 0.03	0.25 0.01
TG (mg/dl)	− 0.30 0.002	0.28 0.008	0.32 <0.001	0.30 0.002
HDL (mg/dl)	0.28 0.004	− 0.23 0.01	− 0.23 0.01	− 0.28 0.004
OXA (pg/ml)	–	− 0.31 0.001	− 0.25 0.01	− 0.27 0.006
Leptin (ng/ml)	− 0.31 0.001	–	0.32 0.001	0.27 0.007
hsCRP (mg/dl)	− 0.25 0.01	0.32 0.001	–	− 0.11 0.55
TNF-α (pg/ml)	− 0.28 0.006	0.27 0.007	− 0.11 0.55	–

Upper and lower values are correlation coefficient (r) and p values respectively. $p \leq 0.05$ was considered as statistically significant

leptin, hsCRP, and TNF-α) were further subjected to multiple linear regression analysis, as represented in Table 3. The results revealed WC, BMI, TG, HDL, and leptin ($p \leq 0.05$) as independent predictors of OXA, while WC, FPI, HOMA-IR, and TG ($p \leq 0.05$) as independent predictors of leptin in group III, i.e., T2DM patients with MetS.

Discussion

In the present study, the serum levels of OXA were found to be decreased while leptin levels were found to be increased in T2DM patients with MetS as compared to T2DM patients without MetS and healthy control. Furthermore, leptin levels showed negative association with OXA. The altered and opposite serum levels of both OXA and leptin are supported by the fact that both have contraregulatory actions to maintain energy

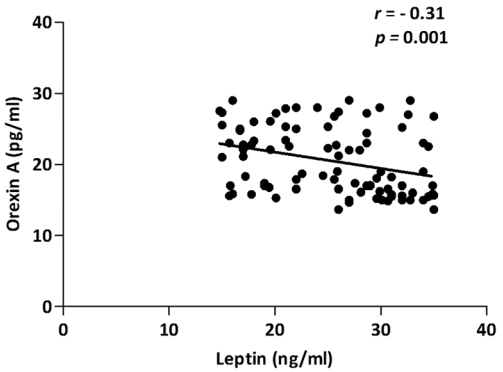

Fig. 1 Correlation graph of OXA with leptin

and metabolic homeostasis. The lateral hypothalamic area (LHA), which is considered as the primary area responsible for maintaining the energy and metabolic homeostasis, has an abundance of leptin receptors and has inhibitory actions on orexin neurons, which proves the contraregulatory relationship between these peptides [22].

Furthermore, decreased OXA levels were found to have inverse while increased leptin levels were found to have positive correlation with FBG, FPI, and HOMA-IR in group III, i.e., T2DM patients with MetS, while no such significant association was observed in group II, i.e., T2DM patients without MetS, and group I, i.e., healthy control. The present study was corroborated with the previous study which has stated the close association of serum OXA level with improved glucose profile in obese patients who had undergone bariatric surgery [12], and hyperleptinemia was reported to have close association with insulin resistance and dyslipidemia in T2DM patients with MetS as compared to T2DM patients without MetS [23]. Leptin, as a regulator of glucose metabolism, acts as a positive modulator of insulin and has been reported to improve insulin sensitivity in pancreatic beta cells and skeletal muscles by promoting the lipid oxidation and inhibiting the lipid synthesis [24]. Furthermore, various preclinical studies have reported that OXA decreases the blood glucose levels in fasting mice and also orexin-deficient animals have been reported to be hyperglycemic and insulin resistant [25, 26], whereas orexin overexpression has been reported to improve insulin sensitivity through activation of peroxisome proliferator-activated gamma receptors (PPAR-γ) [27]. Additionally, the orexin-deficient narcoleptic patients were found to be glucose intolerant and insulin resistant [28]. Thus, the present study is corroborated with these findings as insulin resistance was revealed as an independent predictor for altered levels of OXA and leptin in the study population. The possible mechanism of link between decreased OXA and increased insulin resistance might be the

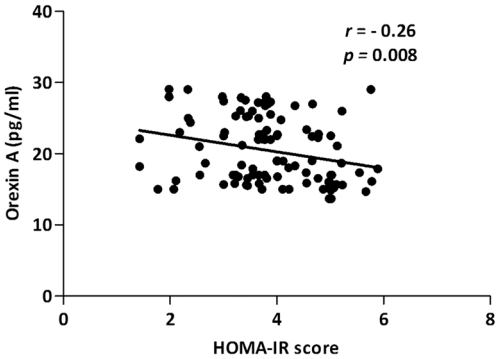

Fig. 2 Correlation graph of OXA with HOMA-IR

reduction of peroxisome proliferator-activated receptor-gamma (PPAR-γ) receptors on adipocytes as OXA was reported to stimulate the expression of these receptors in isolated human subcutaneous adipose tissue [29]. Secondly, the association of decreased level of OXA with increased blood glucose levels in T2DM patients with MetS might be due to decreased GLUT 2 expressions as OXA was found to increase glucose uptake through enhancing GLUT-2 expression in porcine adipocytes and pre-adipocytes of obese rats [30, 31].

Furthermore, WC was found to be the strong predictor of altered levels of OXA and leptin in group III, with no such association in group II and group I. The present result was corroborated with previous clinical studies which reported the altered OXA and leptin levels in obese patients [12, 32]. Animal studies have also revealed that orexin knockout mice developed late onset of obesity despite eating less and increased OX_2R signaling has been reported to prevent diet-induced obesity (DIO) and improve leptin sensitivity [27, 33]. The present study was in liaison to these studies, and the reason behind the reduction of OXA in obese might be negative feedback which increases energy expenditure and neutralizes the effect of eating and thus maintains energy homeostasis. Also, OXA has been reported to decrease the leptin resistance, which further will reduce insulin resistance and will deplete the fat stores and thus might be helpful for the treatment of obesity.

Table 3 Multiple linear regression analysis in T2DM patients with MetS

Independent predictors of OXA		
Independent variables	β	p
WC (in.)	− 0.61	< 0.001
BMI (kg/m^2)	− 0.56	< 0.001
TG (mg/dl)	− 0.01	0.04
HDL (mg/dl)	0.10	0.01
Leptin (ng/ml)	− 0.08	0.02
Independent predictors of leptin		
Independent variables	β	p
WC (in.)	0.49	0.03
FPI (μIU/ml)	0.34	< 0.001
HOMA-IR score	0.56	< 0.001
TG (mg/dl)	0.03	0.01

β, regression coefficient; $p \leq 0.05$ was considered as statistically significant

Furthermore, in group III, a significant association of OXA and leptin was observed with TG and HDL respectively. The present study was supported by the previous study, which reported the direct association of increased orexin levels with an improved lipid profile in obese patients who underwent bariatric surgery [13] and in postmenopausal women suffering from MetS [34]. It also has been reported that orexinergic neurons are triglyceride sensitive and resemble that of insulin sensitizers, i.e., trigger lipogenesis and inhibit lipolysis [35], while leptin inhibits the gene coding for stearoyl-CoA desaturase-1 (enzyme involved in synthesis of TG and VLDL) [36]. OXA also has been reported to enhance PPAR-γ receptors in adipocytes, which are known to be the important regulator of lipogenesis [37]. Also, the association of leptin with altered lipid profile in T2DM patients with MetS was in consensus with the previous study [38].

In the context of hypertensive profile, a negative correlation of OXA was observed with SBP and DBP in group III, which was in liaison to the previous study which also reported the increased blood pressure in orexin-deficient narcoleptic patients [39]. However, Kayaba et al. and others have demonstrated a reduced basal blood pressure of pre-pro-orexin knockout animals [40, 41], so the role of orexins in cardiovascular regulation is controversial. Furthermore, the serum leptin level was found to be positively correlated with SBP and DBP in group III which was in liaison to the clinical studies of obese and T2DM patients [19, 23]. Leptin has been reported to enhance the sympathetic tone by activating the sympathetic nervous system (SNS) and increasing renal sympathetic nerve activity (RSNA) [42], which might be the reason behind the positive correlation of hypertension and higher leptin levels in MetS patients. Furthermore, in the present study, a significant correlation of decreased OXA and increased leptin levels was observed with hsCRP and TNF-α in group III, i.e., T2DM patient with MetS, while no such correlation was observed in group II and group I. This was in consensus with the previous studies which have reported the reduced mRNA expression of OXA under acute inflammatory conditions and TNF-α, a pro-inflammatory cytokine that has also been reported to decrease the level of both pre-pro-orexin and

OX_2R [43]. Moreover, a clinical study has reported the increased blood levels of TNF-α and IL-6 in orexin-deficient narcoleptic patients [44]. Also, an increased hsCRP level has been reported to be inversely correlated with decreased OXA levels in morbidly obese patients who underwent bariatric surgery [13]. Although there are evidences of direct link of OXA with inflammatory biomarkers, interaction with leptin might also be the possible reason of correlation of altered levels of OXA with inflammatory biomarkers as these pro-inflammatory adipokines such as TNF-α and IL-6 have been reported to mediate the production of CRP under the influence of leptin, which itself induces inflammation directly [45, 46].

Conclusion

The inverse relationship of these peptides as such may not prove the cause or consequences of the syndrome, but the trail of compensatory pathways between OXA, leptin, and insulin strongly suggests their role in the origin of metabolic risk factors in T2DM patients. So, possibly, the role of OXA and its interaction with leptin and other metabolic risk factors in the pathophysiology of MetS may indicate OXA as an important biomarker for MetS, but still, there is need to further explore the role and physiological link of these biomarkers in a larger number of patients so that a single target could emerge as a pharmacological tool to assess and manage the associated metabolic risk factors in T2DM patients.

Acknowledgements We acknowledge the Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, Govt. Medical College & Rajindra Hospital, Patiala, and University Grant Commission- Rajiv Gandhi National Fellowship (UGC-RGNF) for the kind assistance in carrying out the research work.

Funding This work was supported by the University Grants Commission, Bahadurshah Zafar Marg, New Delhi under the Rajiv Gandhi National Fellowship (UGC-RGNF), scheme (Award no. F1-17.1/2013-14/RGNF-2013-14-SC-PUN-47198).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The study protocol was approved by the Institutional Ethics Committee (IEC) of Punjabi University, Patiala, Punjab, India, under protocol no. 260/DLS/HG.

Informed consent Informed consent was obtained from all individual participants included in the study.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):654–658
https://doi.org/10.1007/s13410-019-00737-y

ORIGINAL ARTICLE

Results of simultaneous application of hyperbaric oxygen and negative pressure wound therapy in diabetic foot ulcers treatment

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Received: 12 April 2017 / Accepted: 18 March 2019 / Published online: 13 April 2019

Abstract

Background The aim of this paper is to determine which therapy gives best results regarding process of healing of diabetic foot ulcers among three proposed: only negative pressure wound therapy, only hyperbaric oxygen therapy, and both when used in conjunction.
Methods This bicentric prospective study included 60 patients, and they were, consecutively, assigned to one of three groups. The first group consisted of 20 patients who were treated only by hyperbaric oxygen therapy, second group consisted of 20 patients treated with combined hyperbaric oxygen and negative pressure wound therapy, and third group consisted of 20 patients who were treated only by negative pressure wound therapy. In some cases, previous revascularization of lower limb was performed and patients with poor run-off, without possibility to perform revascularization, were excluded from the study.
Results Patients were predominantly men (56.7%) and mean age was 60.57 years. Majority of patients had ulcers of ischemic origin (45%), in 30% of cases, the reason of foot ulceration was neuropathy, and in 25% of patients, the etiology was combined. During the study, in three patients (5%), minor amputations were observed. Regarding Wagner classification of foot ulcers, most dominant was stage II ($\chi = 12.618$, $df = 4$, $p < 0.05$). Statistically significant reduction of wound area was achieved when hyperbaric oxygen and negative pressure wound therapy were used in conjunction comparing to isolated use either of these two modalities of treatment ($\chi = 116.000$, $df = 44$, $p < 0.01$).
Conclusion Our data suggests simultaneous use of hyperbaric oxygen therapy and negative pressure wound therapy in diabetic foot ulcer treatment in order to achieve best results. Of great importance is previous wound debridement and successful limb revascularization.

Keywords Diabetes mellitus · Foot ulcers · Negative pressure wound therapy · Hyperbaric oxygen therapy · Limb revascularization

Introduction

Diabetes mellitus is among most common chronic diseases in elder population. It is estimated that 3.2 million adults in USA above age of 65 have this condition [1]. Nephropathy and neuropathy are associated complications, as well as macrovascular complications such as coronary artery disease, carotid artery disease, and peripheral arterial occlusive disease (PAOD) [2]. In such settings, diabetic foot ulcers (DFU) can develop and lead to extremity amputation [3–5]. One of therapeutic options for DFU is negative pressure wound therapy (NPWT) [6] as well as hyperbaric oxygen therapy (HBOT) that is used as adjunctive treatment, although there are few clinical trials regarding its use in these conditions [7].

Vascular status of extremity should be assessed prior to treatment of DFU. Unrecognized underlying arterial disease, which can be corrected either by open surgery or endovascular procedures, can lead to treatment failure [8]. Therefore, vascular surgeon opinion is needed prior to initiation of DFU treatment. For classification of DFU, we used Wagner scale which considers the depth of wound, whether is there osteomyelitis or gangrene, and tissue necrosis [9] (Table 1).

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Table 1 Wagner classification of foot ulcer

Grade	Lesion
0	No open lesions; may have deformity or cellulitis
1	Superficial diabetic ulcer (partial or full thickness)
2	Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis
3	Deep ulcer with abscess, osteomyelitis, or joint sepsis
4	Gangrene localized to portion of forefoot or heel
5	Extensive gangrenous involvement of the entire foot

Patients and methods

This bicentric prospective study included 60 patients and was conducted from January 2015 to January 2016. Patients were recruited at Cardiovascular Institute "Dedinje," Belgrade, Serbia (15 of them), and Department of Physical Medicine and Rehabilitation "Dr Miroslav Zotovic," Banja Luka, Bosnia and Herzegovina (45 patients). All patients gave informed consent to participate in the study, and Ethics committee of both institutions approved its conduction.

Patients were, previously diagnosed, diabetes mellitus, and all of them had foot ulcers that were assessed by Wagner scale (all of them belonging to stages 1, 2, and 3). Majority of ulcers were located at forefoot (93%), and in 7%, the ulcer was located at foot dorsum.

They were, consecutively, assigned to one of three groups. Prior to initiation of treatment, in selected cases, femoro-distal bypass or angioplasty was performed based on CT angiography. Wound debridement was done in all patients, and adequate antibiotic therapy started according to microorganisms isolated from the wounds. All patients received acetylsalicylic acid, and in 28 patients, in whom stenting of lower extremity arteries was performed, dual antiplatelet therapy (acetylsalicylic acid plus clopidogrel) was administered. Patients were either on insulin or oral hypoglycemic therapy. In some cases, several oral hypoglycemics were used to control diabetes (Fig. 1). The first group consisted of 20 patients who were treated only by hyperbaric oxygen therapy, second group consisted of 20 patients treated with combined hyperbaric oxygen and negative pressure wound therapy, and third group consisted of 20 patients who were treated only by negative pressure wound therapy (KCI USA, San Antonio, TX). Dressings for negative pressure wound therapy were changed three times per week, and 30 sessions of hyperbaric oxygen therapy (100% oxygen, pressure 2.2 ATA, duration 1 h) were performed in each patient belonging to groups 1 and 2. Offloading was conducted in 56 patients (93%). Patients with poor run-off, without possibility to perform revascularization, were excluded from the study.

During study, demographic data were collected, as well as height and weight of the patients. Ankle-brachial index and approximative wound area were determined in all patients. Laboratory findings such as erythrocyte sedimentation rate, CRP, Le count, triglyceride, cholesterol, and HbA1C were collected, also.

Statistical calculation was performed using SPSS 22 for Windows (SPSS Inc., Chicago, Ill). For data analysis, χ^2 test was used as well as Pearson's correlation coefficient, factor analysis, percentage determination, and item total correlation. Results were statistically significant when $p < 0.05$.

Results

Patients were predominantly men (56.7%) and mean age was 60.7 years. Demographic characteristics are summarized in Table 2.

Majority of patients had ulcers of ischemic origin (45%), in 30% of cases, the reason of foot ulceration was neuropathy, and in 25% of patients, the etiology was combined. During study, in three patients (5%), minor amputations were observed.

Regarding Wagner classification of foot ulcers, statistically most dominant was stage II ($\chi^2 = 12.618$, $df = 4$, $p < 0.05$) (Table 3).

To improve blood flow to the foot, regardless of ulcer type, 14 of patients underwent femoro-distal bypass procedure, and in 28 of patients, angioplasty and stenting of infrainguinal arteries were performed. The rest of patients (18) had satisfactory findings on arteries and needed no revascularization (Table 4).

Statistical analysis revealed that there was significantly greater number of surgery and stenting in the first group of patients treated only with hyperbaric oxygen, and stenting was the single most performed procedure in all three treatment groups ($\chi^2 = 12.405$, $df = 4$, $p < 0.05$).

The most important finding of this study was obtained when wound area decrease was assessed (Fig. 2). The area (cm^2) was calculated considering ulcer length and width (length × width × $\pi/4$). It was measured just before, 10 days, and 6 weeks after treatment initiation. Statistical analysis revealed that significant reduction of wound area was achieved when hyperbaric oxygen and negative pressure wound therapy were used in conjunction comparing to isolated use either of these two modalities of treatment ($\chi^2 = 116.000$, $df = 44$, $p < 0.01$).

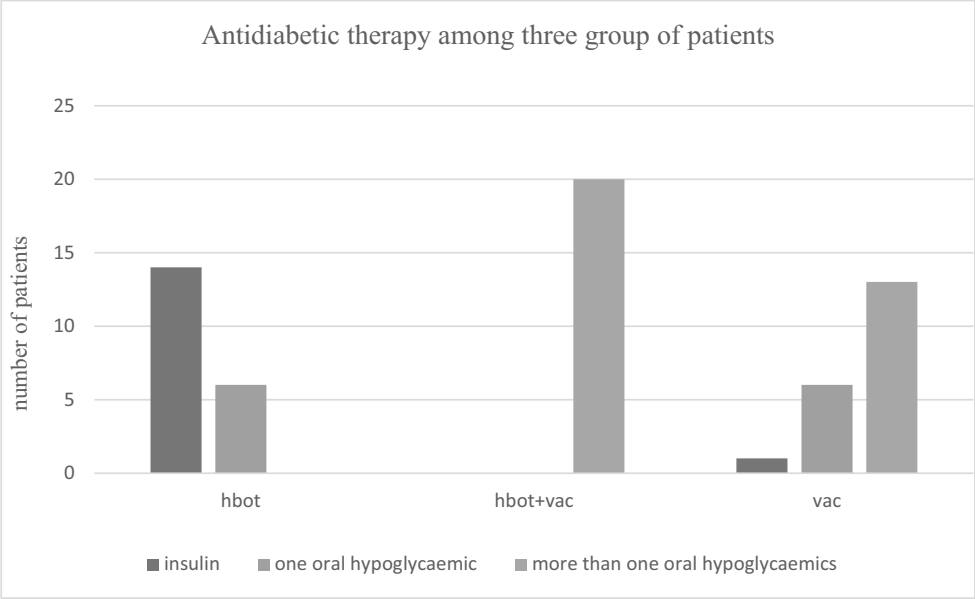

Fig. 1 Antidiabetic therapy among three group of patients

hbot – hyperbaric oxygen therapy

vac – vacuum assisted closure therapy

Discussion

Contemporary literature lacks papers dealing with DFU in such way as we did. A study by Blume and co-workers [10] compared negative pressure wound therapy with advanced moist wound therapy (AMWT). The mean patient population age in his study was 58 years, and the patients were predominantly male (78.5%). Similar results were obtained in our study. Offloading was conducted in 97% of patients, whereas in our study, compliance for offloading was 93%. There was statistically significant difference in achieving wound closure in group of patients treated with NPWT comparing with group treated with AMWT (60.8% versus 40.0%). We found that combined therapy when NPWT and HBOT were used in conjunction showed significantly better results in wound closure when compared with isolated use of either of two modalities of treatment. We observed minor amputations in three (5%) patients during the course of therapy, while Blume et al reported minor amputations in both treated groups (in 4.1% treated with NPWT, and 10.2% treated with AMWT).

Hopf et al. [11] and Saxena and colleagues [12] emphasized wound debridement as key component of initiation of healing process. We used the same principle in our study. Prior to initiation of therapy, in 42 patients, we performed revascularization, and in all of them, necrotic and infected tissue from foot ulcer was removed in order to achieve best possible conditions for wound healing. As adjunctive therapy, adequate antibiotics were given. Saxena et al. [12] also found that negative pressure causes micromechanical deformations that stimulate granulation tissue formation.

Table 2 Demographic data for all patients

Age (years)	60.57 ± 10.48
Sex (male/female)[a]	34/26 (56.7/43.3)
Weight (kg)	76.07 ± 8.42
Height (cm)	173.37 ± 6.71
Current smoker[a]	32 (53.3)
HBA1c (%)	7.5 ± 2.5
Off-loading[a]	56 (93.0)
Wound area in cm^2 (max/min)	20.3/2.0

Data are presented as mean values ± SD and *n* (%)

Table 3 Distribution of patients among different treatment groups and Wagner scale of foot ulcers

Wagner scale				
	Stage I	Stage II	Stage III	Total
HBOT (*n*, %)	9, 45.0	7, 35.0	4, 20.0	20, 100.0
HBOT + NPWT (*n*, %)	2, 10.0	9, 45.0	9, 45.0	20, 100.0
NPWT (*n*, %)	3, 15.0	14, 70.0	3, 15.0	20, 100.0
Total (*n*, %)	14, 23.3	30, 50.0	16, 26.7	60, 100.0

HBOT hyperbaric oxygen therapy, *NPWT* negative pressure wound therapy, *n* number of patients

Table 4 Distribution of patients among different treatment groups in whom surgery, stenting, or no revascularization was performed

	Surgery	Stenting	No revascularization	Total
HBOT (*n*, %)	6, 30.0	13, 65.0	1, 5.0	20, 100.0
HBOT + NPWT (*n*, %)	4, 20.0	10, 50.0	6, 30.0	20, 100.0
NPWT (*n*, %)	4, 20.0	5, 25.0	11, 55.0	20, 100.0
Total (*n*, %)	14, 23.3	28, 46.7	18, 30.0	60, 100.0

HBOT hyperbaric oxygen therapy, *NPWT* negative pressure wound therapy, *n* number of patients

Ali et al. [13] observed that the patients on NPWT therapy showed earlier appearance of granulation tissue when compared to the patients treated by moist saline gauze dressings. They reported average wound area to be 16 cm^2 in group treated with NPWT and in the other group 13.6 cm^2. In our study, average wound area was estimated to be less in all treated patients (9.21 cm^2).

Regarding HBOT therapy in healing leg ulcers, data are inconsistent. Abidia et al. [14] published results of treatment in 16 patients and showed clear benefit in group treated with HBOT when reduction of wound size was measured after 6 weeks. Löndahl et al. [15] reported results of 94 patients (49 in HBOT and 45 in placebo group) and showed better results in group treated with HBOT, also.

On the other hand, Margolis et al. [16], in retrospective study, have not found beneficial effect of HBOT versus standard wound therapy in healing rates. They, also, noticed higher amputation rates in patients treated with hyperbaric oxygen. In our study, no amputations in all three treatment groups were recorded, probably due to small sample size.

Fedorko et al. [17] found similar results as Margolis et al. [16] and could not recommend the use of adjuvant HBOT for reducing rate of amputations or for improving healing process for DFUs.

Possible limitations of our study are small sample size, lack of randomization, short follow-up period, and no control group.

Figure 3 shows good results obtained in a patient treated with simultaneous application of hyperbaric oxygen and negative pressure wound therapy.

At conclusion, despite these drawbacks, our data suggests simultaneous use of HBOT and NPWT in diabetic foot ulcer treatment in order to achieve best results. Of great importance is previous wound debridement and successful limb revascularization.

As previously mentioned, to our knowledge, this is the first study that is dealing with DFU in such a way. Further, larger

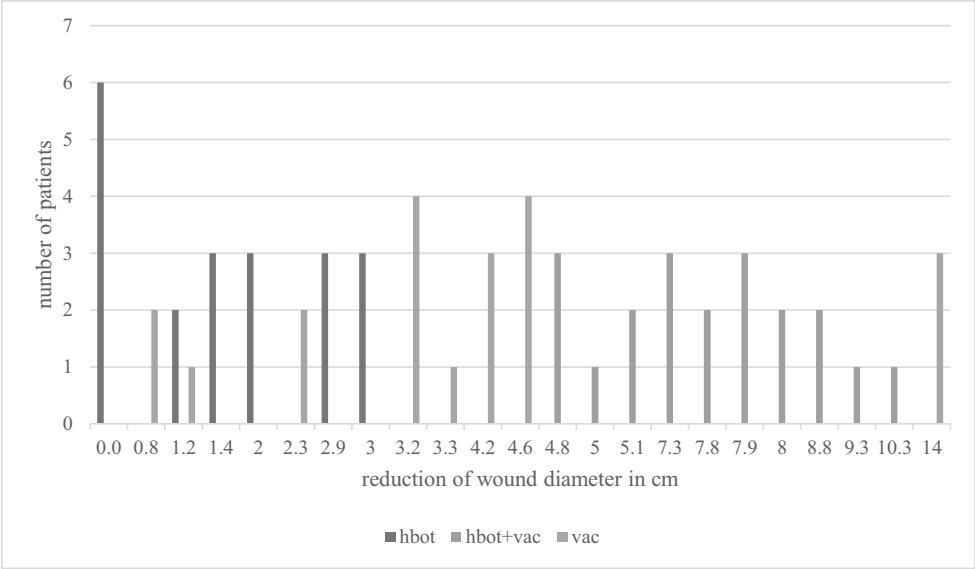

Fig. 2 Reduction rate of wound diameter after 6 weeks of treatment

hbot – hyperbaric oxygen therapy

vac – vacuum assisted closure therapy

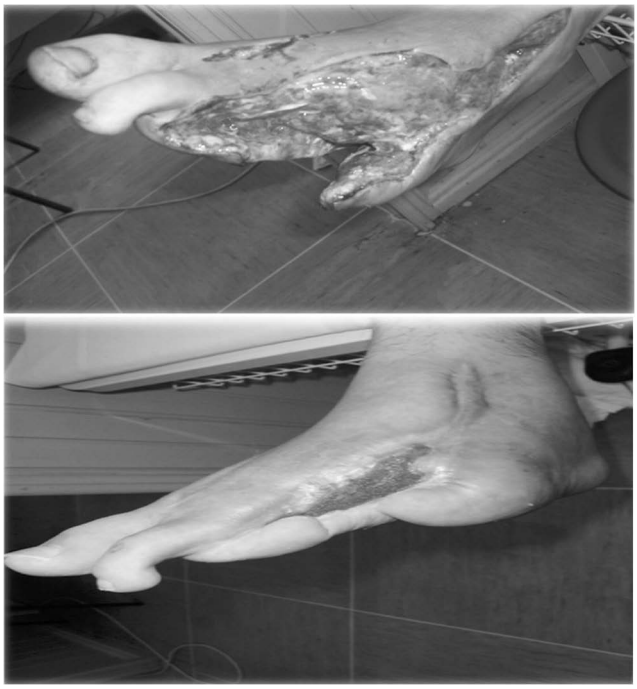

Fig. 3 Diabetic foot wound after debridement (above) and 6 weeks after simultaneous application of hyperbaric oxygen and negative pressure wound therapy (below)

scale studies are needed to elucidate simultaneous application of HBOT and NPWT in these patients.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

All patients gave informed consent to participate in the study, and Ethics committee of both institutions approved the conduct of the study.

Conflict of interest The authors declare that they have no conflict of interest.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):659–666
https://doi.org/10.1007/s13410-019-00736-z

ORIGINAL ARTICLE

The effect of transitional care on the prevention of diabetic foot ulcers in patients at high risk for diabetic foot

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Received: 5 October 2018 / Accepted: 27 February 2019 / Published online: 30 March 2019

Abstract

Objective To study the effect of transitional care on the prevention of diabetic foot ulcers (DFU) in patients at high risk for diabetic foot.

Methods A total of 284 diabetic patients at high risk for DFU were randomly divided into case and control groups (142 cases in each group). The control group was provided with conventional care in hospital. The case group received the transitional care intervention, including individualized education about diabetes mellitus and DFU, instruction in foot care, and the assistant management of calluses and the evaluation on quality of life. Both groups were followed up for 2 years. The levels of blood glucose, blood pressure and serum lipids, and foot dorsal artery pulse, 10-g monofilament nylon fiber probe test, knowledge of foot care, and diabetes quality of life (DQOL) in two groups were compared before and after transitional care intervention.

Results There were statistically significant improvements in the case group compared with the control group in plasma glucose and blood pressure levels, and in foot dorsal artery pulse, 10-g monofilament nylon fiber probe test, knowledge of foot care, and DQOL. The incidence of DFU was lower, and the ulcers also were milder in the case group than in the control group.

Conclusions Transitional care was beneficial to the prevention of DFU and could reduce the development of DFU and improve the patients' quality of life.

Keywords Transitional care · Diabetes mellitus · Diabetic foot ulcer

Introduction

Diabetes is a serious and chronic disorder disease and an important public health problem [1, 2]. Around the world, it affects approximately 425 million people, and this number is estimated to reach 629 million in 2045 [3]. In China, the overall prevalence of diabetes was estimated to be 11.6% in the adult population [4]. The increase in the number of patients with diabetes is likely to bring a concomitant increase in its complications [5]. In those complications, one of the most important is diabetic foot ulcers (DFUs). DFU is a common and complex problem and is one of the most important reasons leading to non-traumatic lower-extremity amputations or even death in diabetes patients [6]. In addition, DFU can engender substantial financial costs; the cost of treatment may account for over one-third of the total cost of diabetes [7]. In some areas of China, the cost to treat a patient with DFU is from 13,000 to 32,000 yuan RMB (about $1900–4700 US) [8, 9]. Although it is difficult to treat DFU, the complication is preventable. Nursing education and intervention to patients with diabetes can improve the self-care ability of patients and control the risk factors for DFU; thereby, it can prevent patients with diabetes from DFU [10]. This study was conducted for the evaluation of the effect of transitional care on preventing the development of DFU in patients at high risk for diabetic foot.

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Materials and methods

Patients

From January 2013 to December 2015, 284 diabetic patients at high risk for DFU were enrolled in the present study. The inclusion criteria were as follows: (1) patients enrolled in the study met the diagnostic criteria for type 2 diabetes mellitus [1]; (2) patients met the high-risk profile for developing DFU; (3) patients were ready to participate in the study. Patients with high-risk DFU were defined as adult diabetics with at least one of the following [11, 12]: callus, foot deformity or history of previous DFU; an ankle-brachial index (ABI) of ≤ 0.9; diabetic peripheral vascular disease; peripheral sensory neuropathy with loss of protective sensation, or positive results of the 10-g monofilament nylon fiber probe test. The exclusion criteria were as follows: (1) patients with severe liver and kidney disease; (2) patients with severe lower-extremity vascular disease or surgery; (3) patients having the speech and hearing problems, history of drug abuse, and having critical conditions. The foot ulcers were graded according to the Wagner's grade; Wagner I and II grade ulcers were determined as mild ulcer, III grade as moderate ulcer, and IV and V grades as severe ulcer [13].

Methods

All patients were matched in terms of age, gender, and diabetes duration and were randomly divided into the case and control groups (142 patients in each group). The general information of every patient was obtained. Physical examinations and laboratory test were performed. Patients in the control group were given conventional care in hospital, including nursing education on knowledge about diabetes and DFU, and instruction on the right way of washing the foot, the care of foot skin, and appropriate choice of shoes and socks. Patients in the case group were given transitional care in addition to the same method as the control group. The transitional care intervention included the following measures: (1) establishing the health records of patients; (2) carrying out individualized education and instruction on risk factors and problems of foot care in every patient, and developing feasible individualized education goals and foot self-management programs; (3) developing programs about regular return visit, follow-up and the monitoring on diabetes condition and foot diseases; (4) once callosity was found, assistant management of callus was applied in time; (5) evaluating the quality of life, the effect of foot care and self-management at every 3-month, and carrying out the targeted instruction to patients according to the results of evaluation, and helping patients to construct good foot care and self-management behaviors. All patients enrolled were followed up for 2 years.

Assessments of measures

The patients' knowledge of foot care was evaluated with a scoring questionnaire before and after transitional care. The questionnaire included the following [11, 14]: risk factors of DFU, the identification and intervention of risk factors for DFU, prevention for DFU, conventional nursing methods of DFU, monitoring methods of DFU, and the treatments of DFU. The questionnaire score of each patient was calculated, and a higher score indicated better awareness of foot care in patients. The patients' quality of life was evaluated using the diabetes quality of life (DQOL) measure [14]. The lower score indicated a higher quality of life of patients. Fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), blood pressure, blood lipids, foot dorsal artery pulse, and 10-g monofilament nylon fiber test were also examined at every 3 months over a 2-year study period.

Statistical analyses

Continuous variables were expressed as mean ± SD (range) and were compared between two groups using a Student's t test. Categorical data were presented as n (%) and compared using χ^2 or Fisher's exact test. p values < 0.05 were considered to be statistically significant and statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) for Windows.

Results

Demographic characteristics

In 284 patients enrolled, the number of males and females was 85 and 57 in the case group and 78 and 64 in the control group, respectively. The mean age was 58.2 ± 9.8 and 59.3 ± 8.7 years in the case and control groups, respectively. The mean diabetes duration was 9.1 ± 6.7 and 8.7 ± 7.3 years in the case and control groups, respectively. Demographic characteristics of participants were shown in (Table 1). The case and control groups were similar in terms of age, gender, duration of diabetes, body mass index (BMI), family history of diabetes mellitus, smoking, exercise, education, marital status, occupation, complication, and callosity, and their differences were not statistically significant ($p > 0.05$). In treatment of diabetes, metformin (0.5 g each time, with meals), acarbose (50 mg each time, with meals), Novolin R (injecting before meals) + Novolin N (injecting before bedtime), and Novolin 30R (injecting at morning and evening) +

Table 1 Comparison of characteristics of patients in the case and control groups

Characteristics	Case ($n = 142$)	Control ($n = 142$)	t/χ^2 value	p value
Age (years)	58.2 ± 9.8	59.3 ± 8.7	1.000	> 0.05
Gender				
Male	85	78	0.711	> 0.05
Female	57	64		
Duration of diabetes (years)	9.1 ± 6.7	8.7 ± 7.3	0.481	> 0.05
BMI (kg/m^2)	25.3 ± 3.1	24.9 ± 2.8	1.142	> 0.05
Family history of diabetes mellitus				
Yes	48	56	0.970	> 0.05
No	94	86		
Smoking				
Yes	59	66	0.700	> 0.05
No	83	76		
Exercise				
Yes	41	35	0.651	> 0.05
No	101	107		
Education				
Lower than high school diploma	95	105	1.792	> 0.05
Higher than high school diploma	47	37		
Marital status				
Married	114	109	0.521	> 0.05
Unmarried	28	33		
Occupation				
Employed	90	95	0.388	> 0.05
Unemployed	52	47		
Complication				
Cardiovascular diseases				
Yes	57	64	0.713	> 0.05
No	85	78		
Cerebrovascular diseases				
Yes	23	30	1.140	> 0.05
No	119	112		
Diabetic nephropathy				
Yes	17	21	0.493	> 0.05
No	125	121		
Diabetic retinopathy				
Yes	51	45	0.629	> 0.05
No	91	98		
Peripheral artery disease				
Yes	24	20	0.247	> 0.05
No	118	122		
Callosity				
Yes	26	31	0.550	> 0.05
No	116	111		

Lantus (injecting before bedtime) were used to improve glycemic control in the case and control groups. The distribution of treatment programs in the case and control groups is shown in Table 2; the difference between the two groups was not statistically significant ($p > 0.05$).

Comparison of factors levels before and after transitional care intervention

The levels of blood glucose, blood lipids and blood pressure, 10-g monofilament nylon fiber test, foot dorsal artery pulse,

Table 2 The distribution of treatment programs in the case and control groups

Characteristics	Case ($n = 142$)	Control ($n = 142$)
Metformin	35	37
Acarbose	32	26
Metformin + Acarbose	21	28
Novolin R + Novolin N	13	15
Novolin 30R + Lantus	11	13
Metformin + Novolin R + Novolin N	10	7
Acarbose + Novolin R + Novolin N	8	6
Metformin + Novolin 30R + Lantus	6	5
Acarbose + Novolin 30R + Lantus	6	5
χ^2 value	2.983	
p value	> 0.05	

scores of knowledge on foot care, and scores of DQOL were compared between two groups before and after transitional care education (Table 3). At the end of the study, FBG, HbA1c levels, and scores of DQOL in the case and control groups were all decreased significantly ($p < 0.05$), and the scores of knowledge about foot care in both the case and control groups increased significantly ($p < 0.05$), but the above-mentioned indexes in the case group were improved over those in the control group ($p < 0.05$). Systolic and diastolic blood pressures, the positive rate of 10-g monofilament nylon fiber test, and the ratio of abnormal foot dorsal artery pulse in the case group were decreased significantly ($p < 0.05$), and those in the case group were lower than the control group ($p < 0.05$), but the changes in the control group were not significant ($p > 0.05$). However, the levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) did not show any significant difference between the two groups before and after transitional care.

Comparison of incidence, Wagner's grade, and prognosis of DFU before and after transitional care intervention

At the end of the study, a total of 33 (23.2%) cases developed DFU in the control group and 16 (11.3%) cases in the case group; the difference was significant ($p < 0.05$). Among the 16 patients in the case group, 9 (56.2%) cases presented with mild ulcer, 4 (25.0%) with moderate ulcer, and 3 (18.8%) with severe ulcer. Among the 33 patients in the control group, 6 (18.2%) cases presented with mild ulcer, 15 (45.5%) with moderate ulcer, and 12 (36.3%) with severe ulcer. The difference between the case and control groups was significant ($p < 0.05$). Four cases needed amputation in the control group, whereas in the case group, no patients needed amputation, but the difference of rate of amputation between the case and control groups wasn't significant ($p > 0.05$) (Table 4). The four amputees in the control group had the poor glycemic control; every patient's level of FBG was higher than 10.1 mmol/L, and the level of HbA1c was higher than 9.5% during follow-up. Two amputees had preexisting peripheral artery disease, callus, and diabetic nephropathy. One had preexisting peripheral artery disease, deformity, and peripheral neuropathy. One had cardiovascular diseases and developed foot severe infection during follow-up.

Discussion

DFU is one of the most important complications of diabetic patients leading to amputation and is recognized to be a common, complex, and costly problem. Among the patients with diabetes mellitus, the prevalence of DFU is 4 to 10%, and the lifetime incidence may be as high as 25% [15], and the amputation rates of patients with DFU is 12% [16]. As we know, the treatment of DFU is very difficult, so the prevention of DFU is particularly important. For the prevention of DFU, effective management and foot care of patients are the keys. A strategy that includes prevention, patient and staff education, multidisciplinary treatment of foot ulcers, and close monitoring can reduce amputation rates of patients with DFU by 49–85% [11]. How to carry out long-term effective management and nursing intervention to patients with high-risk DFU, and how to help them to establish good self-management behavior and reduce the incidence of DFU? In the present study, we carried out transitional care to prevent DFU.

Transitional care refers to the multiple transfers that patients make between healthcare practitioners and/or care settings during an episode of illness [17, 18]. Transitional care includes pre-hospital discharge planning and immediate post-hospital discharge follow-up at the next location of care [19, 20]. In this study, 284 diabetes patients at high risk for DFU were enrolled, 142 patients (case group) were provided with transitional care and 142 patients (control group) were

Table 3 Comparison of factors for subjects before and after transitional care intervention

Factors	Number	Pre-intervention	Post-intervention	t/χ^2 value	p value
FBG (mmol/L)					
Case	142	10.04 ± 3.21	7.52 ± 2.83	7.017	< 0.05
Control	142	9.87 ± 3.05	8.26 ± 2.67	4.743	< 0.05
t value		0.458	2.266		
p value		> 0.05	< 0.05		
HbA1c (%)					
Case	142	9.31 ± 2.26	7.64 ± 1.84	6.828	< 0.05
Control	142	9.16 ± 2.10	8.31 ± 1.73	3.723	< 0.05
t value		0.579	3.161		
p value		> 0.05	< 0.05		
TC (mmol/L)					
Case	142	5.11 ± 1.16	5.04 ± 1.05	0.533	> 0.05
Control	142	5.08 ± 1.12	5.21 ± 1.03	1.018	> 0.05
t value		0.222	1.377		
p value		> 0.05	> 0.05		
LDL-C (mmol/L)					
Case	142	3.14 ± 1.05	3.09 ± 0.92	0.427	> 0.05
Control	142	3.20 ± 1.13	3.21 ± 1.03	0.078	> 0.05
t value		0.464	1.035		
p value		> 0.05	> 0.05		
HDL-C (mmol/L)					
Case	142	1.14 ± 0.35	1.21 ± 0.42	1.526	> 0.05
Control	142	1.20 ± 0.56	1.25 ± 0.63	0.707	> 0.05
t value		1.083	0.630		
p value		> 0.05	> 0.05		
TG (mmol/L)					
Case	142	1.91 ± 1.26	1.87 ± 1.12	0.283	> 0.05
Control	142	1.86 ± 1.16	1.82 ± 1.03	0.307	> 0.05
t value		0.348	0.392		
p value		> 0.05	> 0.05		
Diastolic blood pressure (mmHg)					
Case	142	80.4 ± 9.6	77.5 ± 8.8	2.654	< 0.05
Control	142	81.6 ± 10.6	79.8 ± 9.3	1.521	> 0.05
t value		1.000	2.141		
p value		> 0.05	< 0.05		
Systolic blood pressure (mmHg)					
Case	142	138.4 ± 17.6	130.5 ± 16.4	3.913	< 0.05
Control	142	140.2 ± 20.3	136.3 ± 19.7	1.643	> 0.05
t value		0.798	1.696		
p value		> 0.05	< 0.05		
10-g monofilament nylon fiber test (positive/negative)					
Case	142	22/120	10/132	5.071	< 0.05
Control	142	21/121	23/119	0.108	> 0.05
t value		0.027	5.795		
p value		> 0.05	< 0.05		
Foot dorsal artery pulse (weakened or absent/normal)					
Case	142	64/78	44/98	5.976	< 0.05
Control	142	62/80	61/81	0.014	> 0.05
t value		0.057	4.367		

Table 3 (continued)

Factors	Number	Pre-intervention	Post-intervention	t/χ^2 value	p value
p value		> 0.05	< 0.05		
Scores of knowledge of foot care					
Case	142	46.8 ± 13.7	78.3 ± 10.1	22.054	< 0.05
Control	142	47.6 ± 14.2	55.4 ± 11.6	5.069	< 0.05
t value		0.483	17.742		
p value		> 0.05	< 0.05		
Scores of DQOL					
Case	142	97.2 ± 18.4	83.1 ± 17.9	6.545	< 0.05
Control	142	98.6 ± 19.3	93.2 ± 18.5	2.407	< 0.05
t value		0.626	4.675		
p value		> 0.05	< 0.05		

provided with general care in hospital, and all patients were followed up for 2 years. The results showed that the incidence of DFU (11.3%) in the case group was significantly lower than that in the control group (23.2%), and the ulcers also were milder (lower Wagner's grade) in the case group than in the control group. The results demonstrate the success and feasibility of transitional care in our view.

In addition, the results of our study also showed a significant difference between average scores of knowledge of foot care and DQOL in the case (78.3 and 83.1) and control (55.4 and 93.2) groups after transitional care intervention. The high foot care scores indicate that the patients have good self-care ability; the good self-care ability may reduce the incidence of foot complications. Previous study showed that the increase of disease complications was associated with fewer scores of foot care, and the diabetic feet care education could increase the self-efficacy of patients and significantly improve the disease complications [10, 21].

Table 4 Comparison of incidence, Wagner's grade, and prognosis of DFU before and after transitional care intervention

Factors	Case	Control	χ^2 value	p value
Foot ulceration				
Yes	16	33	7.128	< 0.05
No	126	109		
Total	142	142		
Wagner's grade				
Mild ulcer	9	6	7.356	< 0.05
Moderate ulcer	4	15		
Severe ulcer	3	12		
Total	16	33		
Prognosis				
Amputation	0	4	0.804	> 0.05
No amputation	16	29		
Total	16	33		

The health-related quality of life (HRQoL) outcomes of diabetic patients have been increasingly recognized as essential and valuable information to obtain in the fields of diabetes management and research [22]. Although the HRQoL of patients are measured usually by generic or diabetes-specific instruments, the latter are more sensitive to diabetic impacts on patients' quality of life than the former [23, 24]. The DQOL is one of the most commonly used diabetes-specific instruments [25]. It contains a total of 46 items: 15 items on life satisfaction, 20 on diabetic impacts, 7 on social/vocational-related worries, and 4 on diabetes-related worries. The scores range from 1 to 5 in each item, and the lower scores indicate the less diabetic impact on quality of life. In the present study, the average scores (83) of DQOL of patients in the case group were lower than those (93.2) in the control group after transitional care intervention; this indicated that transitional care could reduce the diabetic impact on patients' quality of life.

Previous study showed that peripheral arterial and sensory neuropathy disease and structural foot abnormalities consistently play an important role in the development of DFU [26–29]. Our study also showed that the patients in the case group had lower levels of FBG, HbA1c, diastolic blood pressure, and systolic blood pressure, and the better physical examination results of neuropathy (10-g monofilament nylon fiber test) and vasculopathy (foot dorsal artery pulse) than patients in the control group after transitional care intervention. The individualized education and instruction on risk factors and problems of foot care to patients in transitional care program can strengthen the capacity and efficacy of patients about their care. The self-efficacy and self-care abilities of patients can promote them to control the blood pressure and blood sugar, and keep their feet in a good situation. The decline in blood pressure and blood sugar levels, and the good

foot care including wearing suitable footwear, washing feet with warm water every day, trimming toenail regularly, and removing callosity may improve the ischemic and hypoxic state of the nerve tissue of the patients' feet and then improve the peripheral sensory neuropathy. Long-term chronic hyperglycemia and insulin resistance in diabetic patients can enhance the oxidative stress, activate protein kinase C (PKC), and create advanced glycation end products (AGEs), which cause damage to vascular endothelial cells, which further causes atherosclerosis and peripheral vascular disease [30]. The transitional care can promote patients to control the blood sugar, the decline in blood sugar levels may reduce the occurrence of microvascular lesions [31], and then reduce the foot dorsal artery pulse. This suggests that transitional care can reduce the risk factors for DFU.

There were several limitations in this study. First, the sample size might be small, and the follow-up duration might be short. Larger samples and longer follow-up duration were still needed to further clarify the effect of transitional care on DFU. Second, although 10-g monofilament nylon fiber probe test was a simple and practicable method to detect the peripheral sensory neuropathy of patients, its sensibility and consistency were not very satisfactory. Third, although the differences in the type of therapies, preexisting peripheral artery disease, callosity, and comorbid conditions were not statistically significant, these factors were not analyzed in subgroup because of small sample size, so the impacts of these factors on the results of this study needed further study. In conclusion, transitional care on diabetes mellitus and diabetic foot diseases, and correct guidance in foot care was beneficial to the prevention and cure of risk factors of diabetic foot diseases and could reduce the development of DFU and improve the patients' quality of life.

Acknowledgments The authors would like to thank the patients enrolled in the study and all doctors and nurses at the Department of Orthopedics, Beijing Shijitan Hospital.

Compliance with ethical standards

The study was approved by the ethics committee of Beijing Shijitan Hospital, and all patients provided written informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):667–672
https://doi.org/10.1007/s13410-019-00744-z

ORIGINAL ARTICLE

Predictive value of the ratio of homocysteine to serum albumin concentrations in the recurrence of diabetic foot ulcer

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Received: 22 June 2018 / Accepted: 29 April 2019 / Published online: 22 May 2019

Abstract

Objective To investigate the predictive value of the ratio of homocysteine to serum albumin concentrations (Hcy/Alb) in the recurrence of diabetic foot ulcer (DFU).

Methods A total of 210 patients hospitalized due to diabetic foot disease from May 2012, to May 2017 were selected and followed up for one year. The value of Hcy/Alb in predicting the recurrence of DFU was determined using receiver operating characteristic (ROC) curve analysis.

Results Hcy (odd ratio = 1.171; 95% confidence interval (CI) 1.101–1.246) was an independent risk factor for the recurrence of DFU. Alb (odd ratio = 0.848; 95% CI 0.792–0.908) was a protective factor for the recurrence of DFU. The area under the ROC curve of Hcy/Alb for predicting the recurrence of DFU was 0.803 (95% CI 0.742–0.864; $p < 0.01$). When the Hcy/Alb was set at the best cutoff value (0.37), its sensitivity in predicting the recurrence of DFU was 97.60%, and the negative predictive value was 98.93%.

Conclusions The sensitivity and negative predictive value of Hcy/Alb in predicting the recurrence of DFU and the overall coincidence rate are high.

Keywords Diabetic foot · Recurrence · Risk factor · Homocysteine · Serum albumin

Introduction

Diabetic foot (DF) refers to infection, ulcer formation, and/or deep tissue destruction of the lower extremity caused by the combination of diabetic neuropathy and varying degrees of vascular disease in patients with diabetes mellitus (DM) [1]. About 15% of diabetics have at least one foot injury during their lifetime [2]. As the prevalence of DM increases year by year, the incidence of DF cannot be underestimated. The International Diabetes Federation reports that more than 50% of non-traumatic amputations are due to DF each year [3]. As a serious complication of diabetes, DF reduces the quality of life of patients and increases the amputation rate and mortality [4, 5]. It has been confirmed that diabetic foot ulcer (DFU) has a high recurrence rate. Two 18-month follow-up studies have shown it to be 42% [6] and 43% [7]; the 1-year recurrence rate of DFU in the USA is as high as 30% [8]. As DFU has a high recurrence rate with poor prognosis, understanding the risk factors for its recurrence can provide early warning, which can be crucial to the prevention and early treatment of DFU. Homocysteine (Hcy) is a sulfur-containing amino acid produced by methionine demethylation and is an intermediate in the metabolism of methionine and cysteine. A large number of studies have shown that hyperhomocysteinemia is closely related to cardiovascular diseases, nervous system diseases, DM, and their complications [9, 10]. Serum albumin (Alb) concentration is commonly used in clinics for evaluating prognosis; DF patients have low

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Alb levels due to infection and other factors. We analyzed and summarized the data of DFU patients hospitalized and successfully followed up at the Endocrine Diabetic Foot Subspeciality in the Department of Endocrinology at Jinzhou Central Hospital, from May 2012, to May 2017, aiming to find a way to predict the recurrence of DFU as early as possible. The results showed that the ratio of Hcy/Alb is a unique predictive value of the recurrence of DFU.

Methods

Subjects

DFU patients hospitalized at the Endocrine Diabetic Foot Subspeciality in the Department of Endocrinology at Jinzhou Central Hospital, from May 2012, to May 2017, were selected. The inclusion criteria were patients who (1) met the 1999 World Health Organization diagnostic criteria for DM; (2) met the 1999 World Health Organization Working Group on the Diabetic Foot diagnostic criteria for DFU [11]; and (3) had DFU ≥ 1 under the Wagner classification [12]. The exclusion criteria were (1) varicose vein–induced lower extremity venous ulcer, (2) failed follow-up, (3) incomplete information, (4) alcoholism, (5) chronic lung disease, (6) malnutrition (body mass index (BMI) < 16 kg/m^2), and (7) chronic inflammation (white blood cell (WBC) count > 12×10^9/μL). Participants were then grouped according to recurrence into the non-recurrence group (N) and the recurrence group (R). Recurrence of DFU was defined as full-thickness epidermal damage of at least 5 mm diameter occurring at the same site or different sites [7].

Data collection

One self-designed questionnaire for DF patients was used in our survey, through which we collected data on their first admission as the baseline. General information included name, sex, age, agricultural/non-agricultural residency (agricultural refers to an economy which is largely peasant, with most people scraping a living from the land; agricultural population is poorer than the non-agricultural people who make a living from industry or service sector), duration of diabetes, duration of DFU, and smoking status. Physical examination included the blood pressure and BMI. Each patient underwent fasting venous blood sampling on admission or after a 12 h fast, for the determination of fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), fasting C-peptide, triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), Alb, aspartate aminotransferase (AST), blood urea nitrogen, Serum creatinine (Scr), Hcy, white blood cells (WBC), red blood cells (RBC), platelet (Plt) count, and hemoglobin (Hb). Hcy was determined via the enzymatic method and Alb via the bromocresol green method. All determinations were performed through one automatic biochemical analyzer (Hitachi 7600; Hitachi High-Tech Corporation, Tokyo, Japan).

Follow-up

All patients were followed up once a month after discharge, from their first-time hospitalization, for 1 year as outpatients, and those who were rehospitalized were followed up to record the details of recurrence of DFU.

Statistical analysis

SPSS version 17.0 (IBM Corp., Armonk, NY, USA) was used for the data analysis. Normally distributed data were expressed as mean ± standard deviation and analyzed using the *t* test to compare the two samples. Non-normally distributed measurement data were expressed as the median and interquartile range, and the comparison between the two samples was performed using the non-parametric Mann-Whitney test. Count data were expressed as the ratio and percentage, and the inter-group comparison was performed using the χ^2 test. Multivariates were analyzed using logistic regression analysis, and the relative risk among variables was expressed as the odd ratio (OR) represented by the 95% confidence interval (CI). Receiver operating characteristic (ROC) curve analysis was used to assess the predictive value of the ratio of Hcy/Alb for the recurrence of DFU, with $p < 0.05$ considered as statistical significance.

Results

General characteristics

A total of 210 DF patients met the inclusion criteria, including 141 males (67.14%,) and 69 females (32.85%), aged 30–92 years, with a mean ± SD age of 64.66 ± 11.69 years. Sixty-seven patients were peasants (31.90%) and 105 patients were smokers (50%). The duration of DM ranged from 0 to 40 years, with a mean ± SD of 11.85 ± 8.05 years. The duration of DFU ranged from 1 day to 6750 days (IQR, 30 (10, 90) days). Among the 210 patients, 41 cases (19.52%) experienced recurrent DFU. The mean ± SD Hcy level in the patients with recurrent DFU was 21.29 ± 10.64 μmol/L; a total of 28 patients had Hcy level > 15 μmol/L, accounting for 68.29%. The mean ± SD Alb level in the patients with recurrent DFU was 35.09 ± 7.84 g/L, and 20 patients with recurrent DFU (48.78%) had Alb levels less than 35 g/L. The data conforming to normal distribution included age ($p = 0.310$), diabetes duration ($p = 0.763$), DFU duration ($p = 0.879$), BMI ($p = 0.123$), SBP ($p = 0.766$), DBP ($p = 0.601$), Fbg ($p = 0.124$), HbA1c ($p = 0.826$), CPS ($p = 0.240$), TC ($p = 0.666$), HDLC ($p = 0.942$), LDLC ($p = 0.865$), Alb ($p = 0.080$), Ast

Table 1 Comparison of general information and laboratory indexes between the two groups

Item	men (*n*)	Age (years)	Agricultural/non-agricultural residence (*n*)	Smoking ones (*n*)	Duration of DM (years)	Duration of DFU (days)	BMI (kg/m^2)
N (*n* = 169)	115/54	64.88 ± 12.06	59/110	81/88	11.82 ± 8.03	128.89 ± 540.66	24.22 ± 3.11
R (*n* = 41)	26/15	63.73 ± 10.07	8/33	24/17	11.95 ± 8.25	136.56 ± 243.53	24.33 ± 3.95
p	0.571	0.573	0.058	0.296	0.930	0.930	0.849

R, recurrence; *N*, non-recurrence

($p = 0.058$), BUN ($p = 0.154$), Scr ($p = 0.113$), WBC ($p = 0.391$), RBC ($p = 0.266$), Hgb ($p = 0.531$), Plt ($p = 0.921$); factors that did not conform to a normal distribution include TG ($p = 0.012$), Alt ($p = 0.035$), and Hcy ($p < 0.001$). For males, the skewness was − 0.735 and the peakedness was − 1.474; for smokers, the skewness was 0.000 and the peakedness was − 2.019; for the agricultural population, the skewness was 0.782 and the peakedness was − 1.402.

Comparison of general information and laboratory indices

There was no statistical significance in the sex ratio, age, proportion of agricultural residency, quantification of smoking status, duration of diabetes, duration of DFU, BMI, or blood pressure between the two groups ($p > 0.05$). There was no statistical significant difference in the fasting blood glucose, HbA1c, centipoise, triglyceride, total cholesterol, high-density lipoprotein cholesterol, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, serum creatinine levels, and WBC, RBC, Hb, or Plt counts between the two groups ($p > 0.05$). The LDLC level in group R was significantly lower than that in group N ($p = 0.028$). The Hcy level in group R was significantly higher than that in group N ($p < 0.001$), but the Alb level in group R was significantly lower than that in group N ($p < 0.001$) (Tables 1, 2, 3 and 4).

Analysis of risk factors associated with the recurrence of DFU

The dependent variable was the recurrence of DFU and the independent variable was LDLC/Alb/Hcy. A logistic regression was applied in a stepwise manner. Hcy (OR = 1.171; 95% CI 1.101–1.246) was an independent risk factor for the recurrence of DFU, and Alb (OR = 0.848; 95% CI 0.792–0.908) was a protective factor for the recurrence of DFU (Table 5).

Predictive value of Alb, Hcy, and Hcy/Alb ratio for the recurrence of DFU

The ROC curve of the predictive value of Alb for the recurrence of DFU (with sensitivity as the ordinate, 1–specificity as the abscissa, and different Alb values as the cutoff points for diagnosis) revealed an AUC of 0.683 (95% CI 0.591–0.775; $p < 0.001$). When the Alb took the best cutoff value as 35.1 g/L, its sensitivity for predicting the recurrence of DFU was 77.50%, specificity was 51.20%, accuracy was 72.38%, positive predictive value was 35.59%, and the negative predictive value was 86.75% (Fig. 1a).

The ROC curve of the predictive value of Hcy for the recurrence of DFU (with sensitivity as the ordinate, 1–specificity as the abscissa, and different Hcy values as the cutoff points for diagnosis) revealed an AUC of 0.693 (95% CI 0.594–0.792; $p < 0.001$). When the Hcy took the best cutoff value as 21.5 μmol/L, its sensitivity, specificity, accuracy, and positive predictive value for predicting, and the negative predictive value for predicting the recurrence of DFU were 43.90%, 89.90%, 80.95%, 51.42%, and 86.85%, respectively (Fig. 1b).

The ROC curve of the predictive value of Hcy/Alb for the recurrence of DFU (with sensitivity as the ordinate and 1–specificity as the abscissa, as well as different Hcy/Alb values as the cutoff points for diagnosis) revealed an AUC of 0.803 (95% CI, 0.742–0.864; $P < 0.001$). When the Hcy/Alb ratio took the best cutoff value as 0.37, the sensitivity, specificity, coincidence rate, positive predictive value, and the negative predictive value for predicting the recurrence of DFU were 97.60%, 55.00%, 66.33%, 34.48%, and 98.93%, respectively (Fig. 1c).

Table 2 Comparison of general information and laboratory indexes between the two groups

Item	SBP (mmHg)	DBP (mmHg)	Fbg (mmol/L)	HBA1C (%)	Cps (ng/mL)	TG (mmol/L)	TC (mmol/L)
N (*n* = 169)	137.77 ± 22.94	79.88 ± 11.41	11.26 ± 6.60	9.11 ± 2.30	2.55 ± 2.09	1.27 (0.45~9.56)	4.49 ± 1.19
R (*n* = 41)	134.15 ± 25.29	79.88 ± 15.22	10.12 ± 3.91	9.20 ± 2.37	2.24 ± 1.46	1.26 (0.63~2.94)	4.29 ± 1.14
p	0.375	0.999	0.290	0.817	0.369	0.582	0.334

R, recurrence; *N*, non-recurrence

Table 3 Comparison of general information and laboratory indexes between the two groups

Item	LDLC (mmol/L)	HDLC (mmol/L)	Alb (g/L)	Ast (IU/L)	Alt (IU/L)	BUN (mmol/L)
N ($n = 169$)	3.04 ± 0.98	1.18 ± 0.48	39.99 ± 6.76	17.23 ± 9.76	13.00 (2.00~64.00)	7.24 ± 5.00
R ($n = 41$)	2.66 ± 1.02	1.18 ± 0.42	35.09 ± 7.84	21.02 ± 28.60	13.00 (4.00~229.00)	6.57 ± 2.07
P	0.028	0.998	< 0.001	0.157	0.945	0.404

R, recurrence; *N*, non-recurrence

Discussion

The prevalence of DM is increasing year by year, and the risk of developing DFU in DM patients is as high as 25% throughout their lives [5]. DFU has a high recurrence rate. Connor and Mahdi [13] reported that the recurrence rates of DFU in the 1, 3, and 5-year of follow-up were 32.5%, 55.1%, and 66.1%, respectively. This study also showed that the recurrence rate of DFU in the 1-year of follow-up among the 210 patients was 19.52%. For a disease with such a high recurrence rate, indicators for early warning of the recurrence of DFU are imminent. Based on the analysis of 210 DF patients, the comparison revealed that Hcy is an independent risk factor for the recurrence of DFU, while Alb is a protective factor. Further studies may show that the Hcy/Alb ratio has a unique predictive value for the recurrence of DFU.

Hcy, an important intermediate in the metabolism of methionine, is a cytotoxic sulfur-containing nonessential amino acid [14]. Diabetic patients with hyperhomocysteinemia have more severe insulin resistance than those with normal Hcy levels, and every increase in serum Hcy level by 5 μmol/L can increase the mortality by 5 times in the following 5 years [10, 15]. Hcy level is associated with the development of diabetic peripheral neuropathy and diabetic retinopathy and is an independent risk factor for early diabetic nephropathy [16–19]. Gazzaruso et al. [20] have confirmed that Hcy level is associated with DF and that it is a risk factor for lower extremity vascular disease of DF and an independent risk factor for ischemic DF. This study showed that hyperhomocysteinemia is an independent risk factor for the recurrence of DFU. Alb is synthesized by the liver and is the main protein component in normal human serum. It plays an important role in maintaining blood colloid osmotic pressure, in vivo metabolism, and nutrient transport, and can better reflect the nutritional status. Jun et al. [21] found that a decrease in the serum albumin concentration is an independent risk factor for the progression of prediabetes to diabetes. Vincent et al. [22] also proposed that hypoalbuminemia was closely related to the severity of diseases and can reflect the status of various complications to a larger extent, which was one of the most important factors affecting the prognosis of diseases. This study also showed that Alb is a protective factor for the recurrence of DFU, consistent with the above studies. We have also found Alb as a protective factor (OR:0.754 (0.650, 0.874)) in our previous study and Hcy as the risk factor (OR:1.702 (1.376, 2.106)) [23].

Early effective DFU management can reduce amputation rate, mortality rate, recurrence rate, and improve the quality of life [24]. We need to find a simple and cost-saving method with high adaptability and accuracy to predict the recurrence of DFU, so as to improve the prognosis of DFU. In this study, according to the risk factors and protective factors obtained from the regression analysis results for the recurrence of DFU, the AUCs of the ROC curve were 0.6–0.7. We attempted to calculate the Hcy/Alb ratio for each patient and drew the ROC curve for the Hcy/Alb ratio. The AUC then increased significantly to 0.803. Thus, we concluded that the Hcy/Alb ratio for predicting the recurrence of DFU was 0.37; the sensitivity, specificity, positive predictive value, and negative predictive value of DFU recurrence were 97.60%, 55.00%, 34.48%, and 98.93%, respectively. Hcy/Alb has high sensitivity and negative predictive value in predicting recurrence of DFU, but its specificity and positive predictive value are relatively low, the reasons may include Hcy and Alb. Previous studies have shown that genetic factors lead to some enzymatic gene deficiencies in the metabolism of Hcy, which can lead to the increase of Hcy. The concentration of Hcy in males is higher than that in females, and the prevalence of hyperglycemia in male is higher than that in females. When the estrogen level decreases during menopause, the Hcy level increases [25]. With the increase of age, the residence time of B vitamins in vivo decreases, and the activity of Hcy metabolic related enzymes decreases, leading to the increase of Hcy level with the increase

Table 4 Comparison of general information and laboratory indexes between the two groups

Item	Scr (umol/L)	Hcy (umol/L)	WBC ($\times 10^9$/L)	RBC ($\times 10^{12}$/L)	Hgb (g/L)	Plt ($\times 10^9$/L)
N ($n = 169$)	98.02 ± 115.44	14.00 (2.00~42.00)	9.15 ± 4.40	4.22 ± 0.69	127.65 ± 21.24	279.81 ± 126.50
R ($n = 41$)	81.58 ± 38.63	20.00 (8.00~60.00)	10.16 ± 4.63	4.23 ± 0.76	122.24 ± 21.14	291.60 ± 112.38
P	0.370	< 0.001	0.194	0.963	0.145	0.585

R, recurrence; *N*, non-recurrence

Table 5 Analysis of risk factors associated with the recurrence of DFU

Item	B	SE	Wals	df	*p*	Exp (B)	95% CI of Exp (B)	
							Lower limit	Upper limit
Alb	− 0.165	0.035	22.176	1	< 0.01	0.848	0.792	0.908
LDLC	− 0.241	0.204	1.400	1	0.237	0.786	0.527	1.172
Hcy	0.158	0.032	24.867	1	< 0.01	1.171	1.101	1.246

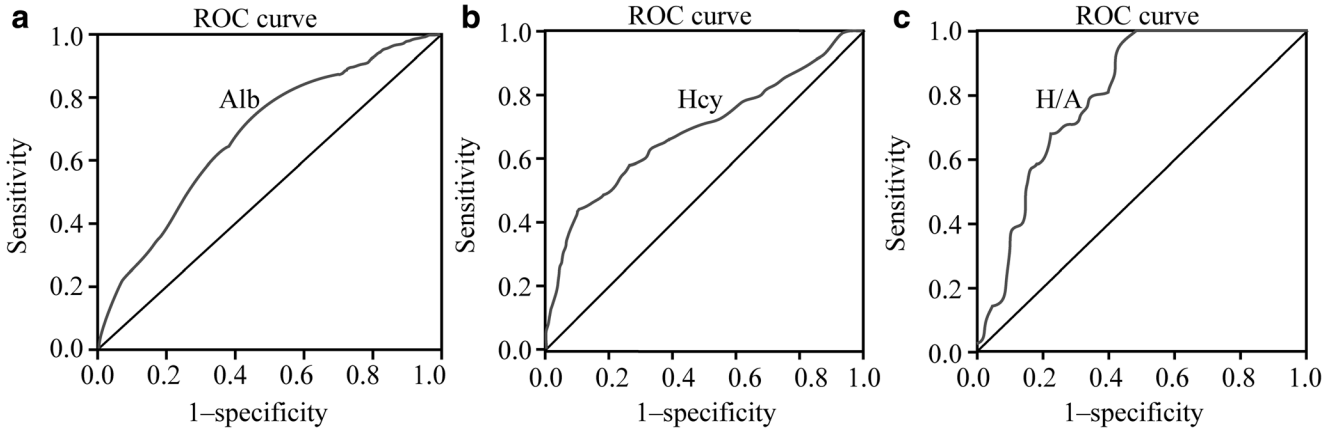

Fig. 1 **a** Predictive value of Alb for the recurrence of DFU, the AUC is 0.683 (95% CI 0.591~0.775, $p < 0.01$). **b** Predictive value of Hcy for the recurrence of DFU, the AUC is 0.693 (95% CI 0.594–0.792, $p < 0.01$). **c** Predictive value of Hcy/Alb ratio for the recurrence of DFU, the AUC is 0.803 (95% CI 0.742–0.864, $p < 0.01$)

of age [26, 27]. All the patients in this study denied the history of hereditary diseases and had no history of B vitamins and folic acid before admission. There was no significant difference in gender and age between non-recurrence group and recurrence group. Therefore, the possibility of positive predictive value decreasing could be excluded which may be caused by the increase of Hcy/Alb with false increase of Hcy. DF patients often suffer from low Alb disease due to inadequate intake of high-quality protein due to calorie control. Previous studies have shown that the level of HbA1C in DF patients is higher than that in non-DF patients, which is one of the risk factors of DF. The level of HbA1c in DF amputated patients is higher than that in non-amputated patients, which is also one of the risk factors of DF amputation [28]. In this study, 55.71% (117/210) patients with HbA1c > 7%, which is consistent with the previous studies. Better glycemic control can significantly improve the prognosis of DFU [24], which also leads to the occurrence of hypoAlb in some patients. In this study, 40–80% of DF patients have got infected [29], 59.04% (124/210) of DF patients had gangrene, and 31.90% (67/210) of DF patients had higher WBC, which was basically consistent with the previous studies. Infection consumed Alb, lower Alb level limited the activity of antibody synthesis enzymes, reduce the body's immunity, and aggravate the infection. These factors caused many DF patients had hypoAlb the ratio of Hcy/Alb increased, which may be the main reason for the low specificity and positive predictive value. The patients in this study were all confirmed DF patients, and could not exclude those with poor glycemic control and DFU infection, which may cause the specificity and positive predictive value of Hcy/Alb low.

As a predicting method, the sensitivity and negative predictive value was more important than the specificity and positive predictive value, so as to reduce the rate of missed diagnosis. The Hcy/Alb missed detection rate of DFU recurrence was only 2.43%, which meant the Hcy/Alb had high clinical significance. However, it was also found that the misdiagnosis rate of predicting DFU recurrence by Hcy/Alb was 44.97%. Therefore, more examinations should be combined with Hcy/Alb. This is also one of the limitations of this study. Secondly, this study is a single center. The collected cases are from the western part of Liaoning Province, China, where the residents had low awareness of diabetes mellitus, as well as diabetes foot. Third, the follow-up time is short, which may need to be confirmed by multicenter studies and longer follow-up.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ethics Committee of Jinzhou Central Hospital, No. 2018-NFM-021) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):673–679
https://doi.org/10.1007/s13410-019-00750-1

ORIGINAL ARTICLE

Effects of diabetic foot infection on vascular and immune function in the lower limbs

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Received: 4 January 2019 / Accepted: 2 May 2019 / Published online: 30 May 2019

Abstract

Object The study investigated the effects of diabetic foot infection on vascular and immune function in the lower limbs.

Methods Seventy-two patients with diabetic foot infection were included in the infected group, while 64 diabetic patients without infection were selected as the control group. Hemodynamic parameters and vascular endothelial function of the dorsalis pedis artery were assessed by color Doppler ultrasonography. Enzyme-linked immunosorbent assay was used to determine the serum levels of interleukin 6 (IL-6), IL-17, tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), and high mobility group box 1 protein (HMGB1). Western blotting was used to quantify expression levels of toll-like receptor 4 (TLR4) and nuclear transcription factor kappa B (NFκB) in human peripheral blood mononuclear cells (PBMC).

Results Compared with the control group, the intima-media thickness and peak systolic velocity of the infected group were increased (both $p < 0.05$), while the inner vascular diameter, blood flow volume, endothelium-dependent dilation, and endothelium-independent dilation were decreased (all $p < 0.05$). Compared with the control group, the serum levels of IL-6, IL-17, TNF-α, CRP, and HMGB1, and the expression levels of TLR4 and NFκB in PBMC were significantly increased in the infected group (all $p < 0.001$).

Conclusion Thus, diabetic foot infection is associated with vascular and immune dysfunction in the lower limbs, possibly in relation to the activation of the HMGB1/TLR4/NFκB signaling pathway.

Keywords Diabetic foot infection · Lower extremity vascular function · Immunity · High mobility group box 1 protein · Toll-like receptor 4 · Nuclear transcription factor kappa B

Introduction

Diabetes mellitus is a common chronic disorder of glucose and lipid metabolism. Global factors such as the worldwide aging of the population and the overall improvement of living environments have driven a significant increase in the prevalence of diabetes; it is estimated that over 500 million people in the world will have been diagnosed with diabetes by the year 2030 [1]. With the extension of the course of diabetes, a series of diabetic complications are expected to rise in prominence, with diabetic foot being one of them. Sensory and autonomic nerve dysfunctions are frequent in diabetic patients, often manifested as impaired regulation of temperature, perspiration, and blood flow in the skin of the feet. In conjunction with repeated external mechanical stress, these factors favor the development of ulcers and subsequently, diabetic foot [2]. Approximately 70% of these cases are complicated with infection, with the characteristics of long treatment cycles or becoming refractory [3]. Indeed, infection is an important factor for poor prognosis in patients with diabetic foot.

Vascular endothelial dysfunction is the main pathophysiological mechanism of diabetic foot, mainly related to the hyperglycemia-induced reduction of vasodilation factors such as nitric oxide, increased production of vasoconstrictors such as endothelin, excessive production of inflammatory factors, imbalance of oxidative stress, and endothelial cell apoptosis [4, 5]. Research has shown the severity of lower limb vascular disease to be closely related to infection in diabetic foot, with active infection management being the key to controlling the progress of foot ulcers [6, 7]. However, few studies have explored the effects of infection on lower limb vascular function in patients with diabetic foot, which was of great significance for exploring the mechanisms of infection in diabetic foot and promoting targeted research on the treatment of this disease.

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Immune dysfunction is also an important pathophysiological component of diabetic foot, manifested as excessive secretion of inflammatory factors and recruitment of inflammatory cells. And meanwhile, infection majorly aggravated inflammation [8]. Studies have found the activation of the HMGB1/TLR4/NFκB signaling pathway triggers the massive secretion of inflammatory factors in bacterial infection. Notably, Sun et al. [9] found serum levels of HMGB1, TLR4, TNF-α, and IL-6 were significantly increased in animal models of sepsis. Inhibition of this pathway could reduce the secretion of inflammatory factors, improve immune function, and prevent damage to multiple organs. However, the involvement of the HMGB1/TLR4/NFκB signaling pathway remains unclear in the context of diabetic foot infection. Therefore, in this study, we evaluated the serum levels of HMGB1 and the expression of TLR4/NFκB in peripheral blood mononuclear cells (PBMC) from patients with diabetic foot infection.

Materials and methods

General data

Seventy-two patients with diabetic foot infection who were treated in The First People's Hospital of Wujiang District of Suzhou from June 2015 to March 2018 were included in the infection group, and 64 non-infected diabetic foot patients were selected as the control group. General clinical data were collected from both groups, including age, gender, body mass index (BMI), fasting blood glucose, urea nitrogen, 24-h urinary protein, and white blood cell (WBC) count.

Inclusion and exclusion criteria

Inclusion criteria in accordance with the 2012 clinical guidelines of the American Infectious Diseases Association for the diagnosis of diabetic foot infection, the inclusion criteria were (1) a clear history of diabetes; (2) clinical manifestations of diabetic foot: dryness without sweating, stinging, burning, numbness, symptoms of neuropathy, and loss of sensation; ischemic manifestations of skin malnutrition, muscle atrophy, hypothermia, hyperpigmentation, and weak or absent pulses; (3) clinical symptoms of diabetic foot infection: local swelling or induration, erythema with extension > 0.5 cm, local tenderness or pain, localized increase in temperature or purulent secretion; and (4) confirmation by identification of pathogens in the secretions from diabetic foot ulcers [10].

Exclusion criteria include (1) foot ulcers and infections of other etiologies, such as long-term chemotherapy or glucocorticoid application, and (2) patients with liver or kidney dysfunction, tumors, autoimmune diseases, cardiovascular and cerebrovascular diseases, and other disorders.

Hemodynamic testing

Philips iU22 equipment (probe frequency 9–12 MHz) was used to assess the hemodynamic parameters of the dorsal foot artery of all patients, including intima-media thickness (IMT), peak systolic velocity (PSV), inner vascular diameter (D), and blood flow volume (V). Parameters were measured with patients in quiescent conditions, sitting and stretching the back of the foot.

Testing of vascular endothelial function

All patients had their vascular endothelial function tested according to the method described by Celermajer et al. [11]. The inner diameter of the dorsal foot artery (D_0) was measured by color Doppler ultrasound when patients were at rest. Then, the cuff was used to pressurize the ankle to 260 mmHg and got deflated after 5 min. Next, the inner diameter of the dorsal foot artery (D_1) was measured after 60 s. After 5 min of rest, 0.5 mg of nitroglycerin was given sublingually, and the internal diameter of the dorsal foot artery (D_2) was measured after 3 min. Endothelium-dependent dilation (EDD) and endothelium-independent dilation (EID) were calculated by the following formulas:

$$\mathrm{EDD} = (D_1 - D_0)/D_0 \times 100\%$$

$$\mathrm{EIDD} = (\mathrm{D_2} - \mathrm{D_0})/\mathrm{D_0} \times 100\%$$

Elisa

The 5 ml of venous blood was drawn from each patient. Samples were allowed to stand at room temperature for 20 min and then were centrifuged at 12,000 rpm for 15 min; then, the supernatant was taken. IL-6 (Jingmei, JM-03204H1), IL-17 (Jingmei, JM-05071H1), TNF-α (Jingmei, JM-03277H1), CRP (Jingmei, JM-03290H2), and HMGB1 (Shino-Test Corporation, 326054329) in the serum were measured with ELISA.

Western blot

The human PBMC separation fluid (Solarbio, P8610) was carefully added to a mixture of 1 ml freshly heparin-treated blood with 1 ml of normal saline, followed by centrifugation at 400 rpm for 20 min. Then, the solution was divided into four layers—a plasma layer, a milky-white mononuclear cell layer, a transparent separation liquid layer, and a red blood cell layer, from top to bottom. Mononuclear cells were carefully pipetted

Table 1 Comparison of general information

Index	Control group ($n = 64$)	Infected group ($n = 72$)	t/χ^2	p
Age (year)	53.64 ± 8.13	54.06 ± 8.39	0.296	0.768
Gender (male/female)	36/28	43/29	0.168	0.682
Body mass index (kg/m^2)	22.64 ± 3.41	21.89 ± 3.65	1.234	0.220
Fasting blood glucose (mmol/l)	7.85 ± 1.49	8.28 ± 1.96	1.426	0.156
Blood urea nitrogen (mmol/l)	7.21 ± 2.59	8.09 ± 2.71	1.930	0.056
24-h urinary protein (g/l)	1.09 ± 0.37	1.21 ± 0.42	1.758	0.081
White blood cell (10^9/l)	4.27 ± 0.82	10.15 ± 4.23	10.940	< 0.001

into 5 ml normal saline, and they were centrifuged at 400 rpm for 20 min. After washing twice, human PBMC were obtained.

A total of 100 μl of protein lysis buffer (Beyotime, P0013) was added to 10^6 cells. After fully lysed, the cells were centrifuged at 12,000 rpm for 5 min, and the supernatant was taken for BCA protein quantification (Beyotime, P0012). Next, polyacrylamide gel electrophoresis was performed using a total protein of 20 μg to obtain the target protein. Transferred to a polyvinylidene fluoride film, the target protein was blocked in 5% bovine serum albumin for 2 h at room temperature, and then incubated overnight at 4 °C with anti-TLR4 antibody (Abeam, ab13556, 1:1000), anti-NFκB antibody (Abcam, ab32360, 1:1000), or anti-GAPDH antibody (Abcam, ab8245, 1:5000), respectively. After washing, the target protein was incubated at room temperature for 1 h with horseradish peroxidase–conjugated goat anti-rabbit secondary antibodies (Proteintech, SA00001–2). After washing again, ECL chromogenic liquid (Beyotime, P0018) was added dropwise, and the Gel imager (Bio-rad, Gel Doc XR+) was used for exposure and photography. The gray value of the straps was measured using Image-Pro Plus 6.0, with the gray value ratio of the target protein in the control group to the GAPDH protein set to 1 [12].

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software. Measurement data was expressed as mean ± standard deviation; comparisons of measurement data between two groups were performed using t test. Enumeration data were expressed as the case number of patients, and comparisons of enumeration data between the two groups were performed with the chi-squared (χ^2) test. Results were considered statistically significant when $p < 0.05$.

Results

Comparison of general data

No significant differences were found in age, gender, BMI, fasting blood glucose, urea nitrogen, and 24-h urinary protein between the two groups (all $p > 0.05$); however, the WBC count was significantly higher in the infected group than the control group ($p < 0.001$) (Table 1).

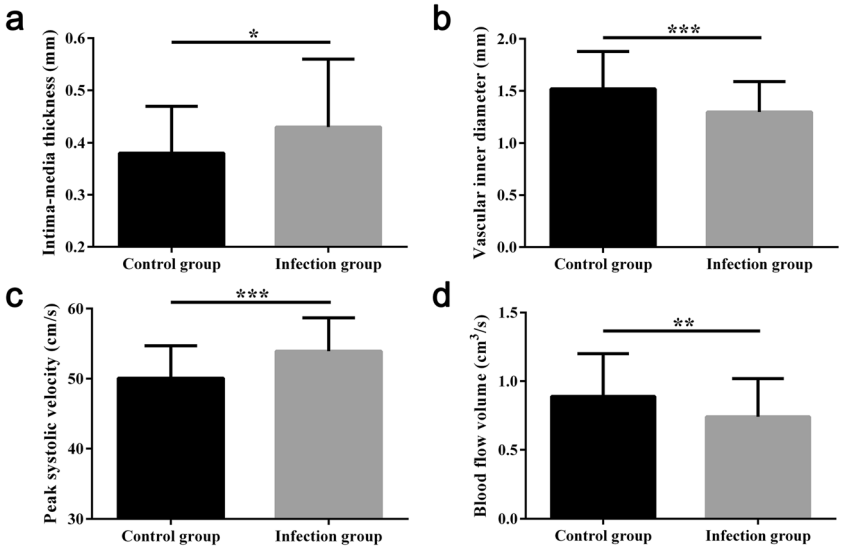

Fig. 1 Comparison of hemodynamic parameters of the dorsal foot artery. **a** Intima-media thickness. **b** Vascular Inner diameter. **c** Peak systolic velocity. **d** Blood flow volume. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

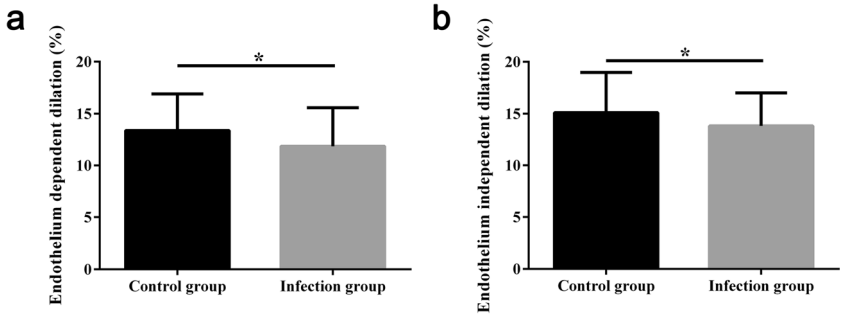

Fig. 2 Comparison of vascular endothelial function in the dorsal foot artery. **a** Endothelium-dependent dilation. **b** Endothelium-independent dilation. $^{*}p < 0.05$

Comparison of hemodynamic parameters of the dorsal foot artery

As shown in Fig. 1, compared with the control group, the infected group showed increased IMT (0.38 ± 0.09 mm vs. 0.43 ± 0.13 mm) and PSV (50.07 ± 4.62 cm/s vs. 53.91 ± 4.77 cm/s), as well as decreased *D* (1.52 ± 0.36 mm vs. 1.30 ± 0.29 mm) and *V* (0.89 ± 0.31 cm^3/s vs. 0.74 ± 0.28 cm^3/s) in the dorsal foot artery (all $p < 0.05$).

Comparison of vascular endothelial function in the dorsal foot artery

Compared with the control group, the infected group had significantly lower EDD (13.37 ± 3.54% vs. 11.86 ± 3.71%) and EIDD (15.11 ± 3.87% vs. 13.82 ± 3.20%) in the dorsal foot artery (both $p < 0.05$) (Fig. 2).

Comparison of serum levels of inflammatory cytokines between the two groups

In comparison with the control group (IL-6, 18.83 ± 3.52 ng/l; IL-17, 14.45 ± 3.01 ng/l; TNF-α, 15.43 ± 4.61 ng/l; CRP, 2.17 ± 0.84 mg/l), serum levels of IL-6 (24.01 ± 4.55 ng/l), IL-17 (21.68 ± 3.84 ng/l), TNF-α (22.67 ± 5.59 ng/l), and CRP (4.73 ± 1.56 mg/l) were significantly higher in the infected group (all $p < 0.001$) (Fig. 3).

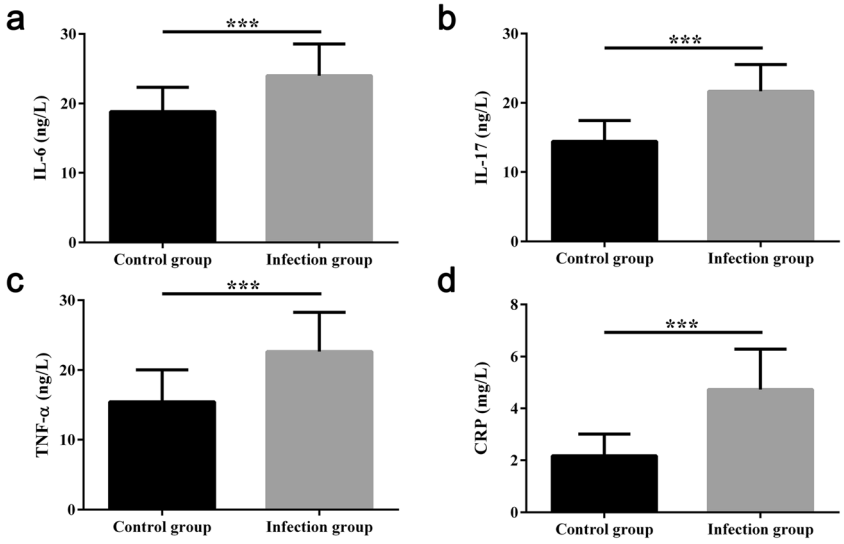

Fig. 3 Comparison of the serum levels of inflammatory factors. **a** Interleukin-6. **b** Interleukin-17. **c** Tumor necrosis factor-α. **d** C-reactive protein. $^{***}p < 0.001$

Comparison of serum HMGB1 levels

As shown in Fig. 4, levels of HMGB1 in the serum were significantly higher in the infected group compared with the control group (97.40 ± 16.08 μg/l vs. 78.46 ± 15.22 μg/l; $p < 0.001$).

Comparison of TLR4 and NFκB expression in peripheral blood mononuclear cells

Expression levels of TLR4 and NFκB in PBMC were higher in the infected group than those in the control group (1.84 ± 0.33 vs. 1.00 ± 0.18 and 2.15 ± 0.47 vs. 1.00 ± 0.24, respectively; both $p < 0.001$) (Fig. 5).

Discussion

Endothelial dysfunction is an early critical event involved in the vascular complications of diabetes, promoting the migration and proliferation of vascular smooth muscle cells, blood stasis, migration of lymphocytes to the endothelium, and

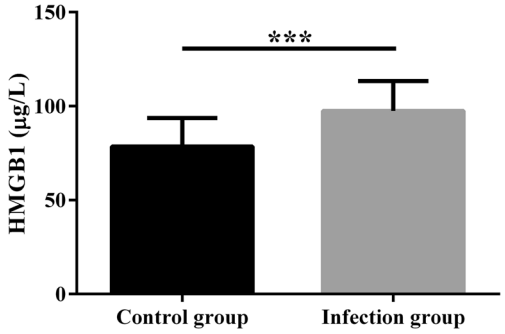

Fig. 4 Comparison of serum HMGB1 levels. $^{***}p < 0.001$. HMGB1, high mobility group box-1 protein

eventually, irreversible vascular disease. Keeping long-term hyperglycemia is the major factor related to endothelial cell injury [13–15]. Xing et al. [16] have reported high glucose can inhibit endothelial cell growth, promote the generation of lactate dehydrogenase and malondialdehyde, enhance caspase-3 activity, induce the apoptosis of endothelial cells, and reduce their capacity for migration and angiogenesis. On the other hand, infection, a well-known risk factor for acute injury of endothelial cells, usually causes vascular barrier dysfunction as seen in disorders of the blood-brain barrier, the blood-gas barrier, and others. Furthermore, repeated infection promotes vascular remodeling through chronic inflammation, leading to decreased blood flow, ischemia, and hypoxia [17, 18]. The purpose of this study was to explore the effects of diabetic foot infection on vascular and immune function in the lower limbs, including two aspects. First, the vascular function was reflected by intima-media thickness, peak systolic velocity, inner vascular diameter, blood flow volume, endothelium-dependent dilation, and endothelium-independent dilation. Next, the serum levels of inflammatory cytokines and the expression of the HMGB1/TLR4/NFκB signaling pathway "reflected" immune function of the lower limbs, rather than "determined" or "equaled" immune function. The purpose of detecting HMGB1/TLR4/NFκB signaling pathway was to further explore the mechanism of a large release of inflammatory cytokines, which also belonged to the category of immunity. In addition, the part of the mechanisms of immune disorder was discussed to some extent, which further confirmed the conclusion of this study. In this study, we found the IMT and PSV of the dorsal foot artery were higher and the *D* and *V* were lower in the infected group than in the control group, indicating infection could further aggravate deterioration of the vascular structure, elasticity, and compliance.

Patients with diabetic foot often suffer immune dysfunction, mainly manifested as a chronic inflammatory state [8]. Although the migration of inflammatory cells and the secretion of inflammatory mediators promote infection control and wound healing in the early stages of ulcer formation, a high-glucose pathological environment leads to dysfunction of immune cells and hypersecretion of inflammatory messengers, especially TNF-α and IL-6. Khanna et al. [19] have reported there were, in the wounds of diabetic mice, significantly increased apoptosis rate of macrophages, decreased phagocytosis, and hypersecretion of TNF-α and IL-6 together with inhibition of anti-inflammatory cytokines IL-10 and TGF-β1, which was further confirmed in diabetic patients. In this paper, we explored whether infection can further aggravate the immune alterations found in patients with diabetic foot. We found the serum levels of inflammatory factors were significantly higher in patients with combined infection, indicating potentiated inflammation caused by infection may contribute to the poor prognosis of this complication.

HMGB1 is a DNA-binding nuclear protein involved in the regulation of gene transcription. Under the stress of infection, trauma, and burns, it is released from the nucleus into the

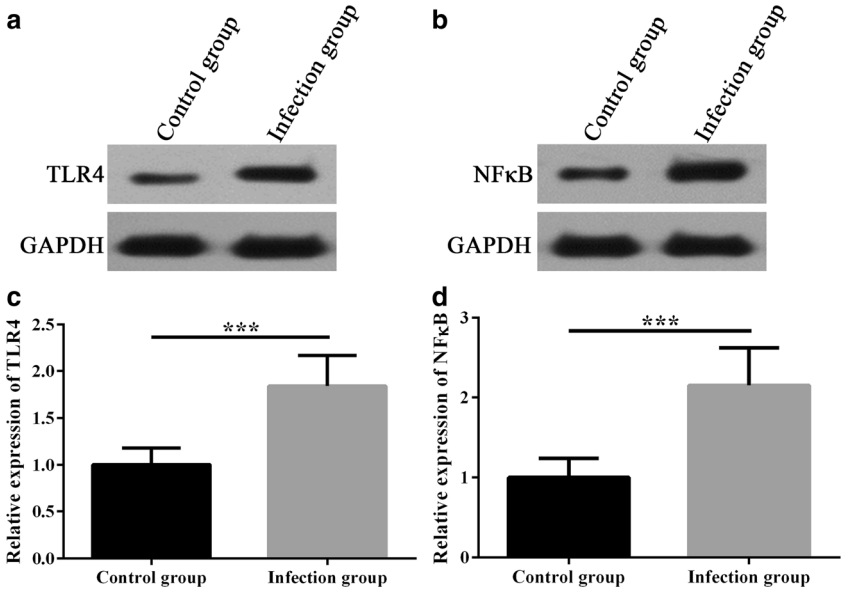

Fig. 5 Comparison of TLR4 and NFκB expression in peripheral blood mononuclear cells. **a** Expression of TLR4. **b** Expression of NFκB. **c** Comparison of gray values of TLR4. **d** Comparison of gray values of NFκB. $^{***}p < 0.001$. TLR4, toll-like receptor 4; NFκB, nuclear transcription factor kappa B; GAPDH, Glyceraldehyde-3-phosphate dehydrogenase

extracellular fluid, where it can recruit and activate inflammatory cells. HMGB1 levels have been closely related to disease severity, so it is often used as a marker to evaluate the disease status [20–22]. Recent studies suggested HMGB1 played a key pathologic role in diabetes. Yan et al. [23] found HMGB1 was highly expressed in diabetic patients and positively correlated with TNF-α, IL-6, and CRP. In addition, Yang et al. [24] proposed HMGB1 could promote migration of NFκB to nucleus and activation of the downstream inflammatory signaling pathway, which is a trigger for hyperglycemia-induced proliferation and migration of vascular smooth muscle cells as well as for vascular endothelial dysfunction, stenosis, and obstruction. Furthermore, infection has been observed to promote massive release of HMGB, with Elfeky et al. [25] suggesting hypersecretion of HMGB1 from RAW 264 macrophages may play a key role in lipopolysaccharide-induced sepsis. Meng et al. [26] have also reported that HMGB1 can activate the TLR4/NFκB signaling pathway and induce great release of inflammatory factors, while blocking HMGB1 expression with RNA-interfering technology alleviated infection-induced inflammation. Although HMGB1 undoubtedly plays an important role in diabetes and infection, it is not clear whether infection can further potentiate HMGB1 expression in patients with diabetic foot. In this paper, we assessed serum HMGB1 levels and markers of TLR4/NFκB activation, finding that infection potentiated both of these parameters. Therefore, they may be key pathophysiological mechanisms underlying the inflammatory state and poor prognosis typical of these patients.

Although we have managed to preliminarily discuss the effect of diabetic foot infection on the vascular and immune function in the lower limbs, some limitations remain: (1) this study did not evaluate differences effect among varying types of bacteria; (2) other factors previously linked to disturbances of vascular function were not assessed in this context, including nitric oxide levels, excessive production of endothelin, and apoptosis of endothelial cells [4]; (3) the involvement of the activation of HMGB1/TLR4/NFκB signaling pathway in the inflammation found in diabetic foot infections should be verified in vitro and in animal models in the future.

Conclusions

We suggested diabetic foot infection may lead to vascular and immune dysfunction in the lower limbs, which may be related to activation of the HMGB1/TLR4/NFκB signaling pathway.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):680–684
https://doi.org/10.1007/s13410-019-00724-3

ORIGINAL ARTICLE

Prevalence and clinical characteristics of individuals with newly detected lean diabetes in Tamil Nadu, South India: a community-based cross-sectional study

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Received: 21 June 2018 / Accepted: 10 February 2019 / Published online: 26 February 2019

Abstract

Background and objectives Lean diabetes is an entity that has been observed to be higher in Asian populations. The estimates of the burden of lean diabetes in India are mainly from hospital-based studies. This study reports the prevalence of lean diabetes among individuals with newly detected diabetes, from Vellore, Tamil Nadu, South India.

Methods A cross-sectional WHO STEPS survey was conducted among adults aged 30–64 years, in one rural block and 48 urban wards, in Vellore. Physical and anthropometric parameters were assessed in addition to fasting lipid profile and plasma glucose. Newly detected diabetes was defined as fasting plasma glucose ≥ 126 mg/dl and lean diabetes as non-ketotic diabetes mellitus, without clinical features to suggest pancreatic diabetes, with a body mass index (BMI) < 18.5 kg/m^2.

Results Among 3445 rural and 2019 urban subjects, the proportion of lean diabetes among 280 subjects (146 rural, 134 urban) with newly detected diabetes was 5.5%, 95% CI: 1.7–9.3% (eight subjects) and 1.5%, 95% CI: 0–3.6% (two subjects), in the rural and urban areas respectively. The proportion of those with a normal BMI (18.5–22.9 kg/m^2) was 25.3% and 18.7% in the rural and urban populations, while 69.2% and 79.9% had a BMI ≥ 23 kg/m^2. Those with lean diabetes were more likely to be older, illiterate, and involved in manual labor, than those with non-lean diabetes ($p < 0.05$).

Conclusion The prevalence of lean diabetes was low (5.5% of newly detected rural diabetes, 1.5% of newly detected urban diabetes) in Vellore, South India. Further documentation of the burden of this condition across India is needed to assess the public health implications for prevention and control.

Keywords Lean diabetes · Prevalence · Population · Burden

Introduction

The rising prevalence of type 2 diabetes mellitus in low and middle-income countries over the last few decades has led to the emergence of a major public health problem [1, 2]. Risk factors such as obesity and unhealthy diets are also increasing, and the relationship between increasing weight and diabetes is well established [2]. However, type 2 diabetes among those with a low body mass index (BMI) is suspected to be higher in Asian and African populations as compared with others, in whom obesity is a more common risk factor [3, 4]. Lean diabetes has been defined as BMI < 18.5 kg/m^2 or as Ketosis Resistant Diabetes of the Young (KRDY) with a BMI < 18.0 kg/m^2, while studies from high income countries have taken higher cutoff values ranging from 18.0–24.9 kg/m^2 [4–6]. Although the exact etiopathology is still unknown, a large-scale analysis of data from multiple genome wide association studies has shown that diabetes in the non-obese may be related to genetic factors, which make individuals susceptible to developing type 2 diabetes, irrespective of obesity and lifestyle factors [7]. Knowledge regarding the burden of disease is essential to judge the public health importance of the condition. Although hospital-based studies of lean diabetes among those with suspected type 2 diabetes have been published, population level burden of this condition in India is not well documented [5, 8]. A study from a diabetes center in urban Chennai, Tamil Nadu, estimated that 3.5% of patients

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with diabetes had lean diabetes (BMI < 18.5 kg/m^2) [5]. A similar result was seen in a hospital-based study from Manipur where 3.9% of those with newly detected diabetes had a BMI < 19.0 kg/m^2 [8]. Given the paucity in population level prevalence of lean diabetes from South Asia, this study estimates the proportion of lean individuals (body mass index < 18.5 kg/m^2) aged 30–64 years with diabetes, in a rural and urban population from Vellore, Tamil Nadu, Southern India.

Methodology

A WHO STEPS cross-sectional survey was carried out in Vellore, in 2011–2012, among adults aged 30–64 years, in a rural block (Kaniyambadi) and in Vellore city [9, 10]. Nine randomly selected villages from the rural block and one randomly selected street in each of 48 urban wards were selected for this study. All adults aged 30–64 years in the nine villages were eligible for the study, while in the selected urban streets, adults aged 30–64 years from the first 40 households were invited for the study. Questionnaire-based data was collected at the homes of the participants by trained field workers, after obtaining consent, while physical and biochemical measurements were collected at a designated clinic, after ensuring 8 h of overnight fasting. The weight of the participants was checked with a digital weighing machine (Essae, Bangalore, India) and height with a SECA 13 (Hamburg, Germany) stadiometer. Further details of this study have been published previously [10]. Fasting plasma glucose (FPG) was used to screen for diabetes, as recommended for WHO STEPS surveys [9]. Biochemical tests were done in an accredited laboratory which is a part of the External Quality Assurance System (EQAS) of a tertiary health institution.

Hypertension was defined as blood pressure ≥ 140/90 mmHg or on medication, diabetes as FPG ≥ 126 g/dl or on medication, and dyslipidemia as on medication or presence of one of the following:

> total cholesterol ≥ 200 mg/dl, triglycerides ≥ 180 mg/dl, low HDL (< 40 mg/dl for males, < 50 mg/dl for females), or LDL cholesterol ≥ 100 mg/dl [9, 11].

Lean diabetes was defined as those with diabetes and a BMI of < 18.5 kg/m^2 [5].

Results

Of the 5464 participants (3445 rural, 2019 urban) aged 30–64 years, 510 (9.3%, 95% confidence interval CI: 8.5–10.5%) were on medications for diabetes (rural 5.9%, 95% CI: 5.1–6.7%; urban 15.3%, 95% CI: 13.7–16.9%). Of the remaining 4954, 90.3% (4474) were screened for diabetes. The prevalence of newly detected probable type 2 diabetes (FPG of ≥ 126 mg/dl) was 6.3% (rural 5.0%, 95% CI: 4.2–5.8%; urban 8.6%, 95% CI: 7.1–10.1%).

Of those who were newly detected to have diabetes (Table 1), 10 out of 280 (3.6%, 95% CI: 1.4–5.8%) had a BMI < 18.5 kg/m^2 (rural 5.5%, 95% CI: 1.7–9.3%; urban 1.5%, 95% CI: 0–3.6%). The proportion of those with newly detected diabetes and BMI of 18.5–22.9 kg/m^2 was 22.1% (rural 25.3%, urban 18.7%), while the remaining 74.3% (rural 69.2%, urban 79.9%) had BMI ≥ 23 kg/m^2. The proportion of those with newly detected type 2 diabetes with a BMI ≥ 25 kg/m^2 was 58.2%.

The overall population prevalence of lean diabetes (newly detected or previously diagnosed diabetes and with BMI < 18.5 kg/m^2) was only 0.6% (95% CI: 0.3–0.9%) in the rural area and 0.3% (95% CI: 0.1–0.5%) in the urban area. However, the overall prevalence of diabetes was 11.2% (95% CI: 10.1–12.3%) in the rural sample and 23.6% (95% CI: 21.7–25.6%) in the urban sample.

Physical and biochemical characteristics were compared between those with lean diabetes and non-lean diabetes, as well as those without diabetes, in 4472 subjects (280 with newly detected diabetes and 4192 without diabetes) for whom complete data was available, Table 1. Of 280 with newly detected diabetes in this study, 146 were from the rural area, while of those with no diabetes, 2757 were from the rural area, Table 1.

The mean BMI of those with newly detected lean diabetes was 16.6 kg/m^2 (SD 1.7 kg/m^2), as compared with 26.4 kg/m^2 (SD 4.1 kg/m^2) for those with newly detected non-lean diabetes and 23.8 kg/m^2 (SD 4.8 kg/m^2) for those without diabetes. Individuals with newly detected lean diabetes were older than others with non-lean diabetes and those without diabetes (Table 1). They were also more likely to be involved in manual labor and less likely to be literate than those with non-lean diabetes ($p < 0.05$). Although the number of those with lean diabetes is too small to make conclusions, most of those with lean diabetes (8 out of 10) were from the rural area, Table 1.

The only difference in physical/metabolic parameters between those with newly detected lean diabetes and non-lean diabetes was that the average diastolic blood pressure was lower for those with lean diabetes (lean diabetes 73.8 mmHg, SD 14 mmHg vs. non-lean diabetes 82.5 mmHg, SD 13.5 mmHg), p value for t test = 0.046.

The mean FPG in those with lean diabetes was 215.7 mg/dl (SD 72.1 mg/dl) as compared with 186.1 mg/dl (SD 74.7 mg/dl) for those with non-lean diabetes, p value for t test = 0.219. As compared with the general population of lean individuals without diabetes, those with lean diabetes were more likely to have hypertension (lean diabetes 30.0% vs. lean normal 6.1%, chi-square p value 0.023) and a higher mean total cholesterol (lean diabetes 193 mg/dl, SD 49.8 mg/dl vs. lean normal 162.5 mg/dl, SD 43.9 mg/dl, p value for t test = 0.029). Other lipid parameters were not significantly different between the lean-diabetic population and others ($p > 0.05$).

Table 1 Socio-demographic and behavioral characteristics of those with newly detected lean diabetes compared with others with and without diabetes

Characteristic (means with standard deviations, percentages within each group a–d)	Individuals with newly detected diabetes mellitus (DM) (FPG ≥ 126 mg/dl), $n = 280$				Individuals without DM (normal) (FPG < 126 mg/dl), $n = 4192$			Lean DM (a) vs. lean normal (c) p value
	Lean DM (a)	Non-lean DM (b)		Lean DM (a) vs. non-lean DM (b) p value[b]	Lean normal (c)	Non-lean normal[c] (d)		
	BMI < 18.5 kg/m^2 $n = 10$	BMI 18.5–22.9 kg/m^2 $n = 62$	BMI ≥ 23.0 kg/m^2 $n = 208$		BMI < 18.5 kg/m^2 $n = 570$	BMI 18.5–22.9 kg/m^2 $n = 1385$	BMI ≥ 23.0 kg/m^2 $n = 2237$	
Age in years (SD)	52.8 (9.5)	48.8 (8.5)	46.3 (8.5)	0.034	45.4 (10.0)	44.8 (9.8)	44.1 (9.1)	0.020
Age 30–37 years[a]	1 (10.0)	5 (8.1)	38 (18.3)	0.016	156 (27.4)	391 (28.2)	650 (29.1)	0.012
38–44 years	1 (10.0)	14 (22.6)	49 (23.6)		121 (21.2)	321 (23.2)	567 (25.3)	
45–53 years	1 (10.0)	23 (37.1)	75 (36.1)		154 (27.0)	356 (25.7)	606 (27.1)	
53–64 years	7 (70.0)	20 (32.3)	46 (22.1)		139 (24.4)	317 (22.9)	414 (18.5)	
Males (%)	2 (20.0)	38 (61.3)	95 (45.7)	0.105	268 (47.0)	647 (46.7)	834 (37.3)	0.115
Rural residence (%)	8 (80.0)	37 (59.7)	101 (48.6)	0.106	445 (78.1%)	1044 (75.4)	1268 (56.7)	1.000
Literate (%)	3 (30.0)	39 (62.9)	164 (78.8)	0.004	331 (58.1)	877 (64.3)	1662 (74.3)	0.106
Manual laborers (%)	6 (60.0)	18 (30.0)	27 (13.7)	0.004	263 (46.5)	543 (39.8)	468 (21.4)	0.527
Physical inactivity (%)	4 (40.0)	26 (41.9)	127 (61.1)	0.343	202 (35.7)	578 (42.1)	1258 (56.5)	0.751
Family history of diabetes (%)	1 (10.0)	8 (13.1)	68 (32.9)	0.293	47 (8.3)	123 (8.9)	436 (19.5)	0.583
Tobacco use (%)	3 (30.0)	16 (25.8)	43 (20.7)	0.466	173 (30.4)	329 (23.8)	296 (13.2)	1.000

[a] Age quartiles

[b] t test for continuous variables, chi-square test/Fisher's exact test for categorical variables

[c] p values (chi-square test/Fisher's exact test) between lean normal (c) and non-lean normal (d) groups were < 0.001, except for age ($p = 0.08$) and % males ($p = 0.006$)

Discussion

This study documents the population level prevalence of lean diabetes, in a district in Tamil Nadu, a state in India which has been experiencing a high level of epidemiological transition [12]. The strength of the study is that the estimate of the proportion of lean diabetes has been obtained from a community-based survey which identified both previously and newly diagnosed diabetes, which enables better estimation of the burden of the disease than hospital-based estimates.

The limitations of the study included the lack of body fat measurement and a low power to assess risk factors for lean diabetes, due to the low numbers of lean diabetes obtained in this community-based study, although the number screened was more than 4000. As only FPG was used to detect diabetes, there is a chance of having missed some people with type 2 diabetes, although this methodology is considered acceptable for epidemiological surveys such as the WHO STEPS surveys [9]. In addition, the absence of GAD (Glutamic Acid Decarboxylase) antibody measurement and screening for pancreatic diabetes may not have identified patients with Type 1 or pancreatic diabetes in this lean cohort of patients. This low proportion of lean diabetes among all newly detected diabetes in the community was similar to the hospital-based prevalence reports from diabetes centers in urban Chennai, Tamil Nadu (3.5% of all diabetic patients had a BMI < 18.5 kg/m^2), and Manipur (3.9% of patients with diabetes had a BMI of < 19 kg/m^2) [5, 8].

Lean diabetes was more common in the rural area (5.5% of all newly detected diabetes) than the urban area (1.5% of all newly detected diabetes). Those with lean diabetes were more likely to be older as well of a lower socio-economic status, than those with non-lean diabetes. A nationally representative study from the USA has also found that hyperglycemia is associated with a lower lean body mass in older adults [13]. The mean FPG of those with lean diabetes was higher than those with non-lean diabetes, as seen in other studies, although not statistically significant [5]. Other metabolic characteristics of those with lean diabetes, such as low levels of hyperlipidemia and lower triglycerides/HDL ratio as have been reported previously [3, 14], were not significant in this study. This is probably because the number with lean diabetes in this population based cross-sectional survey was low when compared with hospital-based comparative studies of lean and non-lean diabetes, and the main objective of this analysis was to document the population level burden of the disease.

Total cholesterol and hypertension were higher in those with lean diabetes when compared with their lean counterparts without diabetes, indicating that among the lean group, these risk factors were independent of body weight, and could be due to other factors. A study from Chennai had also found that lean people with pre-diabetes or diabetes had higher systolic blood pressure compared with centrally obese individuals with normal blood sugars [15]. This implies that deranged blood sugars even in those who are not obese may be worse than central obesity with normal blood sugars [15].

The low prevalence of lean diabetes in this study confirms the results from a previous multicentric study of 900,000 individuals that showed even in Asia, a higher BMI is associated with a higher prevalence of diabetes [16]. However, the World Health Survey data from 49 countries showed that when compared with those who were of normal weight, diabetes was higher among both the underweight as well as the overweight and obese [17]. Although the highest risk of diabetes was among the obese, those who were underweight were more likely to have untreated diabetes than all the other groups (12.28% of underweight compared with 7.87% of obese individuals) [17]. This may indicate that lean diabetes is less likely to get detected when compared with those who are considered classically to be at risk (the overweight and the obese).

As the prevalence of overweight/obesity in the study district (Vellore) has increased by two to three times in the last 20 years [18], the overall proportion of individuals with a low BMI (< 18.5 kg/m^2) is decreasing. As it is not clear if leanness is the cause or effect of this kind of diabetes [17], it can be expected that the prevalence of lean diabetes will decrease if leanness is a causal factor but may remain the same or increase in the future, if it is the effect of the disease process of lean diabetes, a process possibly mediated by genetic factors [7].

Future WHO STEPS surveys being undertaken in the region for surveillance of noncommunicable diseases need to report the burden of lean diabetes, in addition to the overall prevalence of type 2 diabetes, in order to assess its public health significance and the need for interventions, especially better detection of diabetes in this group, whose risk is mostly under-recognized.

Funding The cross-sectional WHO STEPS survey was funded by the Indian Council of Medical Research (ICMR).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Written informed consent was obtained from all participants in the study.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):685–691
https://doi.org/10.1007/s13410-019-00725-2

ORIGINAL ARTICLE

The prevalence of obesity and metabolic abnormalities in eastern China: a cross-sectional study

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Received: 7 July 2018 / Accepted: 11 February 2019 / Published online: 11 March 2019

Abstract

Objective Populations in different countries and regions have different characteristics of cardiovascular risk factors. Grasping these characteristics and developing targeted prevention and management strategies are essential to prevent cardiovascular diseases (CVD). So we conducted this study to investigate the prevalence of overweight/obesity and metabolic abnormalities of adults in eastern China.

Methods We collected data of 103,183 adults who received routine physical examination. Compared the prevalence of overweight/obesity, metabolic indicators, and the proportion of metabolic abnormalities in different age and gender subgroups.

Results Compared with other age and gender subgroups, middle-aged male had a significantly higher prevalence of general and abdominal overweight/obesity (48.8%/15.1% and 43%/13.3%, respectively). In addition, the prevalence of high DBP, hyperuricemia, high TC, TG, LDL, Non-HDLc, and low HDL-C were 24.6%, 15.8%, 34.5%, 45.1%, 19.4%, 23.6%, and 36.7%, respectively in midlife male.

Conclusions Middle-aged male had higher level of CVD risk in eastern China. Government, individuals, and health care professionals should develop targeted age and gender-based intervention to prevent weight gain and manage metabolic abnormalities.

Keywords Obesity · Cardiovascular disease · Risk factors

Introduction

Overweight and obesity have become a global health problem because of the changes in the way of lifestyle and work. There were more than 0.6 billion adults and 0.1 billion children with obesity worldwide in 2015, and accounted for 12% of adults and 5% of children [1]. From 1975 to 2014, the mean body mass index (BMI) increased from 21.7 to 24.2 kg/m^2 in men and from 22.1 to 24.4 kg/m^2 in women, and the prevalence of global obesity will reach 18% in men and 21% in women by 2025 [2]. Although the rising trends in BMI have plateaued in northwestern Europe and other high-income countries, it still maintains a high growth rate in east Asia [3]. In China, the prevalence of overweight increased from 5.2% in 1980 to 25.7% in 2015 in adult males, and the prevalence of obesity from 0.3% in 1980 to 5% in 2015 in adult males [1]. Because high BMI has been identified as a risk factor for cardiovascular disease (CVD) [4], such a rapid rising trends in BMI has resulted in adverse health outcomes and heavy financial burden.

Socioeconomic status (SES) is a powerful predictor of CVD [5]. Over the last decade, a number of new predictors such as educational attainment and neighborhood continue to attract everyone's attention [6]. However, changes in society have changed the predictive effects of traditional factors such as income, region, age, and gender on CVD. This makes integration of SES into the traditional CVD risk prediction

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models a challenge [7]. So, timely information about the condition of obesity and metabolic abnormalities in different regions, ages, and genders is crucial for the development of effective prevention and management policies.

The present work aimed to update the newest data on overweight/obesity and metabolic abnormalities in one of the most developed economic areas of China by analyzing the data of more than 100,000 adults who received routine physical examination in eastern China. We expected this study can provide some clinical evidence for the development of age and gender-based CVD prevention policy.

Methods

Participants

The data of population who received routine physical examination in eastern China (Shanghai Municipality, Zhejiang Province, Shandong Province, and Jiangsu Province) were reviewed between November 2015 and October 2017 in this cross-sectional study. A total of 103,183 adults aged 18–85 years with complete data were included.

Data collection

The data of demographic characteristics, history of CVD and risk factors (cigarette smoking, hypertension, diabetes, and dyslipidemia and the treatment of the above diseases), anthropometric examinations (body height, weight, waist circumference, and hip circumference), and blood pressure (BP) were collected. Metabolic indicators collected included fasting plasma glucose (FPG), plasma uric acid (UA), liver enzymes (alanine aminotransferase and aspartate aminotransferase), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).

After at least 5 min of rest, BP was measured using automatic BP monitor (HEM-1000, OMRON), and three readings were taken at 1-min intervals and averaged. Waist circumference (WC) and hip circumference (HC) were measured using a standard measurement method [8]. The blood samples of participants were collected after a minimum of 8 h of overnight fasting. Blood biochemical detection methods were available in the previous studies [9].

Definitions

BMI was calculated as weight divided by the square of height, and WC divided by the HP was waist to hip ratio (WHR). Non-HDL-C was calculated as TC minus HDL-C, and TC divided by the HDL-C was TC/HDL-C. Hypertension was defined as systolic blood pressure (SBP) $\geq$ 140 mmHg and/or diastolic blood pressure (DBP) $\geq$ 90 mmHg or self-reported current antihypertensive medications use [10]; general overweight and obesity were defined as a BMI of 24–27.9 kg/m^2 and a BMI $\geq$ 28 kg/m^2 according to Chinese standards, abdominal overweight or obesity was defined as WC $\geq$ 85 cm in men and $\geq$ 80 cm in women, or WHR $\geq$ 0.9 in men and $\geq$ 0.85 in women [11].

Prediabetes was defined as FPG between 5.6–6.9 mmol/L and diabetes was defined as an FPG $\geq$ 7.0 mmol/L according to 2018 American Diabetes Association (ADA) criteria [12]; the cut-off points of dyslipidemia were TG $\geq$ 1.7 mmol/L, TC $\geq$ 5.2 mmol/L, LDL-C $\geq$ 3.4 mmol/L, HDL-C < 1.0 mmol/L, non-HDL-C $\geq$ 4.1 mmol/L, and TC/HDL-C $\geq$ 5.0 [13]. Hyperuricemia diagnosis for men and postmenopausal women was UA $\geq$ 420 μmol/L and $\geq$ 350 μmol/L in premenopausal women [14]; aspartate aminotransferase (AST) and alanine aminotransferase (ALT), markers for NAFLD and liver fat content were no set upper limit, so we just made a comparison with their mean value between different groups [15].

Statistical analysis

Data are expressed as numbers (percentage) or means ± SD. Statistical analysis was performed using SPSS 18.0 (SPSS Inc.), the production and processing of figures were performed using GraphPad Prism (GraphPad Software), Microsoft Office PowerPoint, and Adobe Photoshop. Categorical variables were analyzed using the chi-squared test and continuous variables were analyzed using the *t* test. Parametric data of three groups were compared using a one-way ANOVA, and the least-significant difference (LSD)-t test was used for comparisons of two groups that exhibited a significant difference. The p values of < 0.05 were considered significant.

Results

The prevalence of overweight and obesity

A total of 103,183 adults (60.6% in men and 39.4% in women) with a mean age of 45.5 ± 13.0 years who received routine physical examination were included in this analysis. There were 49,934 (48.4%) participants aged 18–45 years (young adults group), 37,887(36.7%) participants aged 45–59 years (midlife group), and 15,362 (14.9%) participants aged $\geq$ 60 years (elderly adults group). The basic characteristics are shown in Table 1.

There was significantly higher prevalence of general overweight/obesity (BMI $\geq$ 24 kg/m^2) in older adults group; the total prevalence of general overweight/obesity was 34.5%,

Table 1 Characteristics of the study population according to age and gender (*n*,%)

Parameters	Overall	18–44 years	45–59 years	≥ 60 years
No.	103,183	49,934 (48.4%)	37,887 (36.7%)	15,362 (14.9%)
Age(years)	45.5 ± 13.0	34.4 ± 5.7	51.5 ± 4.1	66.9 ± 6.7
Male	62,490 (60.6%)	29,573 (59.2%)	23,061 (60.8%)	9856 (64.2%)
Education (college and above)	22,976 (22.3%)	13,532 (27.1%)	7438 (19.6%)	2006 (13.1%)
Marital status (married)	58,492 (56.7%)	23,152 (46.4%)	21,597 (57%)	13,743 (89.5%)
Current smoking	17,199 (16.7%)	6093 (12.2%)	8141 (21.5%)	2965 (19.3)
Diagnosed diabetes	2376 (2.3%)	886 (1.8%)	843 (2.2%)	647 (4.2%)
Diagnosed hypertension	7927 (7.7%)	1660 (3.3%)	3948 (10.4%)	2319 (15.1%)
Statin use	1358 (1.3%)	328 (0.7%)	459 (1.2%)	571 (3.7%)
Anti-obesity agents use	65 (0.06%)	58 (0.1)	7 (0.02%)	0
History of CVD	256 (0.2%)	15 (0.03%)	43 (0.1%)	198 (1.3%)

CVD, cardiovascular disease

52.1%, and 53.7% in the three age groups, respectively. After the gender subgroup analysis, the prevalence of general overweight/obesity in midlife males was higher than that in elderly male (63.9% vs. 58.7). (Fig. 1 a).

The condition of the prevalence of abdominal overweight/obesity (WC ≥ 85 cm in men and ≥ 80 cm in women) was similar to general overweight/obesity; the total prevalence of abdominal overweight/obesity was 25.2%, 44.8%, and 51.2% in the three age groups, respectively. And the prevalence of abdominal overweight/obesity in midlife males also was the highest (56.3%). (Fig. 1 b).

The characteristics of metabolic parameters

The mean BMI, WC, and HC were the highest in middle-aged males, there were no significant difference in WHR in males between the midlife group and older adults group. Consistent with BMI and WC, the mean DBP and lipid profiles were the highest (HDLc was the lowest) in middle-aged males ($p < 0.05$). The results are shown in Table 2 and significantly elevated metabolic indicators of middle-aged males had been marked with an asterisk.

The proportion of metabolic abnormalities

The proportion of metabolic abnormalities in middle-aged women and the proportion of high SBP, prediabetes, diabetes, TC/HDLc, and NAFLD in midlife male were between the other two age groups. But the proportion of elevated DBP (24.6%), hyperuricemia (15.8%), and dyslipidemia (except TC/HDLc) in middle-aged men was higher than that in other two age groups. The prevalence rates of elevated TC, TG, LDL, Non-HDLc, and low HDL-C were 34.5%, 45.1%, 19.4%, 23.6%, and 36.7%, respectively in middle-aged men. The specific values are shown in Table 3 and the proportion of metabolic abnormalities that was significantly increased in middle-aged men had been marked with an asterisk.

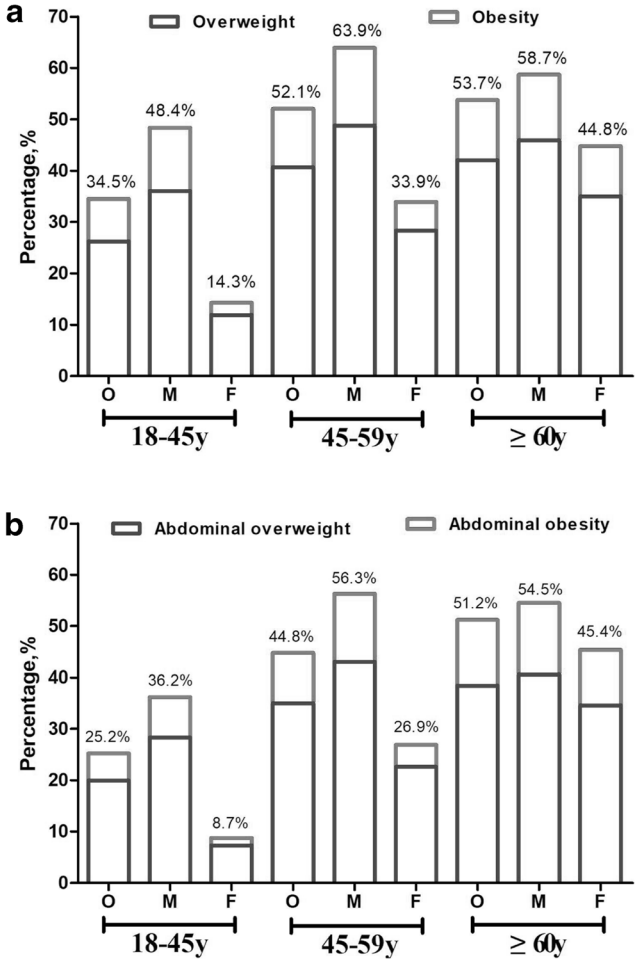

Fig. 1 The prevalence of overweight and obesity in age and gender subgroups. **a** The prevalence of general overweight and obesity. **b** The prevalence of abdominal overweight and obesity. The entire bar represents the sum of the percentage of overweight and obesity. Blue bar indicates the prevalence of overweight; red bar indicates the percentage of obesity; O, overall; M, male; F, female

Table 2 The characteristics of metabolic parameters in subjects stratified by age groups and gender

Parameters	18–44y			45–59 years			≥60 years		
	(*n* = 49,934)			(*n* = 37,887)			(*n* = 15,362)		
	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female
BMI (kg/m^2)	22.9 ± 3.4	24.1 ± 3.3	21.3 ± 2.7	24.3 ± 3.0	25.1 ± 2.9*	23.2 ± 2.8	24.4 ± 3.1	24.7 ± 2.9	23.9 ± 3.1
WC (cm)	76.9 ± 10.1	81.7 ± 8.9	69.6 ± 7.0	81.8 ± 9.3	85.9 ± 8.0*	75.4 ± 7.4	83.1 ± 9.2	85.4 ± 8.7	78.9 ± 8.5
HC (cm)	93.4 ± 6.5	95.4 ± 6.3	90.4 ± 5.5	94.3 ± 5.6	95.5 ± 5.4*	92.3 ± 5.2	93.9 ± 5.8	94.6 ± 5.7	92.6 ± 5.7
WHR	0.82 ± 0.07	0.85 ± 0.05	0.76 ± 0.05	0.87 ± 0.06	0.89 ± 0.05	0.81 ± 0.05	0.88 ± 0.06	0.90 ± 0.05	0.85 ± 0.06
SBP (mm Hg)	118.9 ± 14.6	124.1 ± 13.6	111.5 ± 12.6	125.6 ± 17.1	128.4 ± 16.5	121.1 ± 17.1	136.2 ± 18.5	136.9 ± 18.3	135.1 ± 18.8
DBP (mm Hg)	73.3 ± 10.7	76.4 ± 10.4	68.6 ± 9.3	78.8 ± 12.1	82.1 ± 11.4*	73.7 ± 11.2	79.2 ± 10.9	81.1 ± 10.7	76.1 ± 10.5
UA (μmol/L)	336.4 ± 89.8	385.6 ± 75.5	266.1 ± 55.2	340.8 ± 88.2	383.1 ± 77.4	274.9 ± 58.8	349.5 ± 85.1	376.1 ± 81.5	301.5 ± 69.0
FPG (mmol/L)	5.35 ± 0.72	5.43 ± 0.81	5.23 ± 0.56	5.87 ± 1.38	6.06 ± 1.57	5.57 ± 0.94	6.22 ± 1.57	6.34 ± 1.66	6.01 ± 1.37
TC (mmol/L)	4.55 ± 0.83	4.65 ± 0.86	4.41 ± 0.77	4.93 ± 0.89	4.92 ± 0.90*	4.93 ± 0.88	4.96 ± 0.96	4.80 ± 0.91	5.25 ± 0.96
TG (mmol/L)	1.32 ± 1.11	1.59 ± 1.31	0.93 ± 0.56	1.73 ± 1.47	2.01 ± 1.68*	1.30 ± 0.93	1.6 ± 1.16	1.63 ± 1.25	1.56 ± 0.96
HDLc (mmol/L)	1.51 ± 0.33	1.40 ± 0.29	1.69 ± 0.33	1.48 ± 0.34	1.38 ± 0.3*	1.64 ± 0.35	1.51 ± 0.35	1.44 ± 0.33	1.61 ± 0.36
LDLc (mmol/L)	2.55 ± 0.74	2.67 ± 0.75	2.36 ± 0.66	2.78 ± 0.79	2.78 ± 0.80*	2.77 ± 0.77	2.79 ± 0.82	2.70 ± 0.81	2.95 ± 0.82
Non-HDLc (mmol/L)	3.06 ± 0.87	3.26 ± 0.88	2.72 ± 0.74	3.45 ± 0.91	3.53 ± 0.91*	3.29 ± 0.88	3.43 ± 0.92	3.34 ± 0.90	3.62 ± 0.92
TC/HDLc	3.16 ± 1.0	3.46 ± 1.06	2.69 ± 0.66	3.5 ± 1.24	3.72 ± 1.35*	3.12 ± 0.91	3.42 ± 1.01	3.45 ± 1.07	3.36 ± 0.87
ALT (U/L)	27.5 ± 23.8	34.1 ± 27.1	17.8 ± 13.1	27.7 ± 20.4	31.4 ± 22.4	21.6 ± 15.0	25.0 ± 15.5	26.1 ± 16.5	22.8 ± 13.1
AST (U/L)	20.8 ± 9.4	22.8 ± 10.5	17.8 ± 6.6	22.1 ± 10.7	23.1 ± 11.6	20.3 ± 8.7	22.9 ± 9.0	23.1 ± 9.6	22.6 ± 7.7

BMI, body mass index; *WC,* waist circumference; *HC*, hip circumference; *WHR*, waist to hip ratio; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *UA*, plasma uric acid; *FPG*, fasting plasma glucose; *TC*, total cholesterol; *TG*, triglyceride; *HDLc*, high-density lipoprotein cholesterol; *LDLc*, low-density lipoprotein cholesterol; *Non-HDLc*, calculated as TC- HDLc; *TC/HDLc*, calculated as TC divided by the HDL-C; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; the asterisk indicates that significantly elevated metabolic indicators of middle-aged males than that of young and elderly male

Discussion

This study is the first large cross-sectional study to investigate the age and gender differences in the prevalence of obesity and metabolic characteristics in eastern China. The prevalence of overweight/obesity, elevated DBP, hyperuricemia, elevated TC, TG, LDL, Non-HDLc, and low HDL-C was 48.8%/15.1%, 24.6%, 15.8%, 34.5%, 45.1%, 19.4%, 23.6%, and 36.7%, respectively in midlife male, which was significantly higher than that in in young and elderly male.

Due to the imbalance of regional economic development and the great differences in living habits in China, the epidemic of obesity and the spectrum of metabolic abnormalities have significant differences in different regions, social class, and age groups [16]. The study area we had selected was the eastern coastal area of China, which is one of the most economically developed regions in China [17]. The results of this study showed that the prevalence of overweight/obesity in the eastern region was higher than the national average [1]. The main reason was that China's rapid economic growth had only been for decades, people's health awareness had not kept pace with economic growth. In the face of a rich and accessible energy supply, the body is overwhelmed.

Many factors can lead to overweight and obesity, including genetic and extragenetic factors [18]. Although most of our obesity-related genes have been edited innately [19], obesogenic environment and unhealthy lifestyle can also amplify genetic risk for obesity [20]. In China, not all people can enjoy the benefits of participating in health examinations every year, especially in the economically underdeveloped regions and rural areas. The population selected in this study was ones that participated in the routine physical examination, who often enjoyed higher income, and better medical welfare and resources (enjoy a physical examination every year for free). But they also suffer from the huge impact of modern lifestyle. They were more likely to get high-calorie foods, had more sedentary time and less exercise time, and also needed to withstand huge work stress. The results show that 63.9% of middle-aged men with BMI ≥ 24 kg/m^2 which significantly is higher than that in other age groups and China's average level. This result also shows that middle-aged men were more affected by modern work and lifestyle.

Except lifestyle, SES can also explain some of the increase in middle-aged obesity [21, 22]. Rapid renewal of knowledge and the influx of a large number of young people make middle-aged adults, especially middle-aged men, face tremendous occupational challenge. Except for a few of them have had higher occupational class, most of them are in awkward position. Some are waiting for retirement and some are facing layoffs. The embarrassing situations make them have a higher proportion of job insecurity, job burnout, and work-life conflict. Such work stress can directly lead to obesity and obesity-related diseases [23]. Due to the insufficient attention and lack of uniform scales and standards, the database of this study does not include

Table 3 The proportion of metabolic abnormalities in subjects stratified by age groups and gender

Parameters	18–44 years		45–59 years		≥60 years	
	(*n* = 49,934)		(*n* = 37,887)		(*n* = 15,362)	
	Male	Female	Male	Female	Male	Female
Hypertension, %						
SBP ≥ 140 mmHg	11.6	2.1	22.8	14	42	38.7
DBP ≥ 90 mmHg	10.1	2.2	24.6*	8.7	20.9	10.5
Antihypertensive medication use	1.3	1.7	8.3	5.2	12.5	10.4
Abnormal glucose metabolism, %						
5.6 mmol/L ≤ FPG < 7.0 mmol/L	27.8	16.6	43	32.9	46.8	45.2
FPG ≥7.0 mmol/L	1.9	0.6	12.3	4.1	18.9	11.8
Glucose lowering medication use	0.8	0.4	4.2	5.9	8.2	9.1
Dyslipidemia, %						
TC ≥ 5.2 mmol/L	23.6	14.1	34.5*	34.9	30.8	50
TG ≥ 1.7 mmol/L	30.6	6.4	45.1*	19.2	31.2	30.6
HDL-C < 1.0 mmol/L	10.7	8.4	36.7*	20.3	25.1	21.4
LDL-C ≥ 3.4 mmol/L	15	6.5	19.4*	18.6	18.3	27.6
Non-HDLc ≥ 4.1 mmol/L	15.7	4.5	23.6*	16.8	4.5	3.3
TC/HDLc ≥ 5.0	4.9	0.6	7.1	2.2	18.2	28.9
Statin use	0.1	0.1	3.6	2.3	5.9	5.2
Hyperuricemia, %						
UA ≥ 420 μmol/L, in men and postmenopausal women	6.3	4.6	15.8*	8.3	10.2	9.1
UA ≥ 350 μmol/L in premenopausal women	0	1.4	0	4.2	0	3.6
Urate-lowering therapy	0	0	0.1	0	1.2	1.0
NAFLD, %						
	3.2	3.4	15.3	11.6	16.4	14.8

All figures were percentages; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *FPG*, fasting plasma glucose; *TC*, total cholesterol; *TG*, triglyceride; *HDLc*, high-density lipoprotein cholesterol; *LDLc*, low-density lipoprotein cholesterol; *Non-HDLc*, calculated as TC- HDLc; *TC/HDLc*, calculated as TC divided by the HDL-C; *UA*, plasma uric acid; *NAFLD*, non-alcoholic fatty liver disease. The asterisk indicates that the significantly increase of the proportion of metabolic abnormalities in middle-aged males than that in young and elderly male

complete SES information of the participants. In the next step of health assessment and management, adequate attention should be given to SES.

Consistent with the distribution of obesity/overweight, the metabolic profiles and proportion of metabolic abnormalities among middle-aged men were also higher. Arterial stiffness increases as the age increases and SBP that relates to the vascular wall elasticity also increases accordingly [24]. In this study, the mean value of SBP was the highest in the elderly group. Different from SBP, the middle-aged male group has the highest DBP. This might be because most of middle-aged adults were obesity-related hypertension, which characterized by increased blood volume and increased peripheral resistance [25]. In addition, the aforementioned work stress also played a role in the increase in DBP in the middle-aged men [26].

In this study, a higher proportion of hyperuricemia in middle-aged men also attracted our attention. Obesity leads to hyperuricemia in the traditional concept [27], but more evidence has suggested that hyperuricemia may also be the starting factor for obesity and its associated metabolic abnormalities. The main mechanism is increased serum uric acid levels, promoting mitochondrial oxidative stress, then leading to insulin resistance and low-grade inflammation [28]. This mechanism may explain the consistent phenomenon of hyperuricemia, elevated liver enzymes, and dyslipidemia in middle-aged male in the current study. However, this consistency is not reflected in fasting blood glucose. Because there was no data of postprandial blood glucose for this study, it was difficult to determine if serum uric acid levels were related to glucose tolerance. Therefore, health providers should pay enough attention to the management of

hyperuricemia in middle-aged men. Meanwhile, the Chinese government should also pay attention to the harm caused by sugar-sweetened beverage [29].

There were some limitations in this study. First, this study was not a true epidemiological investigation, so the results of the study cannot represent the situation in the entire region. Second, because the participants of this study were to participate in routine physical examination and the measurement of body composition was not included. So the body fat, body fat percentage, and body fat distribution, which are important variables of metabolic abnormalities [30], were not reported in this study. Similarly, the assessment of physical activity level and SES indicators were also not included in the routine physical examination, so we cannot quantitatively analyze these indicators.

In conclusion, the analysis of the routine physical examination data of more than 100,000 adults could reflect the higher cardiovascular risk of middle-aged men in eastern China. Targeted age and gender-based intervention such as the prevention of weight gain and management and treatment of metabolic abnormalities should be initiated.

Compliance with ethical standards

Ethical approval Ethical approval was obtained from the ethics review boards of the Hangzhou Aeronautical Sanatorium of Chinese Air Force.

Conflict of interest The authors declare that they have no conflict of interest.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):692–697
https://doi.org/10.1007/s13410-019-00718-1

ORIGINAL ARTICLE

Incidence of metabolic syndrome in rural pre-menopausal women and associated risk factors

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Received: 14 June 2018 / Accepted: 19 January 2019 / Published online: 5 February 2019

Abstract
The prevalence of metabolic syndrome (MetS) is increasing in the Asia Pacific region, as well as globally. This study was aimed at determining the incidence of MetS and associated risk factors among pre-menopausal women in rural Vellore, Tamil Nadu, South India. A community-based non-concurrent cohort design was used to study the incidence and risk factors associated with MetS in women from a rural block in Vellore district. Pre-menopausal women aged 38–45 years free of MetS in 2011–2012 were followed up 5 years later, for MetS. Body mass index (BMI), waist circumference, blood pressure, fasting glucose, and lipids were measured in addition to diet and physical activity. Cumulative incidence was calculated, and adjusted odds ratios (OR) obtained using logistic regression to measure association with risk factors. The cumulative 5-year incidence of metabolic syndrome among women aged 38–45 years was 32.5% (95% confidence interval (CI), 25.9–39. 1%). Women engaged in moderate physical activity alone were more likely to have MetS than those with vigorous activity (adjusted odds ratio (OR), 2.68; 95% confidence interval, 1.08–6.69). Those with BMI ≥ 23 kg/m^2 were more likely to have MetS compared to those with a lower BMI (adjusted OR, 10.38; 95% CI, 3.50–30.80). Around one-third of pre-menopausal women aged 38–45 years developed metabolic syndrome within 5 years, in rural Vellore, South India. This high incidence emphasizes the need for raising awareness about risk factors for metabolic syndrome and encouraging lifestyle changes that may eventually help in reducing overall cardiovascular risk.

Keywords Metabolic syndrome · Incidence · Pre-menopausal women

Introduction

Almost three-quarters of all deaths due to non-communicable diseases (NCDs) and the majority of premature deaths (82%) occur in low- and middle-income countries [1]. The WHO acknowledges the metabolic syndrome (MetS) as a major and highly prevalent cardio-metabolic risk factor [2]. The cardiovascular risk rises steeply in women after menopause as compared to men and thereby, are likely to have greater mortality attributable to the cardiac disease [3]. There is an increased risk of adverse changes in metabolic factors and MetS in both peri- and post-menopausal women [4].

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The incidence rate of MetS in a south European population was 47.2/1000 person-years, while a 5-year follow-up among a Japanese-American population revealed an incidence of 15.3% [5, 6]. The prevalence of MetS increases with age and there is an increased risk linked with menopause that is independent of aging [7]. Recent data show that about one-third of the urban population in India's major cities have MetS [8]. The prevalence of MetS in women was 1.5–2 times higher than in males [9, 10]. Chow et al. found a prevalence of MetS of 26.9% in males and 18.4% in females in rural Andhra Pradesh, southern India, while a study from Chennai, Tamil Nadu (CURES-34), found a prevalence of 18.3% [11, 12].

A cross-sectional WHO STEPS study in 2011–12, revealed that 34.5% of rural women aged 30–64 years had MetS, compared to 29.4% among men, in Vellore, South India [13]. This study documents the 5-year incidence of metabolic syndrome among pre-menopausal rural women in Vellore, Tamil Nadu, a state which has been classified as a "high epidemiological transition" state [14].

Materials and methods

This study was a follow-up study based on an earlier baseline cross-sectional WHO STEPS survey conducted in 2011–12 in the same location: urban Vellore and nine randomly selected villages of a rural block in Vellore [13]. Prevalence of cardiovascular risk factors including MetS among the 6196 participants was assessed in the baseline survey [13]. Rural women aged 38–45 years in 2011–12 who were screened in the survey, were eligible to be included in the current follow-up study conducted between October and December 2016 (Fig. 1). Women who had attained menopause (natural or surgical) and all those who had been found to have MetS in 2011–12 were excluded from this list. MetS was defined as three or more of the following components (NCEP ATP III guidelines): blood pressure ≥ 130/85 mmHg; fasting plasma glucose (FPG) ≥ 100 mg/dL; triglycerides ≥ 150 mg/dL; HDL < 50 mg/dL, and waist circumference ≥ 80 cm [15].

Assuming an expected incidence of MetS of 34% [13] and a relative precision of 20%, the sample size needed was 194. Expecting a drop-out rate of 30% (mainly due to migration in the last 5 years), it was decided to follow up 309 eligible women.

Thirty percent of the non-responders were contacted to collect data on height, weight, waist circumference, and blood pressure. This was done to assess the bias that could be due to non-response.

All eligible women were visited by health workers at their homes, explained about the study, and invited to a common location in the village, such as a community hall. Protocols for measurements were standardized to ensure comparability with previous measurements in 2011–12. A structured questionnaire was administered in Tamil by a trained investigator, to assess sociodemographic characteristics, medical history, diet (WHO STEPS questionnaire), and physical activity [16–18]. The International Physical Activity Questionnaire Short Form (IPAQ-SF) was used, for its ease of administration. Physical activity was measured using metabolic equivalent scores (MET minute score). Moderate physical activity was defined as 600 to 3000 MET-minutes per week and vigorous activity as > 3000 MET-minutes per week [16].

One serving of fruit/vegetables was defined as 80 g [18]. Weight was assessed using an analog weighing scale and overweight/obesity was defined as body mass index (BMI) of ≥ 23 kg/m^2 [19]. Blood pressure was assessed using an aneroid sphygmomanometer, taking an average of two readings, as was done in the baseline survey in 2011–12. A venous blood sample was collected after ensuring an overnight fasting of at least 8 h, to assess fasting plasma glucose and lipids. Biochemical tests were done in the same institutional laboratory as the previous cross-sectional survey in 2011–12.

Socioeconomic status was classified using the BG Prasad classification (updated using the current Consumer Price Index for 2017), a scale commonly used for rural populations [20].

Double data entry was done using Epidata v. 3.1 and data analyzed using SPSS version 16.0 [19] for Windows (SPSS Inc., Chicago, Illinois, USA). Frequencies were calculated for categorical variables and means with standard deviations (SD) for continuous variables. Association between the incidence

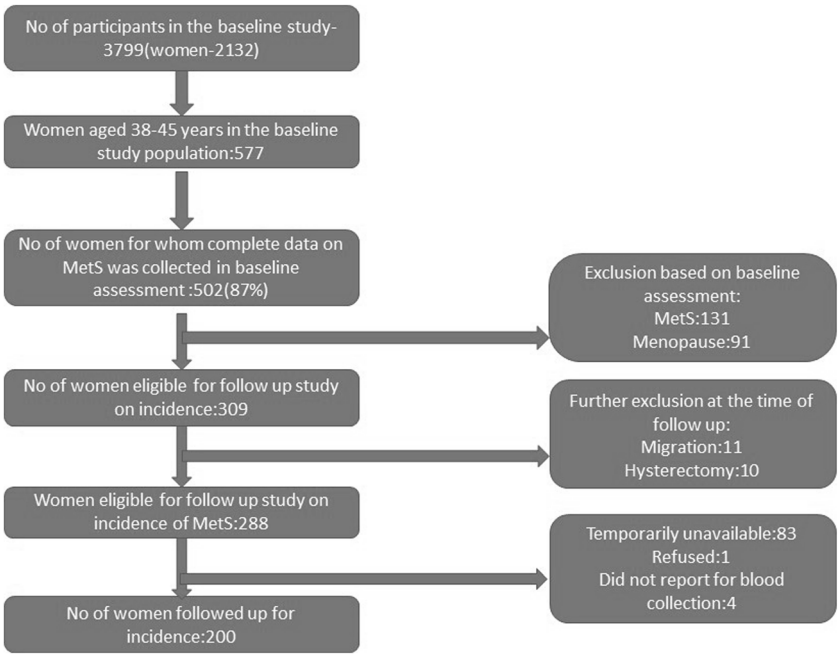

Fig. 1 Women eligible to be included in the current follow-up study conducted between October and December 2016

Table 1 Descriptive characteristics of the study population of rural women ($N = 200$)

Variable	Category	Number (%)
Age at follow-up (years)	47–50	93 (46.5)
	43–46	107 (53.5)
Education in years	0	65 (32.5)
	1–10	128 (64.0)
	> 10	7 (3.5)
Occupation	Housewife	70 (35.0)
	Manual labor	125 (62.5)
	Petty business/others*	5 (2.5)
Marital status	Never married	3 (1.5)
	Separated	4 (2.0)
	Widow	33 (16.5)
	Currently married	160 (80)
Family type	Joint	20 (10)
	Extended nuclear	31 (15.5)
	Nuclear	149 (74.5)
Socioeconomic status**	Upper	5 (2.5)
	Upper-middle	26 (13)
	Middle	37 (18.5)
	Lower-middle	80 (40)
	Lower	52 (26)

*Beedi worker/petty shop owner/tailor/housemaid

**Updated BG Prasad Socioeconomic classification for 2016[20]

of MetS and risk factors was analyzed using chi-square tests and adjusted odds ratios (OR) were obtained using logistic regression.

Results

Two hundred women (69%) of the 288 women who were eligible for the follow-up study from the nine study villages participated in the study (Fig. 1). The sociodemographic characteristics of this cohort of women at the time of follow-up are shown in Table 1. The mean age at inception was 41.1 years (SD, 2.4 years) and at follow-up 46.2 years (SD, 2.2 years), with a mean follow-up period of 4.9 years (SD 0.6 years). The median years of schooling was 5 years. Most participants (80%) were currently married, with only 1.5% who had never been married, and more than half of the women belonged to lower or lower-middle socioeconomic classes (Table 1).

The cumulative 5-year incidence of MetS among rural premenopausal women aged 38–45 years was 32.5% (95% CI, 25.9–39.1%). The proportion of women who had only one component of the MetS was 30%, while 21% had two components. The proportion of women who had none of the three criteria for MetS was 16.5%. Among the women with MetS, 46.2% had four or more of the component risk factors (Table 2).

The mean weight gain in 5 years for the women followed up in this study was 6.4 kg (SD 4.4 kg), while the average BMI increased from 22.7 kg/m^2 (SD 4.3 kg/m^2) to 25.8 kg/m^2 (SD 4.8 kg/m^2) in 5 years.

A sample of the non-responders were contacted after the study to collect data on height, weight, waist circumference, and blood pressure. This was done to assess the possibility of the bias due to non-response. The proportion of women with BMI ≥ 23 kg/m^2 was 64% in the non-responders as compared to 68% among the study participants, while 60% of the non-responders had a waist circumference of ≥ 80 cm as compared to 49% of the study participants ($p > 0.05$).

The incidence of MetS was higher among housewives (45.7%) than among women who were employed outside their homes (25.4%). However, this association was not significant after adjusting for factors such as physical activity (Table 3). Women involved in only moderate physical activity were 2.68 times more likely to have MetS compared to those who were involved in vigorous physical activity. Women with BMI ≥ 23 kg/m^2 were ten times more likely to have MetS than those with BMI < 23 kg/m^2 (adjusted OR, 10.38; 95% CI, 3.50–30.80). The level of physical activity in this group of rural middle-aged women was high, with 82% reporting vigorous activity and 18% reporting moderate physical activity (Table 3).

Table 2 Distribution of component risk factors in women with metabolic syndrome

Component risk factors	Women with each risk factor number (%), $n = 65$
Waist circumference ≥ 80 cm	60 (92.3)
Fasting plasma glucose ≥ 100 mg%	53 (81.5)
Blood pressure ≥ 130/85 mmHg	45 (69.2)
HDL < 50 mg/dL	42 (64.6)
Triglycerides ≥ 150 mg/dL	30 (46.2)
Women with four of the above	25 (38.5)
Women with all five of the above	5 (7.7)

Table 3 Risk factors for incidence of MetS among rural pre-menopausal women

Variable	Category	Incident metabolic syndrome		*p* value*	Adjusted OR (95% confidence interval)	*p* value
		Present (%) *N* = 65	Absent (%) *N* = 135			
Age in years	47–50	31 (33.3)	62 (66.7)	0.815	1.38 (0.69–2.74)	0.361
	43–46	34 (31.8)	73 (68.2)			
Education in years	≤ 5	30 (28.3)	76 (71.7)	0.178	0.94 (0.43–1.92)	0.870
	≥ 6	35 (37.2)	59 (62.8)			
Occupation	Housewife	32 (45.7)	38 (54.3)	0.003	1.51 (0.45–1.96)	0.280
	Employed	33 (25.4)	97 (74.6)			
Physical activity (MET-minutes/week)	Moderate (< 3000)	22 (61.1)	14 (38.9)	< 0.001	2.68 (1.07–6.68)	0.034
	High (≥ 3000)	43 (26.2)	121 (73.8)			
Body mass index in kg/m^2	≥ 23	61 (44.9)	75 (55.1)	< 0.001	10.38 (3.50–30.80)	< 0.001
	< 23	4 (6.3)	60 (93.8)			
Fruit and vegetable servings#/day	< 1.5	33 (28.7)	82 (71.3)	0.182	0.99 (0.40–1.96)	0.973
	≥ 1.5	32 (37.6)	53 (62.4)			

*Chi-square test, # 1 serving = 80 g/day, dichotomized on median intake

Discussion

The metabolic syndrome is a constellation of inter-related risk factors of metabolic origin that promote the development of atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes mellitus [21]. While many cross-sectional studies report the prevalence of MetS in India, the strength of this study is the assessment of incidence in rural pre-menopausal women. However, the precise point in time at which the participants progressed to develop the metabolic syndrome was unknown. Hence, only the 5-year cumulative incidence could be calculated.

The cumulative 5-year incidence of metabolic syndrome among pre-menopausal rural women in Vellore, South India, was high (32.5%), as compared to a 5-year cumulative incidence of 15.3% in a Japanese-American population [6]. The incidence rate of MetS in European population was 47.2/1000 person-years while an Iranian study reported an incidence of 43.4/1000 person-years among women [5, 22]. The prevalence of MetS in pre-menopausal women has previously been found to be lower as compared to age-matched men, while that among post-menopausal women is higher [7, 23, 24]. The Study of Women's Health Across the Nation from the USA showed that the incidence of MetS increased progressively from 6 years before to 6 years after menopause, regardless of aging and known cardiovascular risk factors [4]. In a study conducted in rural Tamil Nadu in Tiruvallur district, among women aged 30–50 years, Selvaraj et al. found a prevalence of 36%. The most common risk component of MetS was found to be abdominal obesity and impaired fasting plasma glucose (present in more than 80% of those with MetS) in the current study from Vellore, while abdominal obesity and low HDL were the most common components in the study from Tiruvallur district [25].

The higher prevalence of obesity in females partly explains the higher risk of MetS. The WHO guidelines for Asians recommend BMI ≥ 23 kg/m^2 as the cut off for public health action for defining overweight in Asians [19]. In the previous baseline study in rural Vellore in 2011–12, 85% of females and 83.5% of males had a BMI ≥ 23 kg/m^2, while the prevalence of MetS was 34.5% in women and 29.4% in men [13]. In the present follow-up study, the proportion of women with MetS was 44.9% in those with BMI ≥ 23 kg/m^2 as compared to only 6.3% in those with BMI < 23 kg/m^2. These findings are similar to the findings by Vaidya et al. in a study from Mumbai where the prevalence of MetS was 45% in pre-menopausal women and 55% in post-menopausal women [26]. Another hospital-based study in Chandigarh had found slightly higher prevalence rates (59.4% in pre-menopausal and 65.7% in post-menopausal women), with BMI being the strongest predictor of MetS [27].

The present study showed that 61.1% of the women with moderate level physical activity had MetS as compared to 26.2% of women with a high level of physical activity. Although the absolute levels of physical activity in this study may have been overestimated, being a limitation of the IPAQ-SF [28], the finding that the higher the level of physical activity, the lower is the risk of MetS was similar to the study from Tiruvallur district, Tamil Nadu [25]. Epidemiological studies suggest that 45–60 min of moderate-intensity physical activity per day may be needed to prevent unhealthy weight gain and obesity [29]. Physical exercise improves insulin sensitivity both acutely and chronically, lowering the risk of diabetes [30]. The variation in response of metabolic and

cardiovascular risk factors to physical activity is influenced by age, sex, health status, body size, and genetic factors [31].

Conclusions

Risk factor surveillance is important for both planning and monitoring NCD control programs. Surveys such as the STEPS surveys on NCD risk factors provide reliable data which can be used to plan towards national targets and policies [18]. Large-scale STEPS surveys are usually cross-sectional surveys in order to obtain trends on risk factors. However, longitudinal studies which estimate incidence are also needed for strengthening NCD surveillance in India and developing countries.

In this study, one in three rural pre-menopausal women aged 38–45 years developed MetS in 5 years. This high incidence of MetS highlights the rapidity of the increase in burden of this cardio-metabolic risk factor, reiterating that even the rural population in India is no exception to the high vulnerability of Indians to MetS. While menopause is known to bring about metabolic dysfunctions, this study shows a high incidence of MetS even in younger pre-menopausal women in a longitudinal design.

Creating awareness in peri-menopausal women about risk factors for MetS and encouraging lifestyle changes that will promote increased physical activity and reduce BMI may help in reducing premature cardiovascular mortality.

Funding This work received financial support from the Fluid Research Grant, Christian Medical College Vellore (IRB Min No 10249).

Compliance with ethical standards

Conflict of interest The authors declare that there was no conflict of interests.

Ethical approval The study was approved by the Institutional Review Board of the institution. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):698–706
https://doi.org/10.1007/s13410-019-00714-5

ORIGINAL ARTICLE

The prevalence and associated factors of type 2 diabetes in rural areas of Ningbo, China

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Received: 17 June 2018 / Accepted: 13 January 2019 / Published online: 1 March 2019

Abstract

This study aimed to investigate the prevalence of T2DM and its risk factors in rural areas in Yinzhou District of Ningbo, China. A cross-sectional study with 4832 participants aged 18 years or older was conducted during the period of March 2013 to May 2013. Among the participants, 4760 completed a self-administered survey and physical examinations. Data collected included demographic characteristics, lifestyle, medical history, anthropometric measurements, and clinical assessment. After an overnight fasting of at least 10 h, participants also underwent an oral glucose tolerance test (OGTT) for diagnosing T2DM. Logistic regression analysis was performed to determine the risk factors associated with T2DM. The area under the receiver operating characteristic curve (AUROC) was used to assess the prediction ability of the models. The age-standardized prevalence of T2DM was 7.86% (95% confidence interval (95% CI = 7.10–8.62%), and the crude prevalence was 15.36%. In multivariate logistic regression models, age (≥ 65), obesity, and hypertension were the common risk factors of T2DM for both males and females. The AUROC of the T2DM model was 0.735 (95% CI = 0.709–0.762), indicating the accuracy of the model in predicting T2DM. Old age, obesity, hypertension, and elevated triglycerides and LDL-C were the risk factors for T2DM. And the predictive power of ROC curve we established for predicting T2DM had a good accuracy. Therefore, diabetes health education and early screening programs should be developed and strengthened for the prevention of T2DM in rural areas.

Keywords Type 2 diabetes mellitus · Rural areas · Risk factors · New rural cooperative medical system · Health education

Ming Zhao and Hongbo Lin contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13410-019-00714-5) contains supplementary material, which is available to authorized users.

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Introduction

The prevalence of type 2 diabetes has been increasing globally, and it has rapidly become a major chronic, noncommunicable disease that threatens public health. Recent data indicate that in 2015, approximately 415 million people were diagnosed with diabetes worldwide. In China, the prevalence of diabetes has been steadily increasing over the past three decades. A national cross-sectional study of 300,000 adults showed that the prevalence of diabetes was 0.67% in 1980 [1]. In subsequent national surveys, the standardized prevalence of diabetes increased from 2.51% in 1994 to 3.21% in 1996 [2, 3] and further increased to 5.49% in 2000 and 9.7% in 2007 [4, 5]. The most recent Chinese national survey conducted in 2010 indicated that the overall prevalence of diabetes was 11.6%, translating into 113.9 million Chinese adults with diabetes, and in rural areas, the prevalence of diabetes had reached 10.3% [6].

The population living in rural areas accounts for almost half of the total population in China. An epidemiological survey indicated that the growth rate of diabetes in China was higher in people living in rural areas than in those living in urban areas [7]. Despite this, the health services and service facilities in almost all rural areas within China are inferior compared to those in urban areas, which may lead to increased risk of undiagnosed diabetes among people living in rural areas. Studies on the risk factors of diabetes in rural areas have been reported, such as in Yunnan [8] and Qingdao [9], but few studies have been conducted on the epidemiological characteristics of diabetes in rural areas of Ningbo, China. The Chinese government initiated a New Rural Cooperative Medical System (NRCMS) in 2003 in order to ensure that the rural population can have the basic medical health care services [10]. As the costs of having blood glucose checked regularly and diabetes and its complications treated are a major concern for residents in rural areas, NRCMS could ease the financial burden of rural residents and improve the rate of diabetes screening.

In addition, diabetes is an independent risk factor for cardiovascular diseases, which have become the leading causes of death among Chinese adults [11]. Thus, early detection of diabetes is of great importance. For individuals with pre-diabetes, early diagnosis can lower the chances of progressing into diabetes.

The aim of this study was to investigate the prevalence and risk factors of type 2 diabetes in the rural population in Ningbo (Yinzhou District). We further assessed the prediction ability of the models for early detection of type 2 diabetes. The study findings will provide useful information for the development of public health policies and interventions for the fight against diabetes in the rural communities of Ningbo, China.

Materials and methods

Subjects and study design

We conducted a cross-sectional study from March 2013 to May 2013, using a multi-stage, stratified, cluster sampling method to investigate the blood glucose level of individuals in Yinzhou District, an administrative region that has the highest population among all districts in Ningbo, China. Hengxi and Jiangshan townships were randomly selected from all of the townships of Yinzhou District. Four administrative villages (Heyi, Rongjiang, Yongjiang, and Zhangcunmiao) were randomly selected from Jiangshan, and four administrative villages (Jin'e, Shangren, Cheng'ao, and Da'ao) were randomly selected from Hengxi. The number of the total adult population from eight villages was around 7000, and residents who were aged ≥ 18 years, resided for more than 6 months in the villages, and covered by the NRCMS were eligible to participate in the study. Pregnant females and residents with serious diseases and other types of diabetes, such as type 1 diabetes, gestational diabetes, and other special types of diabetes, were excluded by self-reporting assessment. A total of 4832 individuals were eligible to participate in the study; of them, 4760 (98.5%) completed the questionnaire and anthropometric and clinical measurements.

Data collection

All participants were requested to complete a self-administered questionnaire, including questions about demographic characteristics (e.g., sex, age, education level, and marital status), health-related lifestyles (e.g., diet status, tobacco and alcohol consumption, and the intensity of physical activity), and personal health history (e.g., hypertension, hyperlipidemia, and diabetes). The categories of educational level were according to the International Standard Classification of Educational Degrees (ISCED), which included preprimary education, primary education, lower secondary education, upper secondary education, post secondary education, first tertiary education, and second-stage tertiary education [12]. However, taking into account the actual situation of the participants, we made a revision of the ISCED classification. We divided the educational levels into five categories: illiterate/preprimary education, primary education, lower secondary education, upper secondary education, and tertiary education. There were three marital status categories (married, unmarried, and divorced/remarried) and three diet status categories (meat-based, vegetable-based, and meat and vegetable balanced); vegetable-based diet and meat-based diet were defined as vegetable intake and meat intake ≥ 3 times a day, respectively; the physical activity was divided into three types according to the frequency of participants taking part in physical activities: low intensity (less than

1 day a week), moderate intensity (1–4 days a week), and high intensity (5–7 days a week).

Screening included anthropometric measurements of anthropometrics and biochemical parameters. Anthropometric measurements include height and weight, and biochemical parameters include blood pressure, blood lipid, and fasting plasma glucose (FPG) in the Health Service Center of each township. Body mass index (BMI) was calculated as the ratio of weight to the square of height (kg/m^2). During the test of FPG, participants without a history of diabetes also took the oral glucose tolerance test (OGTT). Blood was drawn 120 min after the oral glucose challenge to measure plasma glucose (2h-PG). If a participant had a history of diabetes, a steamed bread meal was given for the OGTT. The details of the examination protocol were described in a previous study [13]. All investigators underwent strict training and used standardized protocols and instruments for data collection.

Diagnostic criteria

Hypertension patients were defined as those who had received anti-hypertension drugs in the past 2 weeks or those with systolic blood pressure (SBP) > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg [14]. Participants with BMI ≥ 24 kg/m^2 but < 28 kg/m^2 were considered overweight, and those with BMI ≥ 28 kg/m^2 were considered obese [15].

The classification of plasma glucose was based on the WHO guidelines [16]. The type of glucose intolerance was based on the result of FPG and OGTT. A FPG < 6.1 mmol/L was classified as normal. Pre-diabetes included three categories: isolated impaired fasting glucose (I-IFG) was defined as a FPG of 6.1–7.0 mmol/L and 2h-PG < 7.8 mmol/L, isolated impaired glucose tolerance (I-IGT) was defined as a FPG < 6.1 mmol/L and 2h-PG 7.8–11.1 mmol/L, and IFG combined with IGT (IFG/IGT) was defined as a FPG 6.1–7.0 mmol/L and 2h-PG 7.8–11.1 mmol/L. Diabetes mellitus (DM) was defined as FPG ≥ 7.0 mmol/L or 2h-PG ≥ 11.1 mmol/L or the use of anti-diabetic medication.

Statistical analysis

Statistical analyses were performed using the Statistic Package for Social Science software release 18.0 (SPSS, Chicago, IL, USA). Prevalence rates of diabetes in all participants and different age groups were calculated by the direct standardized method based on the 2000 China population census data. All categorical variables were described and presented as proportions. Continuous variables were tested for normality; if variables satisfied the normal distribution, they were described as mean values with standard deviation, and if not, they were presented as medians and interquartile ranges (IQRs).

Bivariate logistic regression analysis was used as the first step to investigate the factors associated with diabetes, and odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. Then, a multivariate logistic regression analysis was performed by entering all the significant variables from the bivariate analysis into a modeling process. Stratification analysis by sex was also performed for the multivariate logistic analysis.

Receiver operating characteristic (ROC) curve acted as a tool for comprehensively evaluating a diagnostic test for the discriminating power and the prediction effect. The area under the ROC curve (AUROC) and 95% CI were calculated to evaluate the sensitivity of the variables as predictors of diabetes. AUROC was drawn with the false positive rate (1 − specificity) as the abscissa and the true positive rate (1 − sensitivity) as the ordinate. The Youden index (sensitivity + specificity − 1) of each variable was calculated, and the point with the maximum Youden index was used as the cutoff point of the variable for predicting diabetes. A p value < 0.05 was considered statistically significant.

Results

Characteristics of the study population

Table 1 showed the characteristics of participants. The majority of the participants were females (2744/4760, 57.6%), and the median age of all participants was 60 years. The largest age group was the group of 50–64 years, accounting for 45.7% of all participants. However, among people with diabetes, the largest age group was the group of ≥ 65 years (47.1%). Most of the participants were married (84.3%). There were four educational levels: 261 (6.5%) were illiterate or semi-illiterate, 2137 (53.3%) had finished primary school, 1366 (34.1%) had finished junior high school, and 245 (6.1%) had finished high school or above. In total, 1079 (23.3%) were currently smoking, 1582 (34.2%) regularly consumed alcohol, 2818 (66.0%) had hypertension, 1492 (31.7%) were overweight, and 348 (7.4%) were obese.

Prevalence of T2DM

Among the participants, 29.1% (1383/4760) had pre-diabetes, including those who were previously or newly diagnosed. The crude prevalence of T2DM was 15.36% (95% CI = 14.23–16.38%). The age-standardized prevalence was 7.86% (95% CI 7.10–8.62%). There was no statistically significant difference between males and females (7.40%, 95% CI = 6.26–8.54%, and 8.25%, 95% CI 7.22–9.28%, respectively, p > 0.05; Table 2).

Table 1 Characteristics of the survey participants in rural areas of Ningbo, China from March 2013 to May 2013

Variables	T2DM	Total	Percent
Sex			
Male	272	2016	42.4%
Female	459	2744	57.6%
Age (years)			
18–34	5	206	4.3%
35–49	59	872	18.3%
50–64	323	2174	45.7%
≥65	344	1508	31.7%
Marital status			
Married	628	3992	84.3%
Unmarried	39	439	9.3%
Divorced/remarried	57	303	6.4%
Education			
Illiterate/preprimary	56	261	6.5%
Primary	487	2137	53.3%
Lower secondary	156	1366	34.1%
Upper secondary	18	187	4.7%
Tertiary	3	58	1.4%
Smoking			
Non/ex-smoker	543	3554	76.7%
Current smoker	155	1079	23.3%
Alcohol			
Non/ex-drinker	461	3041	65.8%
Current drinker	233	1582	34.2%
Diet			
Meat-based	40	251	5.4%
Vegetable-based	41	190	4.1%
Meat and vegetable balanced	628	4217	90.5%
Physical activity			
Low intensity	179	1505	36.8%
Moderate intensity	224	1188	29.0%
High intensity	271	1402	34.2%
Hypertension			
No	101	1451	34.0%
Yes	593	2818	66.0%
BMI (kg/m^2)			
<24	354	2867	60.9%
24–28	269	1492	31.7%
≥28	98	348	7.4%
TG	1.5 (1.0–2.1)[a]	1.3 (0.9–1.9)[a]	
TC	5.1 ± 1.0[b]	4.9 (4.3–5.5)[a]	
LDL-C	3.0 ± 0.8[b]	2.9 (2.4–3.4)[a]	
HDL-C	1.2 (1.0–1.4)[a]	1.2 (1.1–1.4)[a]	

The column subtotals may not always sum to the total because of missing data, but the missing data account for less than 15% of the total

BMI body mass index, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol

[a] These variables are presented as medians and interquartile ranges because of skewed distributions

[b] These variables are presented as mean values with standard deviation

Factors associated with T2DM

By bivariate analysis, increased age, sex, marital status, educational level, the intensity of physical activity, diet status, overweight, obesity, hypertension, TG, TC, LDL-C, and HDL-C were found to be associated with diabetes. There were no statistically significant differences in tobacco or alcohol consumption between the T2DM group and normal group. Using multivariate logistic regression, we found independent risk factors of T2DM to be age (≥65; adjusted odds ratio (AOR) = 4.32, 95% CI = 1.226–15.240), low intensity physical activity (AOR = 0.63, 95% CI = 0.465–0.856), obesity (AOR = 2.74, 95% CI = 1.819–4.112), hypertension (AOR = 2.84, 95% CI = 2.065–3.908), elevated TG (AOR = 1.21, 95% CI = 1.067–1.379) and LDL-C (AOR = 1.47, 95% CI = 1.147–1.893) after adjusting for sex, marital status, educational level, smoking, alcohol consumption, diet status, TC and HDL-C (Tables 3 and 4).

We then performed a stratified analysis by sex to further explore the association between the factors and T2DM in males and females (Table 5). Old age (≥65), obesity, and hypertension were associated with a high risk of T2DM in both males and females. TG was the risk factor for females with T2DM (AOR = 1.36, 95% CI = 1.092–1.683).

Table 2 The age-standardized prevalence of T2DM stratified by sex and age group

Age group	Total		Male		Female	
	n	%	*n*	%	*n*	%
18–34	5	2.43	3	2.94	2	1.92
35–49	59	6.77	27	7.18	32	6.45
50–64	323	14.86	101	12.64	222	16.15
≥65	344	22.81	141	19.08	203	26.4
Total	731	15.36	272	13.49	459	16.73
Standardized prevalence (%)	7.86		7.40		8.25	

T2DM type 2 diabetes mellitus

Effect of the model evaluated by ROC curves

In addition, we established ROC curves for diabetes based on the results of logistic regression to evaluate the prediction power of models. The AUROC of diabetes was 0.735 (95% CI 0.709–0.762, $p < 0.001$), with the sensitivity being 70.4% and the specificity 67.1%, which indicated that the selected factors (age, BMI, hypertension, and TG) were accurate in predicting diabetes (Fig. 1).

Discussion

In this study, the crude prevalence of diabetes in the rural areas of Ningbo, China, was found to be 15.36%, with the age-standardized prevalence to be 7.86%. This prevalence was lower than the prevalence in the rural areas of Chengdu, China, where the age-adjusted standardized prevalence of diabetes was 12.8% [17]. However, the prevalence of diabetes was higher than what was reported in a previous study conducted

Table 3 Factors associated with T2DM in bivariate logistic regression analysis

Variable	β	SE	Wald χ^2	OR (95% CI)	p
Age (years)					
18–34				1.00 (Reference)	
35–49	0.887	0.477	3.458	2.43 (0.953–6.179)	0.063
50–64	1.762	0.461	14.606	5.82 (2.359–14.371)	< 0.001
≥ 65	2.464	0.462	28.508	11.75 (4.757–29.042)	< 0.001
Sex					
Male				1.00 (Reference)	
Female	0.205	0.086	5.654	1.23 (1.037–1.453)	0.017
Marital status					
Married				1.00 (Reference)	
Unmarried	− 0.576	0.178	10.454	0.56 (0.397–0.797)	0.001
Divorced/remarried	0.289	0.162	3.194	1.34 (0.972–1.833)	0.074
Education					
Tertiary				1.00 (Reference)	
Upper secondary	0.562	0.656	0.734	1.76 (0.485–6.350)	0.391
Lower secondary	0.706	0.611	1.334	2.03 (0.612–6.706)	0.248
Primary	1.164	0.607	3.676	3.20 (0.974–10.517)	0.055
Illiterate/preprimary	1.557	0.626	6.188	4.74 (1.391–16.172)	0.013
Physical activity*					
High intensity				1.00 (Reference)	
Moderate intensity	0.336	0.104	10.501	1.40 (1.142–1.716)	0.001
Low intensity	− 0.226	0.104	4.736	0.80 (0.651–0.978)	0.030
Smoking					
Non/ex-smoker				1.00 (Reference)	
Current smoker	− 0.019	0.102	0.034	0.98 (0.803–1.200)	0.854
Alcohol					
Non/ex-drinker				1.00 (Reference)	
Current drinker	0.002	0.091	0.001	1.00 (0.839–1.197)	0.981
Diet					
Meat and vegetable balanced				1.00 (Reference)	
Vegetable-based	0.819	0.202	16.399	2.27 (1.526–3.371)	< 0.001
Meat-based	0.169	0.186	0.817	1.18 (0.821–1.706)	0.366
BMI (kg/m^2)					
< 24				1.00 (Reference)	
24–28	0.545	0.092	35.222	1.725 (1.441–2.065)	< 0.001
≥ 28	1.285	0.146	77.905	3.164 (2.717–4.806)	< 0.001
Hypertension					
No				1.00 (Reference)	
Yes	1.413	0.116	149.191	4.11 (3.274–5.153)	< 0.001
TG	0.259	0.044	34.033	1.30 (1.188–1.414)	< 0.001
TC	0.223	0.046	23.594	1.25 (1.142–1.368)	< 0.001
LDL-C	0.184	0.067	7.57	1.20 (1.054–1.370)	0.006
HDL-C	− 0.381	0.192	3.938	0.68 (0.469–0.995)	0.047

T2DM type 2 diabetes mellitus, *BMI* body mass index, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *SE* standard error, *OR* odds ratio, *CI* confident interval

*Physical activity: this was a subgroup analysis excluding those without physical activity data

Table 4 Factors associated with T2DM in multivariate logistic regression analysis

Variable	Crude OR (95% CI)	*p*	Adjusted OR[a] (95% CI)	*p*
Age (years)				
18–34	1.00 (Reference)		1.00 (Reference)	
35–49	1.79 (0.586–5.471)	0.306	1.37 (0.388–4.825)	0.626
50–64	3.13 (1.072–9.151)	0.037	2.06 (0.599–7.113)	0.251
≥ 65	5.99 (2.027–17.675)	0.001	4.32 (1.226–15.240)	0.023
Physical activity[b]				
High intensity	1.00 (Reference)		1.00 (Reference)	
Moderate intensity	0.86 (0.632–1.166)	0.328	0.83 (0.602–1.134)	0.238
Low intensity	0.69 (0.516–0.918)	0.011	0.63 (0.465–0.856)	0.003
BMI (kg/m^2)				
< 24	1.00 (Reference)		1.00 (Reference)	
24–28	1.34 (1.035–1.746)	0.027	1.27 (0.969–1.666)	0.083
≥ 28	2.86 (1.925–4.234)	< 0.001	2.74 (1.819–4.112)	< 0.001
Hypertension				
No	1.00 (Reference)		1.00 (Reference)	
Yes	2.78 (2.027–3.790)	< 0.001	2.84 (2.065–3.908)	< 0.001
TG	1.11 (1.007–1.216)	0.035	1.21 (1.067–1.379)	0.003
LDL-C	1.17 (1.011–1.346)	0.034	1.47 (1.147–1.893)	0.002

T2DM type 2 diabetes mellitus, *BMI* body mass index, *TG* triglyceride, *LDL-C* low-density lipoprotein cholesterol, *OR* odds ratio, *CI* confident interval

[a] Adjusted for sex, marital status, education levels, smoking, drinking, diet status, total cholesterol, and high-density lipoprotein cholesterol

[b] Physical activity: this was a subgroup analysis excluding those without physical activity data

in a similar region (crude prevalence 7.09% and standardized prevalence 5.19%) [18]. The differences between the findings may be due to the time difference of various studies or the age structures of the participants recruited in the studies.

There was no significant difference between male and female respondents with diabetes in this study. This result was similar to a previous study, which also reported no gender difference in diabetes among their participants [19]. In addition, more females were recruited in this study than males, and most respondents were aged 50–64 and ≥ 65 years with only 4.3% of the respondents aged less than 35 years. This may be explained by a number of reasons. First, females had better compliance in participating in the survey than males. Second, the majority of young adults was in the workforce or schools outside the region and did not live in the villages. Because migrant workers were not included in this study, a large part of younger people may have been missed, which can explain why the sample size of the participants aged 18–34 years was smaller than that of other age groups. A comparison among the participants with diabetes in this study with the registration data provided by the Yinzhou District Center for Disease Control and Prevention, stratified by sex and age group, was conducted (Table S1). The results showed no statistically significant differences in different age groups and sex between the two groups, suggesting that the potential bias in sample selection was minimal.

Similar to previous studies [20–23], increased age, obesity, hypertension, and elevated TG were the independent risk factors for diabetes in this study, while the educational level was negatively correlated with the risk of diabetes. The reason might be that people with a higher level of education would have a better self-awareness for health maintenance and better knowledge about diabetes, they would be more likely to be able to afford access to health service and facilities, and they would be willing to take measurements to improve their health condition and reduce the risk of diabetes. A meta-analysis conducted by Zhou et al [24] showed that smoking and drinking were the only influencing factors of diabetes in China, and smoking was the persistent factor. The reasons for smoking and drinking to be independent risk factors for type 2 diabetes may be that smoking and excessive alcohol consumption affect the distribution of body fat and lead to insulin resistance [25, 26]. Unexpectedly, smoking and alcohol drinking were not shown to be significant risk predictors of diabetes in the current study. The possible reasons are that the rates of tobacco smoking and alcohol consumption were much lower in this study population than in other study populations, but the effects of smoking and alcohol consumption on diabetes need to be further explored. Moreover, high-intensity physical activity acted as a high-risk factor of diabetes in the multivariate logistic regression model. This was inconsistent with other studies [27–29]. We suspect that this may be due to the substantially missing data on physical activity measures.

Table 5 Multivariate logistic regression analysis stratified by sex

Variables	Male		Female	
	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Age (years)				
18–34	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
35–49	1.63 (0.343–7.749)	1.51 (0.238–9.598)	2.06 (0.416–10.225)	1.00 (0.178–5.642)
50–64	2.67 (0.594–11.986)	2.18 (0.354–13.415)	3.67 (1.292–16.967)*	4.51 (1.178–8.221)*
≥65	4.42 (1.097–20.062)*	4.03 (1.063–25.454)*	7.89 (1.676–37.104)**	5.24 (1.753–18.278)**
Physical activity[b]				
High intensity	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Moderate intensity	0.94 (0.585–1.497)	0.97 (0.594–1.597)	0.81 (0.539–1.220)	0.79 (0.513–1.203)
Low intensity	0.85 (0.548–1.317)	0.82 (0.510–1.327)	0.59 (0.399–0.867)*	0.57 (0.376–0.855)*
BMI (kg/m^2)				
<24	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
24–28	1.03 (0.692–1.529)	1.04 (0.685–1.568)	1.66 (1.166–2.365)**	1.51 (1.053–2.190)**
≥28	2.36 (1.169–4.751)*	2.44 (1.191–5.017)*	3.06 (1.880–4.990)**	2.80 (1.681–4.657)**
Hypertension				
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	2.56 (1.612–4.064)**	2.62 (1.629–4.225)**	2.78 (1.811–4.278)**	2.91 (1.872–4.507)**
TG	1.02 (0.901–1.162)	1.11 (0.926–1.327)	1.29 (1.092–1.531)**	1.36 (1.092–1.683)**
LDL-C	1.17 (0.940–1.451)	1.36 (0.952–1.953)	1.13 (0.932–1.379)	1.54 (1.066–2.224)*

BMI body mass index, *TG* triglyceride, *LDL-C* low-density lipoprotein cholesterol, *OR* odds ratio, *CI* confident interval

[a] Adjusted for sex, marital status, educational levels, smoking, drinking, diet status, total cholesterol, and high-density lipoprotein cholesterol

[b] Physical activity: this was a subgroup analysis excluding those without physical activity data

*$p < 0.05$; **$p < 0.01$

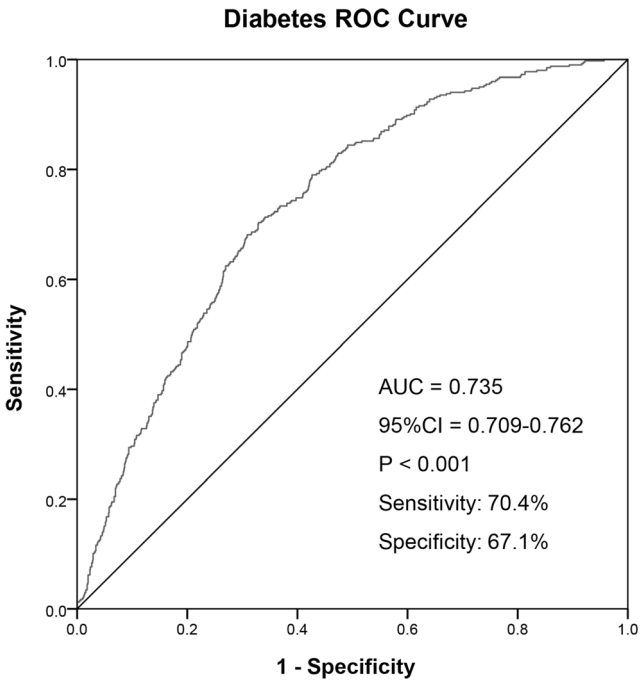

Fig. 1 The receiver operating characteristic (ROC) curve of diabetes. AUC area under curve, 95% CI 95% confidence interval

Based on the results of the gender-stratified analysis, we found that old age, obesity, and hypertension were the common risk factors of diabetes in both males and females. We also found that elevated TG and LDL-C levels were only associated with diabetes in females, which was inconsistent with studies reporting that high levels of TG and LDL-C were risk factors for diabetes in both males and females [30, 31]. The reason for this discrepancy might be that work intensity and physical exertion were higher in males than females in rural areas in China, so the obesity ratio in females was higher than in males.

The AUROC of diabetes risk scores in our study was 0.735 (95% CI 0.709–0.762), with the sensitivity and specificity being 70.4% and 67.1%, respectively. Similar results were observed in another study [32], which was a cohort study of a rural adult Chinese population with the model including age, BMI, TG, and FPG as predictors and the AUROC of the model being 0.768 (95% CI 0.760–0.776). However, this was lower than the AUROC of risk scores (0.82–0.98) obtained by a study preformed in USA [33]. Difference in race and lifestyle may contribute to this discrepancy.

In rural areas of China, due to the family economic constraints and the low awareness of health care services, people lack enthusiasm to receive health examinations. The general

public services and medical infrastructures in rural areas are also fewer than in urban areas, which contributes to the high prevalence of chronic, non-communicable diseases and related complications [34]. This may affect the quality of life of people and seriously hamper the economic development of rural areas. The implementation of NRCMS policy benefits the majority of people in rural areas and enhances the awareness of self-care [35]. In this study, we conducted a large-scale cross-sectional survey, screening for diabetes while performing health examinations using NRCMS. We found that the prevalence of diabetes in Ningbo was higher than in other regions, such as the rural areas of Jilin province and Henan province (the prevalence of diabetes was 7.2% and 6.12%, respectively) [36, 37]. Therefore, it is necessary to carry out the new rural cooperative medical examination every year, which could detect diabetes in the early stage. Health awareness and health education campaigns conducted by community public health professionals should help residents to pay more attention to controlling the blood pressure, blood lipid, and plasma glucose through healthy diets, thereby reducing the risk of diabetes and related complications. The NRCMS should provide rural residents access to health services.

There were several limitations in our study. First, occupation information was not collected in our study, but farmers accounted for a large proportion of the study participants. In addition, the types of occupation were limited, which may cause potential bias in the results. Second, young people were under-sampled, and the median age of the respondents was 60 years, because the majority of young people worked outside the villages or went to university. Third, in our study, the participants were all from rural areas; thus, no comparisons of diabetes determinants between rural and urban areas were made. Fourth, the information of family history of diabetes was not included due to poor data collection. Besides, the diet status record of each individual was obtained by the retrospective method instead of through a food frequency questionnaire, which also could lead to recall bias in the results. Finally, this study was a cross-sectional survey with limited determination of the causal relationship, so future prospective studies with a quality sampling and questionnaires are needed to confirm the findings.

In conclusion, the results of this study show that the prevalence of type 2 diabetes in rural areas of Ningbo, China, increased rapidly in recent decades. Old age, hypertension, obesity, and elevated TG and LDL-C were the risk factors associated with diabetes. With an increasing rate of type 2 diabetes, our study findings can plan the development of diabetes programs specifically targeting rural populations. Diabetes health education should be developed with clear and improved messages and early screening strengthened in order to control the epidemiological trend of diabetes and provide treatment to patients timely.

Acknowledgments The authors acknowledge the contributions of all involved investigators and clinical staffs of Yinzhou District Center for Disease Control and Prevention, Ningbo.

Funding This work was supported by Ningbo Science and Technology Innovation Team Program (2014B82002 to S.B.), the National Natural Science Foundation of China (81370165 to S.B., 81501421 to F.W., and 31301068 to Y.X.), the Natural Science Foundation of Zhejiang Province (LY17C060002 to Y.X.), the Natural Science Foundation of Ningbo (2015A610176 to F.W.), Fang Runhua Fund of Hong Kong, and K. C. Wong Magna Fund in Ningbo University.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study involving human participants were approved by the ethics committee of School of Medicine, Ningbo University. All procedures performed in this study were in accordance with the ethical standards of the ethics committee of School of Medicine, Ningbo University and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):707–714
https://doi.org/10.1007/s13410-019-00732-3

ORIGINAL ARTICLE

Glycaemic control among adults with self-reported diabetes in health and demographic surveillance site (HDSS) of rural North India

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Received: 25 January 2018 / Accepted: 27 February 2019 / Published online: 25 March 2019

Abstract

Background Achievement of adequate glycaemic control is important to alleviate complications, improve quality of life and reduce mortality among persons with diabetes. This study estimated the level of glycaemic control and determinants of poor glycaemic control among persons with diabetes in a rural population of North India.

Methods We randomly selected 245 persons aged ≥ 18 years with self-reported diabetes from the information of 100,000 individuals available in Health Information Management System of Health Demographic Surveillance Site (HDSS) Ballabgarh. Glycaemic control was assessed by measurement of glycated haemoglobin (HbA1c). Blood pressure, weight, height, waist and hip circumference were measured with standard procedures. Information regarding disease and treatment history was recorded.

Results Mean age of participants was 56.2 (± 11.3) years. Mean HbA1c was 8.04% (± 2.54), with no significant difference across age and sex. Good glycaemic control (HbA1c < 7%) was observed in 41.3%. On multivariate logistic regression, duration of > 10 years since diagnosis of diabetes (OR = 2.71, 95% C.I. 1.08–6.81), and high serum triglyceride (OR = 2.17, 95% C.I. 1.19–3.98) levels were significantly associated with poor glycaemic control, while persons aged > 60 years were less likely of poor glycaemic control.

Conclusion Achievement of adequate glycaemic control in this population is poor and warrants prompt interventions.

Keywords HbA1c · Glycaemic control · Person with diabetes · Ballabgarh

Introduction

Globally, there are approximately 415 million individuals living with diabetes mellitus as of 2016 and are expected to reach 645 million by 2040 [1]. In 2013, 8.4% of all cause deaths in adults were estimated to be attributable to diabetes [2]. Despite high mortality and morbidity, nearly 45% of all diabetes cases are estimated to be undiagnosed globally [3]. This coupled with low awareness about their diabetic status and poor treatment and adherence practices achieving good glycaemic control among persons with diabetes remains a tough task. Poor glycaemic control is an important independent predictor for development of complications due to diabetes leading to loss of organ or its function, impaired quality of life, accentuated mortality rates, and economic burden to healthcare system and patients. Achieving good glycaemic control in diabetic patients is of profound public health importance.

However, data regarding glycaemic control among diabetic patients from India is sparse. Most of the studies which have been done earlier provide varying level of estimates of glycaemic control and have been done mostly in Southern states. Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study [4] done in both rural and urban parts of four states of India (i.e. Jharkhand, Maharashtra, Tamil Nadu and urban Chandigarh) provided information on glycaemic control among persons with self-reported diabetes.

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Particularly, none of the previous studies were done in a rural population of North India. Glycaemic control among diabetic patients is dependent on socio-demographic characteristics, health system issues and overall awareness of the population and may vary across different settings in different parts of the country [5–7]. Thus, there is need to generate more evidence related to glycaemic control in various settings. Measurement of glycated haemoglobin (HbA1c) is the most reliable indicator of long-term glycaemic control and reflects the overall quality of care and treatment adherence [8].

This study explores the level of glycaemic control and various determinants of poor glycaemic control among persons with self-reported diabetes assessed by HbA1c in a rural population of Haryana, North India.

Methods

We conducted this cross-sectional study in 28 villages of Ballabgarh block of Faridabad district in Haryana, a state in north India. These 28 villages comprising of approximately 100,000 population was a Health and Demographic Surveillance Site (HDSS) under International Network for the Demographic Evaluation of Populations and their Health (INDEPTH) network [9]. Health Management Information System (HMIS) is functional in Ballabgarh, wherein routine population surveillance is done through bi-weekly house-to-house visits by trained health workers. They collect information related to vital events, socio-demographic characteristics and chronic conditions such as tuberculosis, hypertension and diabetes mellitus and health service utilization. The system's database is updated once every month and further updated with missing data and special morbidity surveillance data during the annual census. The information is also provided to different agencies for health-management purposes, which can be made available to researchers [10]. A list of all individuals (≥ 18 years) with self-reported diabetes was extracted from HMIS. A person is recorded as self-reported diabetic in HMIS database if he/she provided with a history of intake of oral/injectable antidiabetics (sulfonamides, thiazides, biguanides, α-glucosidase inhibitors, meglitinides, etc.) or physician prescription mentioning the diagnosis of diabetes mellitus during routine house visits made by health workers. The data regarding type 1 and type 2 diabetes mellitus was not captured in HMIS.

Required sample size was estimated to be 245 based on the prevalence of adequate glycaemic control (HbA1c < 7%) of 31% reported in rural component of ICMR-INDIAB study [4], with a confidence level of 95%, relative precision of 20% and anticipated 10% non- response rate. After the list of self-reported diabetic patients was extracted, the designated data entry operator under HMIS who was briefed about the objectives of the study provided the required 245 random numbers (with the help of random number sequence generator software). This method is followed for routine random sample selection at CRHSP, Ballabgarh. The data entry operator was not involved in any part of the study. Thus, 245 self-reported diabetes individuals were randomly selected from the available list of HMIS. Initial home visits were made by trained project staff member who explained to the patients about the study and asked them to visit the health facility (under Comprehensive Rural Health Services Project) on the given date. Participants who were seriously ill, bed ridden and unable to comprehend the interview questions were planned to be excluded from the study.

At the health facility, a structured questionnaire was administered to collect information regarding socio-demographic characteristics, self-reported dietary intake using 24-h dietary recall and dietary restrictions, alcohol and tobacco use, duration of diabetes, self-monitoring of blood glucose, treatment status and adherence, and presence of co-morbidities such as hypertension. Anthropometric evaluation was done to measure weight, height, hip circumference and waist circumference. Body mass index (BMI) and waist circumference were calculated. Two blood pressure readings were taken 5 min apart in right arm in sitting position using electronic digital apparatus (OMRON Hem 7101; Omron Corp., Tokyo, Japan), and average of the two readings was taken as final blood pressure. This instrument has been found to be reliable as compared to mercury sphygmomanometer [4]. Five millilitre of venous blood sample was taken for assessment of glycated haemoglobin (HbA1c), serum creatinine and lipids. Blood sample was transported immediately to the laboratory under 2–8 ° C and was centrifuged within 1 h of collection. All the laboratory tests were done at a single laboratory attached with Ballabgarh hospital. Samples were analysed by automated analyser following all quality assurances protocol by a single team of laboratory staff.

For this study, hypertension was defined as taking antihypertensive medication and/or systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg [11]. Overweight was defined as a BMI ≥ 23 kg/m^2 but < 25 kg/m^2 for both sexes. Generalised obesity (GO) was defined as a BMI ≥ 25 kg/m^2 for both sexes with or without abdominal obesity (AO) [12]. AO was defined as a waist circumference (WC) ≥ 90 cm for men and ≥ 80 cm for women [13]. Dyslipidaemia was defined as follows: hypercholesterolemia—serum cholesterol levels ≥ 200 mg/dl (≥ 5.2 mmol/l). Hypertriglyceridemia—serum triglyceride levels ≥ 150 mg/dl (≥ 1.7 mmol/l) [14]. Adequate glycaemic control was said to be present when HbA1C level was < 7% [10]. Adherence to treatment was considered adequate if patient reported, based on recall, consuming 90% of total prescribed tablets for diabetes in last 30 days [15].

Statistical analysis

The data was entered in Epi Info 4.3.5 (CDC, Atlanta). All the statistical analyses were performed using Stata 13.0 (developed by StataCorp). Results of descriptive analysis were presented as proportion with 95% confidence interval (CI) or mean ± standard deviation (SD), as applicable. Student's *t* test and chi-square test were done for comparison of continuous and categorical variables respectively. One-way ANOVA was applied to assess the significant differences of HbA1c values among different age groups. Multivariate logistic regression analysis was done with glycaemic control as a dependent variable and all other exposure variables significant in univariate analysis (p value < 0.25) as independent variables. In multivariate analysis, p value < 0.05 was considered as statistically significant. Results were presented as odds ratio (OR) with 95% C.I.

Results

Out of 245 randomly selected persons with diabetes, 243 (99.2%) completed the questionnaire and were tested for HbA1c out of which weight, height and other biochemical tests were done in 227 (92.6%) individuals. Out of these 227, waist circumference was measured for 217 (88.6) individuals.

Table 1 shows the socio-demographic and behavioural characteristics, disease related and biochemical parameters of the subjects with self-reported diabetes. Nearly half of them were in age group of 45–60 years (46.9%). Mean age of the participants was 56.2 ± 11.3 years with no significant difference between males and females. Significant sex difference was observed with respect to educational status ($p < 0.001$). Regarding smoking status, 37.7% of males were current smokers as compared to 18.3% of the females, the difference being statistically significant ($p < 0.001$). Mean duration since diagnosis of diabetes was 8.41 ± 9.91 years, and there was significant difference ($p = 0.03$) between males (9.97 ± 10.91) and females (7.19 ± 8.85). Nearly 2/3rd (61.3%) of persons with diabetes had taken treatment for diabetes in last 1 month. Out of them, 80.5% reported adequate adherence to treatment. Mean BMI and mean waist circumference were 26.8 ± 6.5 kg/m^2 and 96.8 ± 12.3 cm, respectively, with no sex differences in BMI. However, high waist circumference was observed in 70.8% of males as compared to 86.8% of females ($p = 0.04$). Mean serum cholesterol was significantly higher among females (217.5 ± 43.1 mg/dl) as compared to males (204.6 ± 43.6 mg/dl) ($p = 0.02$). Mean triglyceride level was 189.1 ± 92.1 mg/dl, and there was no difference among males and females.

Mean HbA1c was 8.04% ± 2.54, and no significant sex difference was observed. Good glycaemic control (HbA1c < 7%) was observed in 40.3% persons with diabetes. Among the study subjects, 16.5% had HbA1c between 7.0–7.9% and 23.8% had HbA1c above 10% (Fig. 1). There was no significant difference in mean HbA1c across the age groups as observed from one-way ANOVA results (p value = 0.77) and from overlapping 95% confidence intervals (Fig. 2).

On bivariate analysis, longer duration since diagnosis of diabetes was found to be significantly associated with poor glycaemic control. With ≤ 1 year since diagnosis of diabetes as reference, OR of poor glycaemic control among persons having diabetes from 2 to 10 years was 4.69 (0.96–22.8) and 6.58 (1.13–38.3) for persons having diabetes for more than 10 years (Table 2). High triglyceride levels were also significantly associated with poor glycaemic control (OR = 3.41, 95% C.I. 1.25, 9.26) (Table 2). On multivariate logistic regression (with all the variables significant at level of $P < 0.25$ in bivariate analysis included in the model), increased duration since diagnosis of diabetes (2 to 10 years—OR = 2.39 (95% C.I. 1.06–5.37); > 10 years: OR = 2.71 (95% C.I. 1.08–6.81) and high serum triglyceride (OR = 2.17, 95% C.I. 1.19–3.98) were significantly associated with poor glycaemic control. Persons aged > 60 years were more likely to have good glycaemic control (OR = 0.11, 95% C.I. 0.20–0.67) as compared to those aged < 45 years (Table 2).

Discussion

In this community-based study among self-reported diabetics aged 18 years and above to estimate glycaemic control, age and sex distribution of population was comparable to other similar studies done in India. Mean age of self-reported diabetics participated in the DiabCare 2011 study [16] was 51.9 ± 12.4 years, whereas in our study, the mean age was 56 years. However, prevalence of important risk factors like dyslipidemia (high serum cholesterol—59.5%, high serum triglyceride—58.6%) was higher in the present study as compared to the ICMR-INDIAB [4] (where prevalence of high serum cholesterol is 13.9% and high serum triglyceride is 29.5%) and DiabCare India study [16] (prevalence of dyslipidemia is 14.6%). Prevalence of obesity in the present study (59%) is also much higher compared to ICMR-INDIAB study (24.6% in Tamil Nadu, 16.6% in Maharashtra, 11.8% in Jharkhand and 31.3% in Chandigarh) [4]. Thus, overall, there was a higher prevalence of dyslipidemia and obesity in our study as compared to other studies. This may be due to difference in the population characteristics in terms of skewness of age towards right side. However, it may be also be due to other factors or population characteristics which we have not studied.

Mean HbA1c level of 8.04 reported in this study was marginally lower than that reported in ICMR-INDIAB study (8.2 ± 2.0% in Tamil Nadu, 8.0 ± 2.1% in Maharashtra, 8.2 ± 2.4%

Table 1 General characteristics, life-style practices, treatment related factors and biochemical parameters

Parameter	Overall *N* (%)	Male *N* (%)	Female *N* (%)	*p* value
No. of subjects	243	106 (43.6)	137 (56.4)	< 0.001
Age group				
< 45 years	38 (15.6)	18 (17.0)	20 (14.6)	0.62
45–60 years	114 (46.9)	46 (43.4)	68 (49.6)	
> 60 years	91 (37.5)	42 (39.6)	49 (35.8)	
Mean age in years (± SD)	56.2 (11.3)	56.2 (11.9)	56.1 (11.3)	0.97
Education level				
≤5th standard	139 (57.2)	28 (26.5)	111 (81.0)	< 0.001
6th standard and above	104 (42.8)	78 (73.5)	26 (19.0)	
Caste				
General	142 (58.4)	62 (58.5)	80 (58.4)	0.72
OBC	73 (30.1)	30 (28.3)	43 (31.4)	
SC/ST	28 (11.5)	14 (13.2)	14 (10.2)	
Monthly income of participant (in Indian rupees)				
No income	103 (42.4)	21 (19.8)	82 (59.8)	< 0.001
≤5000	81 (33.3)	33 (31.1)	48 (59.3)	
>5000	59 (24.3)	52 (49.1)	7 (11.9)	
Mean monthly income (S.D.)	4049.1 (7650.1)	8165.1 (10,089.3)	865.9 (1775.5)	< 0.001
Marital status				
Currently married	199 (81.9)	94 (88.7)	105 (76.6)	0.04
Alcohol				
Current	19 (7.8)	19 (17.9)	0	< 0.001
Former	23 (9.5)	23 (21.7)	0	
Smoking				
Current	65 (26.7)	40 (37.7)	25 (18.3)	< 0.001
Former	15 (6.2)	10 (9.4)	5 (3.6)	
Self-monitoring of blood glucose				
Yes	57 (23.5)	27 (25.5)	30 (21.9)	0.5
Duration since diagnosis of diabetes				
≤5 years	137 (52.2)	50 (47.2)	77 (56.2)	0.11
>5 to 10 years	44 (18.1)	21 (19.8)	23 (16.8)	
>11 to 20 years	38 (15.6)	24 (17.5)	14 (13.2)	
>20 years	34 (14.0)	21 (19.8)	13 (9.5)	
Mean duration since diagnosis	8.41 (9.91)	9.97 (10.91)	7.19 (8.85)	0.03
Taking treatment				
Yes	149 (61.3)	67 (63.2)	82 (59.9)	0.59
Adequate adherence to treatment ($n = 149$)				
Yes	120 (80.5)	54 (80.6)	66 (80.5)	0.98
Body mass index ($n = 227$)				
Overweight	31 (13.7)	19 (19.2)	12 (9.4)	0.07
Obese	134 (59.0)	52 (52.5)	82 (64.1)	
Mean BMI (± S.D.)	26.8 (6.5)	26.5 (7.3)	27.0 (5.8)	0.56
Waist circumference ($n = 217$)				
High	173 (79.7)	68 (70.8)	105 (86.8)	0.04
Mean WC (± S.D.)	96.8 (12.3)	96.1 (11.6)	97.4 (12.8)	0.45
Serum total cholesterol level ($n = 227$)				
High	135 (59.5)	53 (53.0)	82 (64.6)	0.07
Mean cholesterol (± S.D.)	211. 1 (43.6)	204.6 (43.6)	217.5 (43.1)	0.02
Serum triglyceride level ($n = 227$)				
High	133 (58.6)	60 (60.0)	73 (57.5)	0.71
Mean triglyceride (± S.D.)	189.1 (92.1)	199.3 (98.7)	188.8 (86.1)	0.14
Glycated haemoglobin level				
< 7%	98 (41.3)	42 (40.4)	56 (42.1)	0.79
≥ 7%	139 (58.7)	62 (59.6)	77 (57.9)	
Mean HbA1c (± S.D.)	8.04 (2.54)	8.07 (2.31)	8.06 (2.56)	0.79

in Jharkhand and 9.1 ± 2.3% in Chandigarh) [4]. In this study, only 40% of persons with diabetes had an optimal glycaemic control (HbA1c < 7%). In ICMR-INDIAB study [4], only 31% had optimal glycaemic control, whereas in a large multicentre DiabCare-India study [16], only 17% had HbA1c < 7%. Other smaller studies from Kerala [17], Delhi [18] and Tamil Nadu [19] estimated optimal glycaemic control among patients as 40%, 62% and 29% respectively. Studies from other developing countries such as China and Brazil demonstrated similar results. A study done in China [20] showed that only 38% had adequate glycaemic control, whereas, it was 26% in a study done in Brazil [21]. Even in

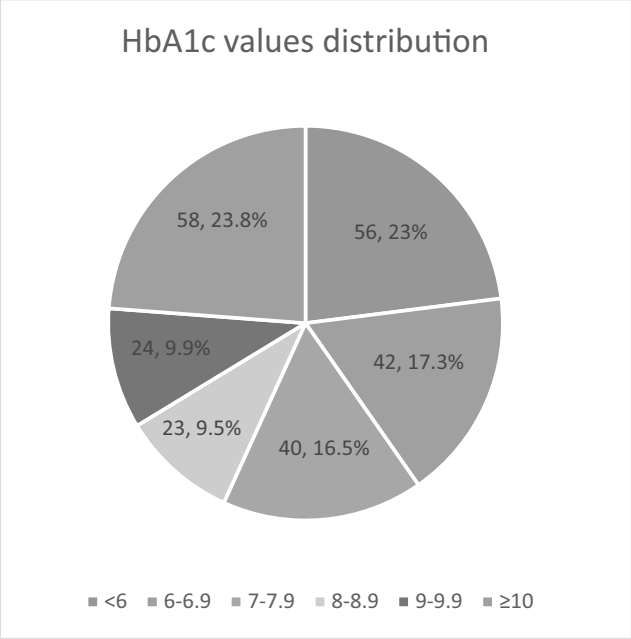

Fig. 1 Distribution of study participants according to glycated haemoglobin (HbA1c) levels

developed countries, large number of diabetic people fail to achieve optimal glycaemic control. In USA, as per the National Health and Nutrition Examination Survey (NHANES) of 2003–04 [22], a staggering 50% of diabetics were reported to have HbA1c higher than 7%.

The results of the present study show that the levels of glycaemic control among persons with diabetes living in rural North India are poor. Evidence exists to suggest that poor glycaemic control is associated with increased risk of all-cause mortality, higher incidence of diabetes related complications and poorer quality of life [6, 23, 24].

Several prospective trials, such as Diabetes Control and Complications Trial in type 1 diabetes [25] and the United Kingdom Prospective Diabetes Study [26], have reported that strict glycaemic control during treatment among diabetics leads to lesser incidence of diabetes related micro-vascular complications. Poor glycaemic control in the rural population is even more perilous in the context of lesser availability of resource in these settings for timely identification and treatment of complications. Moreover, in the resource-constrained settings, emergence of complication also leads to higher cost of treatment.

Findings of the present study also showed a three-time increased risk of poor glycaemic control among persons aged < 45 years as compared to those aged > 60 years. Though, we could not offer a suitable explanation for such a result, similar findings were noted in the ICMR-INDIAB study [4] and the other study in Delhi [18]. Good glycaemic control in the older age can be due to survival bias as impaired glycaemic status is associated with emergence of complications and mortality. This is an important pragmatic aspect in diabetic care as younger diabetics are going to be exposed to higher hyperglycemic level for longer duration leading to development of micro-vascular complications. Moreover, persons with longer duration of diabetes were also at significant higher risk of poor glycaemic control which might augment the effect of chronic hyperglycemia among these individuals. Similar result of increase in HbA1c level with increase in duration of diabetes was seen in DiabCare Asia-India study and ICMR-INDIAB study [27]. Since diabetes is a chronic and progressive disease, poor

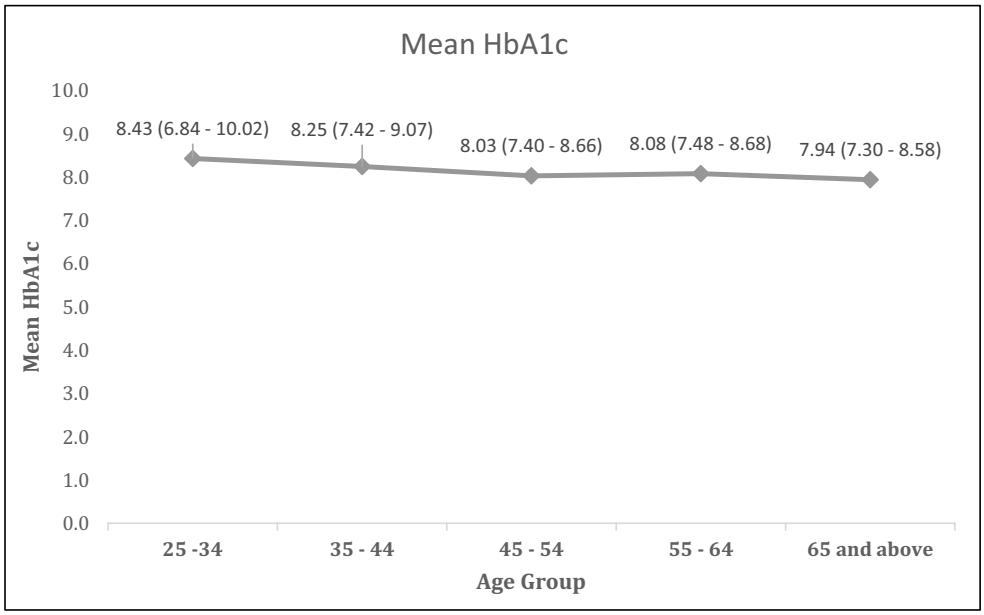

Fig. 2 Distribution of study participants according to age and mean glycated haemoglobin (HbA1c)

Table 2 Logistic regression to show the association of various factors with poor glycaemic control (HbA1c ≥ 7%)

Parameter	Unadjusted OR (95% C.I.)*	*p* value	Adjusted OR (95% C.I.)*	*p* value
Sex				
Male	Reference	–		
Female	1.46 (0.33–6.37)	0.61	–	–
Age group				
<45 years	Reference	–	Reference	–
45–60 years	0.54 (0.11–2.49)	0.43	0.54 (0.21–1.36)	0.19
>60 years	0.28 (0.04–1.64)	0.16	0.34 (0.12–0.75)	0.02
Education level				
Illiterate—5th standard	Reference	–		
6th standard and above	1.77 (0.58–5.35)	0.30	–	–
Caste				
General	Reference	–	Reference	
OBC	0.43 (0.15–1.21)	0.11	0.61 (0.32–1.16)	0.13
SC/ST	1.48 (0.41–6.05)	0.50		
Monthly income of participant				
No income	Reference	–		
≤5000	0.79 (0.22–2.80)	0.71	–	–
>5000	0.91(0.21–3.80)	0.89	–	–
Alcohol				
Non-user	Reference	–		
Former	2.09 (0.42–10.4)	0.36	–	–
Current	0.62 (0.11–3.30)	0.58	–	–
Smoking				
Non-user	Reference	–		
Former	1.02 (0.17–8.16)	0.93	–	–
Current	2.00 (0.66–6.07)	1.13	–	–
Self-monitoring of blood glucose				
Yes	Reference	–		
No	1.99 (0.54–7.37)	0.29	–	–
Adequate adherence to treatment				
Yes	Reference	–		
No	2.28 (0.64–5.09)	0.28	–	–
Duration since diagnosis of diabetes				
≤1 year	Reference	–	Reference	–
2 to 10 years	4.69 (0.96–22.8)	0.05	2.39 (1.06–5.37)	0.03
>10 years	6.58 (1.13–38.3)	0.03	2.71 (1.08–6.81)	0.03
BMI ($n = 227$)				
Normal and underweight	Reference	–		
Overweight	2.79 (0.43–17.5)	0.27	–	–
Obese	1.54 (0.30–7.69)	0.60	–	–
Waist circumference ($n = 217$)				
Normal	Reference	–		
High	0.34 (0.06–1.90)	0.22	–	–
Total cholesterol ($n = 227$)				
Normal	Reference	–		
High	1.11 (0.40–3.07)	0.53	–	–
Triglyceride ($n = 227$)				
Normal	Reference	–	Reference	–
High	3.41 (1.25–9.26)	0.02	2.17 (1.19–3.98)	0.01

*All the variables significant at $p < 0.25$ in the bivariate model were included in the multivariate model. Multivariate analysis was performed with backward elimination method

glycaemic control with increasing duration of diabetes is plausible. Association of poor control of diabetes with increasing duration coupled with poor control among younger population poses a double risk to younger diabetic population. Hypertriglyceridemia was also significantly associated with poor glycaemic control. Hypertriglyceridemia and poor glycaemic control have a vicious association as the former may lead to insulin resistance and thus poor glycaemic control. Similarly, poor glycaemic control can also lead to higher triglyceride levels. Similar association was also reported in ICMR-INDIAB study [4]. Association of higher triglyceride level with higher HbA1c level is important in the context of treatment goals as both are outcomes of poor treatment practices and compliance.

The main strength of this study is that this is one of the few population-based studies done in rural part of North India. Glycaemic control is largely affected by the available treatment and diagnostic opportunities and may vary widely across the settings. Treatment practices in turn are determined by the

socio-economic status of the population and adequacy of the health system. Persons with diabetes sampled in this study are representatives of the population of this region as the area is under continuous demographic and health surveillance for many years and has robust enumeration related to vital statistics and chronic disease morbidity pattern. We collected data on many covariates of glycaemic control and other risk factors such as obesity, hypertriglyceridemia, smoking and alcohol consumption practices. However, our study has few limitations. Being cross-sectional in nature, the study could not elaborate on the cause effect relationship of the determinants for glycaemic control. Moreover, a single estimation of HbA1c may not be representative of long-term glycaemic status. A high proportion of elderly population in this study needs to be considered while interpreting the findings of the study. In a setting with high prevalence of anemia, the results of HbA1c should be interpreted with caution as haemoglobin level is known to influence HbA1c. Since, we did not estimate the haemoglobin level, possible correction of HbA1c with respect to haemoglobin level could not be done. We did not report insulin use as only few participants were on insulin.

Conclusion

In conclusion, our study from rural North India suggests that optimal glycaemic control among self-reported diabetics is poor with only 40% having HbA1c < 7%. Also, there is three times higher risk of poor glycaemic control in people less than 45 years. There is a need to focus on good glycaemic control which may be in the form of improved follow-up from the time of diagnosis of diabetes especially in young diabetics. The findings are important in the context of rural health settings. Glycaemic control in rural population of India is not adequate which alarms for the need of preventive and therapeutic strategies targeting hyperglycemia in this population.

Sources of funding The funding was granted by institution (AIIMS, New Delhi) as a part of intra-mural project.

Compliance with ethical standards

Ethical approval Ethical clearance for the study was obtained from the Institutional Ethics Committee with the approval number IEC/NP-341/08.10.2014. This article does not contain any experiments done on animal or human subjects by any of the authors. This study contains data obtained from human subjects. Written informed consent was taken from the participant for inclusion in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):715–720
https://doi.org/10.1007/s13410-019-00733-2

ORIGINAL ARTICLE

Percent body fat and adiposity indicators: a study among tribal and non-tribal females of India

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Received: 8 August 2018 / Accepted: 27 February 2019 / Published online: 14 March 2019

Abstract

Background During the past few decades, overweight and obesity have become a global health hazard. The estimation and documentation of obesity are important in countries like India that have a broad diversity of populations. However, there is discrepancy in the various adiposity indicators used to estimate obesity. The present study examines population-specific associations between percent body fat (%BF) and adiposity variables among females in three population groups.

Materials and methods A cross-sectional study was conducted among Jat, Mizo, and Liangmai communities of India. Data were collected using interview schedules and somatometric measurements based on ISAK protocols. Body density was calculated from skinfold measurements and the Siri equation was used to determine %BF. WHO cut-offs were used for waist circumference (WC), waist-to-hip ratio (WHR), and body mass index (BMI), whereas Ashwell and Gibson and American Council for Exercise cut-offs were used for waist-to-height ratio (WHtR) and %BF, respectively.

Results Obesity variables are differentially distributed across the three populations. The mean values of %BF and WHtR were the highest among the Liangmai, whereas BMI, WC, and WHR were the highest among the Mizo.

Conclusion All of the selected adiposity indicators (WC, WHR, WHtR, and BMI) in all three populations were significantly positively correlated with %BF. Thus, %BF should be incorporated with other adiposity indicators as well, for a better understanding and categorisation of obesity among different populations.

Keywords Obesity · Percent body fat · Tribal · Non-tribal · Ethnicity

Introduction

Overweight and obesity have considerably become a global health hazard as the prevalence of obesity has increased during the last few decades [1]. It has also become the most frequently diagnosed chronic disease in many countries affecting all age groups. Whenever excessive fat gets accumulated in the body leading to health impairment, the person is said to be suffering from obesity [2]. Obesity is diagnosed on the basis of excess body fat; thus, measuring body fat is important for the diagnosis of obesity and its associated comorbidities [3]. Years ago, it was considered as a problem of high-income countries but now, low- and middle-income countries like India have shown an increase in the prevalence of obesity [4].

Obesity can be characterised by various adiposity indicators, with body mass index (BMI) being most frequently used followed by waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR). But, all of these adiposity indicators have been shown to be of limited use for distinguishing lean mass from fat mass [5]. If BMI is the sole measure for estimation of obesity, individuals with high percent body fat (%BF) and low BMI will escape the detection of obesity-related diseases [6, 7]. Moreover, the prediction of central obesity through WC, WHR, and WHtR using a standard cut-off seems to be less accurate, as differences in body composition exist between different age groups and ethnic groups [8]. Thus, the estimation of %BF has now become an important measure for assessing obesity [9]. Among women, a higher level of essential body fat is observed as compared to

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13410-019-00733-2) contains supplementary material, which is available to authorized users.

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men, because sex-characteristic fat is essential for child-bearing. Moreover, the fat deposition and weight gain before, during, and after pregnancy not only affect current pregnancy but also act as primary contributors to the development of obesity among women in later stages of life [10].

Although a number of obesity variables have been studied and reported, identification of feasible, cost-effective, and relatively common variable is needed. The number of deaths due to non-communicable diseases is rapidly increasing; therefore, it is essential to spread awareness among the general population about maintenance of desirable amount of fat in body. Thus, estimation of body fat will not only provide an overall impression of health but will also set a good baseline, and later provide a quantitative number on which a fitness programme can be developed for any population. Specifically in Indian context, where there is a huge diversity at every level, population-based studies associating percent body fat with other adiposity variables using anthropometry are almost negligible. Thus, the present study aims to estimate obesity using %BF and by comparing it with other adiposity indicators (WC, WHR, BMI, WHtR) among tribal (Mizo and Liangmai) and non-tribal (Jat) females of India.

Materials and methods

Study population

A cross-sectional study was conducted across three different communities, namely, the Jat, Mizo, and Liangmai. Data were collected from 1483 females among whom 1070 were from the Jat community residing in the Palwal district of Haryana, 227 were from the Mizo community from the Churachandpur district of Manipur, and 186 were from the Liangmai community from the Tamenglong and Senapati districts of Manipur, India. The age group of the Jat females was 30 to 65 years and the age groups of the Mizo and Liangmai females were 18 to 65 years. The presently studied non-tribal population Jat inhabits the plain area of Haryana, whereas the studied tribal populations Mizo and Liangmai inhabit the hilly terrain of Manipur. Jat has a Eurasian ancestry and speaks language belonging to Indo-European linguistic group. Their major staple food is wheat and they follow vegetarianism. In contrast, Mizo and Liangmai females belonged to East-Asian ancestry and speak languages categorised under Tibeto-Burman linguistic group. Their major staple food is rice and they are non-vegetarians.

The data used in the present study were collected through household survey carried out as part of different projects where genetic analyses were done. Thus, the major criteria for recruitment of participants in this study were that the participants should not be blood related up to at least the first cousin. The study was approved by the Ethical Committee of the Department of Anthropology, University of Delhi, Delhi, India.

Data collection

Data related to general information like age, sex, educational status, lifestyle, occupation, and dietary pattern were collected with the help of pre-tested and modified interview schedules. Eight somatometric measurements were carried out, namely height, body weight, waist circumference, hip circumference, and skinfold at biceps, triceps, and subscapular and supra-spinale locations using standardised protocols established by the International Society for the Advancement of Kinanthropometry (ISAK) [11]. Height was measured in centimetres (cm) using an anthropometric rod and was recorded to the nearest 0.1 cm. Body weight was measured to the nearest 0.1 kilogrammes (kg) using a portable spring balance. Waist circumference (WC) and hip circumference (HC) were taken using a flexible steel tape in centimetres. WC was measured at the level of the narrowest point between the lower costal (10th rib) border and the iliac crest. HC was measured at the level of the greatest posterior protuberance of the buttocks which usually corresponds anteriorly to about the level of the symphysis pubis.

Skinfold thickness was measured in millimetres (mm) using Harpenden skinfold calliper to the nearest of 0.1 mm. Skinfold at biceps and triceps was taken at the place where the mid upper arm circumference has been measured and above the biceps and triceps muscles, respectively, when the arm is hanging freely. Subscapular skinfold was taken at the point immediately below the inferior angle of the scapula and skinfold at supra-spinale was taken above the anterior superior iliac spine on a line to the anterior axillary border and on a diagonal line going downwards and medially at 45°.

Percent body fat and other adiposity parameters

Body density was calculated using the age- and sex-specific Durnin and Womersley equation (1974) [12] and, after that, the Siri equation (1961) [13] was used to determine %BF. The age- and sex-specific equations of the Durnin and Womersley (where D= predicted density of the body (g/ml), and L= log of the total of the 4 skinfolds) and Siri equation are as follows:

1. Age—Less than 17 years

Males—$D = 1.1533 - (0.0643 \times L)$ Females—$D = 1.1369 - (0.0598 \times L)$

2. Age—17–19 years

Males—$D = 1.1620 - (0.0630 \times L)$ Females—$D = 1.1549 - (0.0678 \times L)$

3. Age—20–29 years

Males—$D = 1.1631 - (0.0632 \times L)$ Females—$D = 1.1599 - (0.0717 \times L)$

4. Age—30–39 years

Males—$D = 1.1422 - (0.0544 \times L)$ Females—$D = 1.1423 - (0.0632 \times L)$

5. Age—40–49 years

Males—$D = 1.1620 - (0.0700 \times L)$ Females—$D = 1.1333 - (0.0612 \times L)$

6. Age—more than 50 years

Males—$D = 1.1715 - (0.0779 \times L)$ Females—$D = 1.1339 - (0.0645 \times L)$

$$\text{Siri Equation (1961)} : \%\text{Body Fat} = (495/\text{Body Density}) - 450$$

Various adiposity indicators like WC, BMI, WHR, and WHtR were calculated. BMI was calculated as weight in kilogrammes divided by height in metres square. Waist-to-hip ratio was calculated as waist circumference divided by hip circumference. Waist-to-height ratio was calculated as waist circumference divided by height. Females with WHR > 0.85, WC ≥ 80 cm, BMI ≥ 27.5 [2, 14], WHtR ≥ 0.5 [15], and %BF ≥ 32.00 were considered to be at risk [16].

Statistical analysis

Statistical analyses were carried out using MS Excel 2010 and SPSS 20. Basic descriptive statistics (mean and standard deviation) were calculated to understand the diversity of various adiposity indicators and somatometric measurements among females in all three population groups. Between-group differences in somatometric variables were tested using one-way analysis of variance (ANOVA) followed by *Bonferroni* post hoc test. Pearson's correlation coefficients (r) were calculated to determine the relation of %BF with BMI, WC, WHR, and WHtR. Results with p values < 0.05 were considered significant.

Results

A differential distribution of various adiposity indicators was found, where high WHR was observed in 62.3% (667/1070) Jat females, whereas 52.8% (565/1070) females had central obesity, 48.9% (524/1070) females had high %BF, 37.6% (403/1070) females had high WHtR, and 21.21% (227/1070) females had high BMI. On the other hand, 19.5% (209/1070) Jat females were found to be underweight. In the case of Mizo females, 80.1% (182/227) had high WHR, 73.1% (166/227) had central obesity, 52.8% (120/227) had high WHtR, 45.81% (104/227) had high BMI, and 29.9% (68/227) had high %BF. On the other hand, 3.5% (8/227) females were found to be underweight. Also, among Liangmai, high WHR was observed in 84.9% (158/186) females, whereas 73.1% (136/186) females had central obesity (WC), 63% (119/186) had high WHtR, 53.7% (100/186) had high %BF, and 43.01% (80/186) had high BMI. On the other hand, 1% (2/186) females were found to be underweight (Table 1).

Correlation analyses indicated that all the selected adiposity indicators (BMI, WC, WHR, WHtR) in all three populations demonstrated statistically significant positive correlations with %BF (Table 2).

All the adiposity indicators in all three populations are found to be higher than the normal ranges except for BMI in the Jat population. The mean values of BMI (21.99 kg/m^2), WC (81.16 cm), WHR (0.87), and WHtR (0.52) were lowest among Jat females when compared with Mizo and Liangmai females. However, significantly higher mean values of BMI (24.84 kg/m^2) and WC (86.61 cm) were found among Mizo females. On the other hand, Liangmai females have comparatively higher statistically significant mean values of %BF (31.73%), WHR (0.92), and all skinfold thicknesses (S-Table 1).

The percentages of Jat females classified by BMI as being normal body weight and as overweight but classified as obese by %BF were 41.3% and 75%, respectively. In Mizo females, 11.1% and 35.7% of those classified by BMI as being normal body weight and as overweight, respectively, were found to be obese by %BF. In Liangmai females, 25% and 66.2% of those classified by BMI as being normal body weight and as overweight, respectively, were found to be obese by %BF. In all the three populations, 89.7%, 50%, and 80.9% of those classified as obese by BMI were also found to be obese by %BF among Jat, Mizo, and Liangmai females, respectively (S-Table 2a).

The percentages of Jat females classified by WC as being normal body weight and at risk for obesity but classified as obese by %BF were 21.3% and 73.6%, respectively. In the case of Mizo females, 1.63% and 40.4% of those classified by WC as being normal body weight and at risk for obesity, respectively, were found to be obese by %BF. In Liangmai females, 20% and 66.2% of those classified by WC as being normal body weight and at risk for obesity, respectively, were found to be obese by %BF (S-Table 2b).

The percentages of Jat females classified by WHR as being normal body weight and at risk for obesity but classified as obese by %BF were 15% and 55.8%, respectively. In the case of Mizo females, 5.5% and 32.1% of those classified by WHR as being normal body weight and at risk for obesity, respectively, were found to be obese by %BF. In Liangmai females, 25.1% and 58.6% of those classified by WHR as being normal body weight and at risk for obesity, respectively, were found to be obese by %BF (S-Table 2c).

Table 1 Prevalence of underweight and increased %BF, BMI, WC, WHR, and WHtR among females of Jat, Mizo, and Liangmai populations

Variables	Jat	Mizo	Liangmai	*p* value
Increased %BF	524/1070 (48.9%)	68/227 (29.9%)	100/186 (53.7%)	< 0.000*
Increased BMI	227/1070 (21.21%)	104/227 (45.81%)	80/186 (43.01%)	< 0.001*
Underweight	209/1070 (19.5%)	8/227 (3.5%)	2/186 (1.0%)	< 0.001*
Increased WC	565/1070 (52.8%)	166/227 (73.1%)	136/186 (73.1%)	< 0.001*
Increased WHR	667/1070 (62.3%)	182/227 (80.1%)	158/186 (84.9%)	< 0.001*
Increased WHtR	403/1070 (37.6%)	120/227 (52.8%)	119/186 (63.0%)	< 0.001*

%BF, percent body fat; *BMI*, body mass index; *WC*, waist circumference; *WHR*, waist-to-hip ratio; *WHtR*, waist-to-height ratio; *$p < 0.05$ are significant

The percentages of Jat females classified by WHtR as being normal body weight and at morbidly high risk for obesity but classified as obese by %BF were 19.1% and 86.4%, respectively. In the case of Mizo females, 53.5% of those classified by WHR as being at morbidly high risk for obesity were found to be obese by %BF. In Liangmai females, 14.8% and 83.3% of those classified by WHtR as being normal body weight and at morbidly high risk for obesity, respectively, were found to be obese by %BF (S-Table 2d).

Discussion

The identification of true obese individuals in a population is highly essential for the detection of obesity-related diseases, specifically in countries like India where the levels of obesity have increased extensively in the past few years [17]. The results of the present study showed a significant difference in estimates of body composition among all three populations. Even though a modified criterion for defining overweight and obesity in the Indian population was used, it does not always indicate the degree of obesity. According to this criterion, all the adiposity indicators in all three populations were found to be higher than the prescribed normal ranges [2, 15] except for BMI in the Jat population (S-Table 1 and Table 1). This seems to indicate a burden of obesity in the three selected populations in terms of various adiposity indicators. However, the mean %BF was in normal range in all the populations (S-Table 1).

Table 2 Correlation between percent body fat and various adiposity indicators among Jat, Mizo, and Liangmai females

Adiposity indicators	Populations		
	Jat	Mizo	Liangmai
BMI	0.61**	0.51**	0.58**
WC	0.61**	0.54**	0.54**
WHR	0.32**	0.28**	0.34**
WHtR	0.62**	0.52**	0.52**

**Correlation is significant at 0.01 level (2-tailed)

Generally, obesity has been measured using various adiposity indicators like BMI, WC, WHR, and WHtR, but until now, no common consensus has been derived on the best predictor of obesity. Earlier, BMI was considered to be a better predictor of obesity and its associated risk factors; then later on, evidence suggested a greater association of WC and WHR with obesity [18] and metabolic syndromes in comparison with BMI [19–22]. Few recent studies have also revealed WHtR to be a better predictor of obesity and metabolic risk compared with other adiposity indicators [15, 23–25]. The reason being, height of an individual influences the distribution of body fat, and so, by keeping waist circumference to less than half of height, the body fat will get distributed evenly. However, there is an inconsistency in the use of these adiposity indicators for predicting the levels of obesity and its related disorders, in terms of different ethnicities [26].

Further, the estimation of general and central obesity through BMI, WC, and WHtR does not take body fat distribution into account. All these adiposity indicators poorly distinguish between total body fat, total body lean mass, and bone mass [27]. The existing literature also suggests %BF to be a relatively better measure of excess adiposity and obesity [28–30]. Also, individuals with high %BF will tend to escape from being screened for the risk of obesity and its related diseases even if other adiposity variables are found to be normal. The similar type of discrepancy has been found in our results, where 41.3%, 11.1%, and 25% females classified earlier as normal by BMI were found to be obese by %BF among Jat, Mizo, and Liangmai, respectively (S-Table 2a). Thus, these BMI-classified normal females would be at higher risk for obesity-related diseases, if %BF was not measured simultaneously. Moreover, the prediction of obesity using %BF among the obese individuals by BMI is different in different populations, as 89.7% and 80.9% females were identified as obese by both BMI and %BF among Jat and Liangmai, respectively. On the other hand, only 50% females were identified as obese by both BMI and %BF among Mizo.

Another interesting finding of the present study is that, in the case of Jat females who were classified as underweight by BMI, 8.6% turned out to be obese when their %BF was measured. Similar results have been found for other adiposity

indicators (WC, WHR, and WHtR) where females have been misclassified as normal according to these adiposity indicators (S-Table 2b, c, and d). These results are in accordance with the existing literature that suggests individuals with high %BF and normal BMI are more likely to develop metabolic syndrome [31] and cardiovascular diseases [32–34]. Also, various previous studies reported that increased cardiovascular risk is associated with high %BF regardless of BMI which may lead to underestimation of participants with CVD risk factors [35, 36].

Thus, for assessing obesity among populations, BMI and other adiposity indicators like WC, WHR, and WHtR alone could not be considered as sole indicators [37, 38], as individuals get masked from the screening of underlying excess adiposity characterised by an increased percentage of fat mass and reduced muscle mass. Rather, percent body fat using appropriate formula along with other adiposity indicators should be considered to capture and categorise obesity in populations [39, 40].

Conclusion

The study concludes that %BF measurement should be incorporated with other adiposity variables in order to reduce the discrepancy in the classification of true obese individuals and for a better understanding of obesity-related diseases. However, the results of the present study need to be validated with larger sample size including males.

Acknowledgements The authors are grateful to the Department of Biotechnology, Ministry of Science and Technology and Research, and Development Grant, 2014–2015, University of Delhi, for providing grants to carry out this study and all the participants of Jat, Mizo, and Liangmai populations for their generous participation in this study.

Grant sponsorship This study was sponsored by Research and Development Grant, 2014–2015, University of Delhi, and Department of Biotechnology, Ministry of Science and Technology.

Author contributions Shivani Chandel, Monika Kulshreshtha, and Sukhmani Kaur analysed the data and drafted the manuscript. Kallur Nava Saraswathy and Naorem Kiranmala Devi designed the study and directed implementation and data collection. Somorjit Singh Ningombam, Masan Kambo Newmei, and Varhlun Chhungi collected the data and Suniti Yadav provided necessary logistic support. Shivani Chandel, Monika Kulshreshtha, Sukhmani Kaur, and Kallur Nava Saraswathy edited the manuscript for intellectual content and provided critical comments on the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent An informed written consent was obtained from all the recruited participants.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):721–729
https://doi.org/10.1007/s13410-019-00743-0

ORIGINAL ARTICLE

Association between major dietary patterns and metabolic syndrome components: a population-based study from north-west of Iran

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Received: 5 July 2018 / Accepted: 15 April 2019 / Published online: 11 May 2019

Abstract

Introduction Considering the importance of determining the association between dietary patterns and diseases in each population, the association of major dietary patterns with metabolic syndrome (MetS) and its components in an adult population of north-west of Iran was studied.

Methods In this cross-sectional study, the data of the major Lifestyle Promotion Project conducted in north-west of Iran in 2015 was used. Anthropometric characteristics, blood pressure, and biochemical profile of 531 participants were measured. MetS was determined according to the adult panel III criteria. Dietary patterns were derived by factor analysis using a validated food frequency questionnaire (FFQ). The logistic regression analysis was adjusted for age, sex, smoking status, education, and physical activity level (model 1) and further for BMI and energy intake (model 2).

Results Three major dietary patterns including animal food, healthy, and Western patterns were identified. Fasting blood sugar was significantly lower in the first tertiles of the Western dietary pattern (p value of the fully adjusted model (model 2), 0.02). According to the results of logistic regression, in both unadjusted model (OR: 2.02, 95% CI: 1.10, 3.69) and adjusted (demographic factors) model (OR: 1.95; 95% CI: 1.02, 3.75), individuals in the second tertile of animal food dietary pattern had significantly higher odds for high diastolic blood pressure.

Conclusions Avoidance from animal food dietary pattern could be suggested by dietitians for prevention of hypertension in the adult population.

Keywords Dietary pattern · Factor analysis · Hypertension · Metabolic syndrome

Introduction

Metabolic syndrome is a clustering of different risk factors related to cardiovascular disease (CVD) and diabetes including hypertension, abdominal obesity, hyperglycemia, and dyslipidemia [1]. The prevalence of metabolic syndrome in Asia, mostly in Middle Eastern countries, seems to be high [1–3]. A recent systematic review and meta-analysis showed that the prevalence of metabolic syndrome in Iran was 36.5%. Many factors including ethnic predisposition, lifestyle, and environmental factors are associated with an increased prevalence of metabolic syndrome [4]. Moreover, diet is considered one of

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the important factors in developing metabolic syndrome [5] and many attempts have been made to identify the important food and nutrients associated with metabolic syndrome [5, 6]. However, nutrients or foods are not consumed isolated and the etiology of the chronic disease including the metabolic syndrome could not be explained only by the assessment of a single nutrient or food [7]. One of the approaches for assessment of the combined effect of nutrients and food is the dietary pattern approach [8, 9]. Using this approach, the complete picture of food and nutrient interactions and their synergic effects could be achieved and the link between diet and chronic disease could be evaluated [10].

Previously, few studies have assessed the link between dietary patterns and metabolic biomarkers using cluster and factor analysis and provided mixed results in different populations [11]. In some populations, the "Western" dietary pattern was associated with metabolic syndrome [12–14]; however, in German and Korean populations, the "traditional" dietary pattern was associated with the increased risk of metabolic syndrome [15, 16]. In recent years, Iran faced with nutrition transition, namely the adoption of a Western diet; and its combination with traditional dietary pattern provides a specific opportunity for more researches in the field of dietary intake in this country [17]. There are limited studies conducted in Iran that assessed the association between the metabolic syndrome and dietary pattern in women and individuals with insulin resistance and showed the significant associations among major dietary patterns and obesity and metabolic syndrome [18–20]. However, to the best of our knowledge, there is no study to assess this association in the general population. So, in the current study, the association of dietary patterns identified by factor analysis with metabolic syndrome was assessed in Tabriz-Iran.

Methods

In the cross-sectional analysis, the data set of the Lifestyle Promotion Project (LPP) conducted in 2015 in East-Azerbaijan, Iran, was used. The probability proportional to size multistage stratified cluster sampling was used as a sampling method. The detailed method of sampling is described previously [21]. Briefly, 550 participants from 150 clusters were enrolled. Incomplete information was excluded and 531 final samples were subjected to statistical analysis. People were included in the present study if their original nationality was Iranian and aged between 15 and 64 years. Subjects with active liver injury, severe chronic illness requiring bed rest, physical disability, mental disability, and pregnant women were excluded. The Ethics Committee of Tabriz University of Medical Sciences approved the present study (registration number: 1394.383). This study was reported in accordance with the STROBE guidelines.

The trained health professionals visited households and gathered the dietary and demographic information. The demographic information included age, education, smoking status, and physical activity level. The socio-demographic characteristics and smoking status were collected through a questionnaire. The short form of international physical activity questionnaire (IPAQ) was used for assessing the physical activity level [22, 23]. The body weight was measured to the nearest 0.1 kg on a Seca digital weighing scale (Dubai, United Arab Emirates), and height was measured to the nearest 0.1 cm, with bare feet using a stadiometer fixed to the wall and body mass index (BMI) was calculated by dividing weight (kg) to height^2 (m^2).

For determining the metabolic syndrome status, waist circumference, blood pressure, the serum level of triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and fasting blood glucose were measured according to standard methods. Briefly, 10 ml 12-h fasting blood sample was collected. After centrifuging blood samples at 2000 rpm for 10 min at room temperature, the levels of serum HDL-C, TG, and glucose were measured by enzymatic colorimetric methods with a commercially available kit (Pars Azmoon, Tehran, Iran) on an automatic analyzer (Abbott, model Alcyon 300, USA). Blood pressure was measured with a standard manual sphygmomanometer in sitting position. Waist circumference was measured at the minimum circumference between the iliac crest and the rib cage with an anthropometric tape while the subjects were wearing light clothing. Participants were classified as having metabolic syndrome according to the internationally recognized criteria of NCEP-ATP III [24], if a subject met more than three of the following criteria: waist circumference ≥ 102 cm in men and ≥ 88 in women; TG ≥ 150 mg/dl or on drug treatment for hypertriglyceridemia; HDL-C < 40 mg/dl in men and < 50 mg/dl in women or on drug treatment for hypo-high-density lipoprotein (HDL) cholesterolemia; systolic blood pressure $\geq$ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or using antihypertensive drug and fasting glucose ≥ 100 mg/dl or on drug treatment for hyperglycemia. Moreover, the new components of metabolic syndrome including ALT and AST [25, 26] were also measured using the ultraviolet method.

For food pattern determination, a quantitative food frequency questionnaire (FFQ), asking about the consumption of food and beverages over the past year was used. The FFQ included 80 questions which was developed and validated for LPP study and reference portions were defined based on the most reported portion sizes in the 24-h recall [27]. This questionnaire was completed by face-to-face personal interviews by expert dietitians. For each item, respondents indicated the number of times and also the amount of consumption of each food item per day, per week, per month, or per year in an open-ended format. Then, the reported frequency of each food item was converted into a daily consumption. Each food item was

assigned to one of the defined food groups according to their nutrient content (Table 1).

For statistical analyses, SPSS V18 was used. The principal component analysis was used to determine major dietary patterns. The factors were rotated by varimax rotation and our choice to retain factors was based on natural interpretation of the factors, eigenvalues > 1, and scree plots [28]. By interpretation of the data and also considering the prior literature, the derived dietary patterns were labeled. The factor score for each pattern was calculated and for each dietary pattern, participants received a factor score. Participants were categorized according to tertiles of dietary pattern scores. The first tertile (T1) of each dietary pattern indicated the lower adherence to that certain dietary pattern. The differences in continuous variables across different tertiles of dietary pattern scores were determined using one-way ANOVA. The χ^2 test was used to compare the categorical variables across tertiles. ANCOVA was used to estimate the adjusted mean of metabolic syndrome components across tertiles of dietary pattern scores. Age, sex, smoking, BMI, and energy intake were used as covariates. Logistic regression was used to determine the association between tertiles of dietary patterns (as independent factors) and metabolic syndrome components (as dependent factor) and also age, sex, smoking status, education and physical activity level, BMI, and energy intake as covariates. A significance level of 0.05 was used and confidence intervals (CIs) were calculated at 95% level.

Results

The mean age of the participants was 42.40 ± 12.38 years and the mean BMI was 27.69 ± 4.94 kg/m^2. About 59.1% of the population was female. The prevalence of high waist circumference, hypertriglyceridemia, hyperglycemia, high systolic blood pressure and diastolic blood pressure, hypo-HDL-cholesterolemia, and metabolic syndrome were 48.2%, 41.4%, 14.7%, 16.4%, 20.2%, 65.9%, and 36.4% respectively.

Using a factor analysis method, three major dietary patterns were recognized: (1) animal food pattern (variance 9.01%) included organ meat (liver, heart, kidney, and other animal organs), fish, pickles, red meat, nuts, and dry fruits; (2) Healthy dietary pattern (variance 7.06%) included dairies, fruit and fruit juice, legumes, and vegetables; and (3) Western-like dietary pattern (variance 6.56%) included pastries, chips, fast foods and animal fats, soft drinks, and refined grains. The identified dietary patterns explained 22.66% of the whole variance in dietary intakes (Table 2).

The participants' characteristics across tertiles of dietary patterns are presented in Table 3. In both sexes, there were

Table 1 Food grouping used for dietary pattern analysis

Food groups	Food items
Red meat	Beef, lamb
Organ meat	Liver, kidney, heart
Fish	All types of fish, canned tuna
Poultry	Chicken
Nuts	Walnuts, peanuts, hazelnuts, pistachio, almond, roasted seeds
Egg	Eggs
Dairy products	All types of milk, yoghurt, cheese
Tea	Tea
Coffee	Coffee
Fruits	Different kind of fruits
Fruit juices	All types of fruit juice
Vegetables	Yellow, green leafy, and all other types of vegetables
Legumes	Different kind of beans, peas, lentil, soy
Whole grains	Dark Iranian bread and barley bread, wheat germ
Refined grains	White bread including Lavash, pasta, rice, white flour, starch, and biscuits
Fast foods	Pizza, sandwich, potato chips, French fries
Dry fruits	Dried dates, dried figs, and all other types of dried fruits
Sweet and desserts	Confectionary products, sugar, chocolate, cookies, cakes
Animal fats	Hydrogenated animal fat
Liquid vegetable oil	Sunflower oil, canola oil, and all other types of vegetable oils
Soft drinks	Soft drinks
Salt	Salt
Pickle	Pickle

Table 2 Factor-loading matrix for major dietary patterns

Food groups	Animal food pattern	Healthy pattern	Western pattern
Red meat	0.31	–	–
Organ meat	0.54	–	–
Fish	0.35	–	–
Poultry	0.47	–	–
Nuts	0.55	–	–
Egg	–	–	0.38
Dairy products	–	0.54	–
Tea	–	− 0.22	–
Coffee	–	− 0.25	–
Fruits	–	0.51	–
Fruit juices	–	0.55	–
Vegetables	–	0.41	–
Legumes	–	0.42	–
Whole grains	–	–	− 0.45
Refined grains	–	–	0.37
Fast foods	–	–	0.46
Dry fruits	0.36	–	− 0.35
Sweet and desserts	–	–	0.46
Animal fats	–	–	0.45
Liquid vegetable oil	–	–	− 0.41
Soft drinks	0.45	–	0.30
Salt	–	–	0.27
Pickle	0.25	–	–

significant differences in protein ($p = 0.02$) and fat intake ($p = 0.02$) across different tertiles of animal dietary pattern. In men, smoking habits (0.02) and carbohydrate intake ($p = 0.002$) and in women, protein intake ($p = 0.005$) were significantly different across tertiles of healthy dietary pattern. Across different tertiles of Western dietary pattern, there were significant differences in physical activity ($p = 0.01$) in men and age ($p = 0.006$), energy ($p = 0.01$), and protein intake ($p = 0.01$) in women.

The unadjusted and adjusted (demographic characteristics, physical activity, BMI, and energy intake) mean anthropometric and biochemical characteristics of participants across tertiles of dietary patterns are shown in Table 4. In the case of waist circumference, the participants in the lowest tertile of the Western dietary pattern had significantly lower waist circumference ($p = 0.02$); however, this difference disappeared after further adjusting for BMI and calorie intake. Moreover, the participants in the higher tertile of the Western dietary pattern (p value$_{uadj} = 0.03$, p value$_{adj} = 0.02$) had significantly higher FBS in both unadjusted and adjusted models.

The results of multivariable-adjusted odds ratios for traditional (waist circumference, Triglyceride, HDL-C, blood pressure, and fasting blood sugar) and new (ALT and AST) metabolic syndrome components by tertiles of different dietary patterns indicated that in an unadjusted model, those in the top tertile of the Western dietary pattern (OR = 2.14; 95% CI: 1.04, 4.39) tended to have 2.14-fold higher odds for higher serum fasting sugar compared with those in the lowest tertile. However, after adjusting for demographic characteristics, dietary factors, and physical activity level, this association was no longer statistically significant. In the case of blood pressure, in the unadjusted model (OR: 2.02, 95% CI: 1.10, 3.69) and after adjusting for age, sex, and educational and smoking status (OR: 1.95, 95% CI: 1.02, 3.75), those in the second tertile of animal food dietary pattern had significantly higher odds for higher diastolic blood pressure compared with those in the lowest tertile.

Discussion

Iran faced with nutrition transition, namely the adoption of a Western diet, and its combination with traditional dietary pattern provides a specific opportunity for more researches in the field of dietary intake in this country [17]. Considering the importance of determining the dietary pattern in population and its association with disease risk, in the present study, we aimed to determine the association between food pattern and metabolic syndrome in general population of the north-west, Iran.

Using a factor analysis method, three major dietary patterns were identified in East-Azerbaijan population: animal food

Table 3 The baseline characteristics of study population stratified by sex and dietary pattern

Variable	Animal food dietary pattern			*p*	Healthy dietary pattern			*p*	Western dietary pattern			*p*
	Tertile 1	Tertile 2	Tertile 3		Tertile 1	Tertile 2	Tertile 3		Tertile 1	Tertile 2	Tertile 3	
Men												
Age	46.18 ± 12.28	44.07 ± 14.59	41.76 ± 14.67	0.22*	44.83 ± 14.67	43.32 ± 12.06	44.87 ± 13.68	0.82*	45.60 ± 12.72	41.51 ± 14.11	44.94 ± 13.32	0.22*
Education												
Illiterate	5 (9.1)	8 (14.3)	2 (3.6)	0.15**	5 (9.1)	6 (10.7)	4 (7.3)	0.32**	3 (15.5)	4 (7.1)	8 (14.3)	0.17**
≤ High school/diploma	44 (80)	38 (67.91)	40 (72.2)		45 (81.8)	39 (69.9)	38 (69.1)		43 (78.2)	37 (66.1)	42 (76.4)	
≥ College degree	6 (10.9)	10 (17.9)	13 (23.6)		5 (9.1)	71 (19.6)	13 (23.6)		9 (16.4)	15 (26.1)	5 (9.1)	
Physical activity												
No physical activity	16 (29.1)	20 (35.7)	16 (29.1)	0.64**	21 (38.2)	14 (25)	17 (30.9)	0.19**	21 (38.2)	18 (32.1)	13 (23.6)	*0.01***
Low	12 (21.8)	11 (19.6)	15 (27.3)		13 (23.6)	16 (28.6)	9 (16.4)		19 (34.5)	9 (16.0)	10 (18.2)	
High	22 (40)	16 (28.6)	16 (29.1)		12 (21.8)	21 (37.5)	21 (38.2)		12 (21.8)	20 (35.7)	22 (40)	
Current smoker	16 (29.1)	14 (25)	11 (20)	0.52**	19 (34.5)	15 (26.8)	7 (12.7)	*0.02***	12 (21.8)	14 (25)	15 (27.3)	0.61**
Energy (Kcal)	4280 ± 1545	3612 ± 1426	2801 ± 1335	0.05*	3891 ± 1489	3668 ± 1477	4136 ± 1388	0.25*	3802 ± 1532	3978 ± 1373	3907 ± 1481	0.83*
Carbohydrate (g)	213 ± 70	216.43 ± 108.78	248 ± 123.35	0.22*	215 ± 88	204.18 ± 70	269.24 ± 13	*0.002**	219 ± 107	235 ± 85	233 ± 116	0.71*
Protein (g)	233 ± 100	191 ± 91	189 ± 79.79	*0.02**	209 ± 106	118.10 ± 80.57	219.27 ± 88	0.15*	211 ± 111	200 ± 81	201 ± 83	0.79*
Fat (g)	292 ± 118	243 ± 133	230 ± 99.21	*0.02**	267 ± 134.53	237.77 ± 109.21	261.46 ± 116	0.40*	267 ± 104	245,107	252 ± 102	0.63*
MetS (%)	12 (21.8)	13 (23.2)	18 (32.7)	0.28**	13 (23.6)	15 (26.8)	15 (27.3)	0.96**	16 (29.1)	13 (23.2)	14 (25.5)	0.73**
Women												
Age	43.55 ± 11.76	4.05 ± 11.61	41.18 ± 11.18	0.32*	43.02 ± 11.67	39.94 ± 11.89	42.82 ± 10.88	0.18*	45.34 ± 987	40.68 ± 11.26	39.76 ± 12.72	*0.006**
Education												
Illiterate	26 (34.2)	13 (16.9)	11 (14.5)	*0.02***	18 (23.7)	18 (23.4)	14 (18.4)	0.14**	17 (22.4)	14 (18.2)	19 (25)	0.43**
≤ High school/diploma	45 (59.2)	54 (70.1)	57 (70.0)		52 (68.4)	55 (71.4)	49 (64.5)		48 (63.2)	56 (72.7)	52 (68.4)	
≥ College degree	5 (6.6)	10 (13.0)	8 (10.5)		6 (7.9)	4 (5.2)	13 (17.11)		11 (14.5)	7 (9.1)	5 (6.6)	
Physical activity												
No physical activity	23 (30.3)	24 (31.2)	26 (34.2)	0.96**	32 (42.1)	19 (24.7)	22 (38.9)	0.05**	35 (46.1)	16 (20.8)	22 (28.9)	0.06**
Low	20 (26.3)	20 (26)	19 (25.0)		21 (27.6)	15 (19.5)	23 (30.3)		15 (19.7)	25 (32.5)	19 (25)	
High	25 (32.9)	29 (37.7)	24 (31.6)		20 (26.3)	34 (44.2)	24 (31.6)		21 (27.2)	27 (35.1)	30 (39.5)	
Current smoker	1 (1.3)	2 (2.6)	0 (0)	0.13**	1 (1.3)	1 (1.3)	0 (0)	0.60**	1 (1.3)	0 (0)	1 (1.3)	0.60**
Energy	3427 ± 1287	3171 ± 1380	2741 ± 1097	*0.004**	2962 ± 1369	2995 ± 12.08	3417 ± 1252	0.05*	3299 ± 1213	3204 ± 1429	2847 ± 178	0.07*
Carbohydrate	198 ± 78	211 ± 96	207 ± 107	0.68*	197 ± 110	194 ± 77	225 ± 91	0.08*	222 ± 122	196 ± 73	198 ± 81	0.18*
Protein	174 ± 74	153 ± 73	127 ± 54	*0.001**	136 ± 67	145 ± 67	172 ± 72	*0.005**	164 ± 59	158 ± 86	132 ± 59	*0.01**
Fat	220 ± 97	196 ± 99	160 ± 73	*0.001**	187 ± 98	186 ± 90	205 ± 92	0.38*	202 ± 81	201 ± 109	174 ± 85	0.10*
MetS (%)	34 (44.7)	26 (33.8)	26 (34.2)	0.20**	28 (36.8)	35 (45.5)	23 (30.3)	0.08**	29 (38.2)	26 (33.8)	31 (40.8)	0.85**

MetS, metabolic syndrome; **p* value of ANOVA; ***p* value of chi-square. Italic numbers indicate significant differences

Table 4 Multivariate-adjusted means for anthropometric and biochemical measures across tertiles of dietary intake

Variable	Animal food dietary pattern			*p*	Healthy dietary pattern			*p*	Western dietary pattern			*p*
	Tertile 1	Tertile 2	Tertile 3		Tertile 1	Tertile 2	Tertile 3		Tertile 1	Tertile 2	Tertile 3	
BMI	28.15 ± 5.00	27.39 ± 5.19	27.62 ± 4.87	0.32	27.67 ± 5.39	27.28 ± 5.05	28.23 ± 4.57	0.32	27.01 ± 4.52	28.08 ± 5.44	28.03 ± 5.00	0.17
M 1	27.89 ± 0.43	27.58 ± 0.42	27.63 ± 0.44	0.17	27.46 ± 0.43	27.30 ± 0.42	28.36 ± 0.43	0.17	26.89 ± 0.43	28.30 ± 0.42	27.91 ± 0.43	0.06
M 2	27.89 ± 0.43	27.58 ± 0.42	27.63 ± 0.44	0.11	27.45 ± 0.44	27.30 ± 0.42	28.36 ± 0.43	0.11	26.89 ± 0.44	28.30 ± 0.42	27.91 ± 0.43	0.06
WC	93.30 ± 14.99	92.17 ± 11.97	93.84 ± 14.12	0.39	93.58 ± 14.38	91.77 ± 13.06	93.97 ± 13.73	0.39	91.24 ± 13.73	95.04 ± 14.62	92.94 ± 12.58	0.08
M 1	92.58 ± 1.17	92.72 ± 1.15	93.73 ± 1.19	0.29	92.53 ± 1.18	92.04 ± 1.16	94.46 ± 1.15	0.29	91.11 ± 1.17	95.47 ± 1.15	92.44 ± 1.17	*0.02*
M 2	912.19 ± 0.92	92.77 ± 0.89	93.25 ± 0.93	0.93	93.00 ± 0.94	92.51 ± 0.89	92.70 ± 0.91	0.93	92.41 ± 0.92	94.86 ± 0.89	91.24 ± 0.93	0.18
TG	162.05 ± 93.69	152.11 ± 100.94	161.44 ± 95.77	0.98	159.6 ± 96.88	158.24 ± 96.72	157.64 ± 97.32	0.98	157.53 ± 100.89	156.77 ± 95.20	161.23 ± 94.68	0.93
M 1	159.9 ± 8.62	154.5 ± 8.52	161.1 ± 8.72	0.96	156.70 ± 8.58	158.3 ± 8.56	116.1 ± 8.54	0.96	157.6 ± 8.62	156.4 ± 8.52	161.1 ± 8.71	0.92
M 2	158.20 ± 1.72	154.9 ± 8.39	159.8 ± 8.81	0.94	157.5 ± 8.78	159.6 ± 8.52	155.7 ± 8.75	0.94	160.8 ± 7.35	153.1 ± 5.72	158.9 ± 6.28	0.80
HDL-C	43.90 ± 9.56	44.77 ± 10.71	42.90 ± 10.08	0.49	43.99 ± 10.97	43.07 ± 9.72	44.54 ± 9.69	0.49	43.83 ± 10.23	43.18 ± 9.50	44.58 ± 10.67	0.53
M 1	43.71 ± 0.86	44.71 ± 0.85	43.15 ± 0.87	0.45	44.04 ± 0.85	43.02 ± 0.85	44.51 ± 0.85	0.45	43.86 ± 0.86	43.47 ± 0.80	44.24 ± 0.87	0.82
M 2	43.62 ± 0.88	44.73 ± 0.86	43.28 ± 0.89	0.24	43.61 ± 0.88	43.00 ± 0.86	40.02 ± 0.88	0.24	43.62 ± 0.85	43.68 ± 0.84	44.27 ± 0.86	0.69
FBS	93.54 ± 25.91	90.10 ± 27.67	81.34 ± 14.82	0.60	86.62 ± 29.35	89.38 ± 19.13	88.96 ± 22.39	0.60	91.66 ± 26.82	84.25 ± 19.27	89.19 ± 24.91	0.03
M 1	91.97 ± 2.02	90.35 ± 2.03	82.49 ± 2.04	0.79	87.28 ± 2.01	88.28 ± 2.10	89.25 ± 2.02	0.79	91.25 ± 2.04	86.06 ± 1.99	87.49 ± 2.05	0.17
M 2	92.81 ± 1.98	89.37 ± 1.96	82.32 ± 2.01	0.91	87.50 ± 2.00	88.65 ± 1.95	88.35 ± 2.00	0.91	92.68 ± 2.04	85.32 ± 1.94	86.48 ± 1.99	*0.02*
SBP	122.04 ± 16.42	120.35 ± 17.87	121.60 ± 19.68	0.08	124.22 ± 21.64	119.57 ± 15.82	120.16 ± 15.62	0.08	121.30 ± 20.21	122.43 ± 18.76	120.25 ± 14.78	0.62
M 1	121.4 ± 1.47	121.4 ± 1.44	120.6 ± 1.47	0.49	122.4 ± 1.45	119.9 ± 1.45	121.1 ± 1.45	0.49	121.0 ± 1.48	123.3 ± 1.44	118.8 ± 1.46	0.07
M 2	121.6 ± 1.45	121.1 ± 1.40	119.8 ± 1.45	0.48	122.3 ± 1.45	120.0 ± 1.41	120.3 ± 1.44	0.48	121.1 ± 1.47	123.1 ± 1.40	118.4 ± 1.42	0.07
DBP	79.14 ± 9.92	77.55 ± 11.86	79.44 ± 13.66	0.22	80.07 ± 13.70	77.25 ± 10.62	78.59 ± 11.11	0.22	78.53 ± 12.09	79.68 ± 13.21	77.90 ± 10.28	0.47
M 1	79.95 ± 1.03	78.02 ± 1.01	78.92 ± 1.03	0.52	79.16 ± 1.01	77.69 ± 1.01	79.04 ± 1.02	0.52	78.38 ± 1.03	80.16 ± 1.01	77.45 ± 1.02	0.14
M 2	79.19 ± 1.03	77.87 ± 1.00	78.13 ± 1.03	0.48	79.34 ± 1.03	77.60 ± 1.00	78.26 ± 1.02	0.48	78.36 ± 1.04	79.84 ± 1.00	77.10 ± 1.01	0.19

BMI, body mass index; *WC*, waist circumference; *HDL-C*, high-density lipoprotein cholesterol; *FBS*, fasting blood sugar; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure. Italic numbers indicate significant association

Model 1: adjusted for age, sex, smoking status, education, and physical activity level. Model 2: model 1 + BMI and energy intake

dietary pattern, healthy dietary pattern, and Western dietary pattern. Previous studies in Iran reported different categories of food pattern in different populations; in a study in female teachers of Tehran-Iran, Esmaillzadeh et al. reported three major food patterns including healthy, Western, and animal food dietary patterns [14]. In other studies conducted on individuals with impaired glucose tolerance and metabolic syndrome, respectively, five [20] [Western, prudent, vegetarian, dairy, and chicken plant patterns] and four [29] [healthy, sweet, meats and fats, and refined grain patterns] major dietary patterns were determined which were different from patterns determined in the present study. The difference in the number and also type of food patterns determined in different studies may be due to the differences in included population (population with insulin resistance and metabolic syndrome compared with the general population in the present study) and also the region where the study was done (Tehran versus Azerbaijan).

The mean level of FBS in both unadjusted and adjusted models was significantly higher in individuals in the last tertile of Western dietary pattern. Moreover, according to the results of regression analysis, there is a positive association between Western dietary pattern and high fasting blood sugar. This may be due to high consumption of refined grains [30, 31] and sweetened beverages [7, 32] and also lower intake of fiber [30, 33, 34], in this dietary pattern. However, the observed association becomes weaker and insignificant after adjusting for demographic characteristics, dietary factors, and physical activity status. This indicates that these factors could significantly affect the relationships between this dietary pattern and fasting blood sugar. Moreover, unlike other studies conducted in Iran [14], we did not show a positive association between Western dietary pattern metabolic syndromes that may be related to the significantly higher level of physical activity in individuals in the highest tertile of Western dietary pattern. In the previous meta-analysis of prospective studies, it was shown that a higher level of physical activity is associated with a lower risk of metabolic syndrome [35].

According to the results of the regression analysis, there was a positive association between animal food dietary pattern (second tertile) and hypertension. This dietary pattern is dominated by red meat and animal food. Previously, the positive association of meat products intake and higher blood pressure was confirmed [36]. The justification for the observed significant association between the second tertile (and not the third tertile) of animal dietary pattern and DBP may possibly be attributed to the higher fat and protein intake of participants in the second tertile compared with the third tertile. The previous study has shown that higher intake of dietary fat was associated with higher blood pressure [37]. Moreover, the results of the INTERMAP (The INTERnational study on MAcro/micronutrients and blood Pressure) study reported the significant positive association between total protein intake and blood pressure. [38]. In line with a study conducted in Japan [39], we did not detect any association between animal food dietary pattern and metabolic syndrome. This might be due to complex nature of this dietary pattern in the present study which includes both foods that can be consumed frequently (nuts and dry fruits) and foods that should be consumed occasionally (meats and animal food) that counteract their effects on metabolic syndrome components [40].

Dairy products, fruits, vegetables, juices, and legumes dominate the healthy dietary pattern identified in the present study. This pattern was not associated with the lower prevalence of metabolic syndrome. These results are in line with the results of studies conducted in Japan [39], Australia [41], and Mexico [12]. It should be noted that the healthy dietary pattern in our study has been characterized by high consumption of dairy products. In Iranian population, it is traditionally common to consume full-fat dairy products [42]. In a recent study, it has been shown that consumption of high-fat dairy products is contributing risk factors for metabolic syndrome [14]. So, this may somewhat explain the lack of a protective association of this dietary pattern and metabolic syndrome in our population.

The results of the present study should be interpreted considering the following limitations: (1) the cross-sectional design of the study, which implies that no causal inferences could be made. (2) For assessing dietary pattern, only the food intake data was considered and the data about eating behavior such as portion size and the number of meal/day was not studied. (3) Considering the use of FFQ in the dietary pattern approach, the limitations of this questionnaire also apply to the dietary pattern approach. However, in the present study, we used a trained health professional for the administration of FFQ instead of the self-employed questionnaire, which increases the validity of data. The strength of the present study is that we involved a large sample size and also we used the appropriate method of sampling. So, this sample could be representative of East-Azerbaijan province population.

In conclusion, based on the results of the present study, among the general population of north-west of Iran, three main dietary patterns including healthy, Western, and animal food dietary patterns were obtained. We also found an independent association between animal food dietary pattern and hypertension. From the practical point of view, avoidance from animal food dietary pattern high in organ meat could be suggested by dietitians for the prevention of metabolic syndrome components especially hypertension among the Iranian population. From the research point of view, more longitudinal studies with standard food frequency questionnaire and assessing the eating behavior are needed to investigate the association of dietary pattern and metabolic syndrome components.

Funding information This study was financially supported by the Tabriz Health services management research center at Tabriz University of Medical Sciences and Eastern Azerbaijan Governor General.

Compliance with ethical standards

The Ethics Committee of Tabriz University of Medical Sciences approved the present study (registration number: 1394.383). This study was reported in accordance with the STROBE guidelines.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent All participants have signed the written informed consent.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):730–738
https://doi.org/10.1007/s13410-019-00740-3

ORIGINAL ARTICLE

The association of diabetes risk score and body mass index with incidence of diabetes among urban and rural adult communities in Qingdao, China

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Received: 16 November 2018 / Accepted: 29 March 2019 / Published online: 25 May 2019

Abstract

Background The Qingdao diabetes risk score (QDRS) is an accurate tool for identifying individuals who are at a high risk for diabetes. This study was designed to determine the association of the QDRS with the incidence of diabetes in the general population in urban and rural settings.

Methods A stratified, random, cluster-sampling method was used to select representative individuals in 2006 and 2009, and the follow-up survey was conducted from 2012 to 2015. Of 5851 participants, 3248 were available in cohort study. The individuals without data of FPG, 2 h PG was excluded in follow-up survey. Finally, a total of 3033 participants were included. Waist circumference, age, and family history of diabetes were collected to determine the QDRS. Cox proportional hazards regression models were used to evaluate the association of QDRS and BMI with the incidence of diabetes. Further, we assessed the relative excess risk due to interaction (RERI), synergy index (S), and attributable proportion due to interaction (AP).

Results Their age-standardized cumulative incidence of diabetes was 16.9% and 10.8% among the urban and rural populations, respectively. In both urban and rural settings, individuals with a QDRS ≥ 14 had a significantly higher risk for diabetes than the individuals with a QDRS < 14 (hazard ratio (HR): 2.37 vs. 1.49; 95% CI 1.35–4.15 vs. 1.09–2.04). Further, having a QDRS of ≥ 14 concurrently with being overweight/obese showed an additive effect on the risk for diabetes in urban settings (RERI = 1.59, S = 2.34, AP = 42.06%). In contrast, a negative interaction was noted in rural settings (RERI = 0.07, S = 0.89, AP = 4.55%).

Conclusions Having a QDRS ≥ 14 demonstrated a strong positive association with the incidence of diabetes. An elevated QDRS combined with BMI showed value in predicting the incidence of diabetes among high-risk populations for diabetes in urban but not rural settings.

Keywords Diabetes risk score · Incidence · Type 2 diabetes · Body mass index · Qingdao diabetes · Risk score

Abbreviations

AP	attributable proportion due to interaction
CNY	Chinese Yuan
CI	confidence intervals
DBP	diastolic blood pressure
DRS	diabetes risk score

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FPG	fasting plasma glucose
HR	hazard ratios
HC	hip circumference
2-hPG	2-h post-load plasma glucose
IDF	International Diabetes Federation
OGTT	oral glucose tolerance test
OR	odds ratios
PA	physical activity
QDDPP	Qingdao Diabetes Prevention Program
RERI	the relative excess risk due to interaction
S	Synergy index
SBP	systolic blood pressure
WC	waist circumference
WHO	World Health Organization
WHR	waist-to-hip ratio
ZDRS	Zung Depression Rating Scale

Background

Diabetes, a chronic and non-communicable disease, is one of the most common health problems in the world. The International Diabetes Federation (IDF) estimated that 415 million adults aged 20–79 years were affected with diabetes in the world in 2015, including 193 million(46.5%) who remain undiagnosed [1]. In China, the prevalence of diabetes is high and continues to increase [2, 3]. In 2007, the occurrence of diabetes was 9.7% [3], which was three times that in 1994 (2.5%) [2]. A national survey conducted in 2010 estimates that 113.9 million Chinese adults have diabetes and that the prevalence rate of diabetes was 11.6% [4]. Thus, diabetes is a leading financial burden on families and society in China [5].

During the last decade, a risk assessment survey has been reported from China [6, 7] and other countries [8, 9]. The diabetes risk score (DRS) was developed in Qingdao China and is considered to be a reasonable, cheap, and effective tool [7, 10]. It enables a large number of individuals to be identified as having a high risk for diabetes. Population-based studies found that risk-assessment questionnaires are a useful screening tool to predict the incidence of diabetes among high-risk populations [11, 12].

Several predictive risk-assessment surveys to identify individuals who are at a high risk for diabetes have been developed [11–13] for use in daily clinical practice. However, some questionnaires need complex personal information [11, 13] and specific blood test results [12], which limit their extensive application in primary care clinics and general hospitals. The Qingdao DRS (QDRS), which is based on waist circumference (WC), age, and family history of diabetes, is an accurate tool for identifying individuals who are at a high risk for diabetes [7]. However, the QDRS does not account for the body mass index, which is used to define being overweight or obese [14]. Several population-based studies have shown that being overweight or having obesity are significant risk factors for diabetes [15–17]. In addition, the study by Yang et al. [3] showed that the prevalence of diabetes was significantly higher in urban (12.8% vs. 10.1% in men and women, respectively) than rural (8.9% vs. 7.7% in men and women, respectively) populations. Our previous study in 2006 [18] also found similar results. This study was designed to assess the association of QDRS with incidence of diabetes and determine whether QDRS exerts a potential effect in the general population under both urban and rural settings.

Materials and methods

Study population

This study was from Qingdao Diabetes Prevention Program (QDDPP). A stratified, random, cluster-sampling method was used to select a representative sample of individuals in 2006 and 2009. In the first stage, three urban districts (Shinan, Shibei, and Sifang) and three rural districts (Huangdao, Jiaonan, and Jimo) were randomly selected. In second stage, five neighborhood committees or towns were randomly selected from three rurals and three cities. In third stage, one community or one village was randomly selected from the selected neighborhood committees or towns. In fourth stage, 100 males and 100 females who resided in Qingdao for at least 5 years and were 35–74 years old were randomly selected from communities or villages. Of 12,100 participants, 7824 participants were enrolled from two population-based cohorts who were involved in diabetes surveys initiated at the baseline of both surveys. The follow-up survey was conducted from Mar 2012 to Dec 2015. In follow-up study, we excluded those participants with diagnosed diabetes ($n = 912$), or no data of BMI ($n = 41$), WC ($n = 63$), age ($n = 0$), family history of diabetes ($n = 148$), FPG ($n = 436$), 2 h PG ($n = 836$) at baseline. Participants (5851) who did not have diabetes and missing data at the baseline were invited for a follow-up and a face-to-face interview. Of these individuals, 3248 participated in the follow-up, with an overall response rate of 55.5%. In this analysis, we also excluded those without data of FPG ($n = 109$), 2 h PG ($n = 123$) in follow-up. Finally, a total of 3033 participants were included this analysis.

Questionnaires

The same standardized questionnaires were administered during the baseline and follow-up interviews. All participants were interviewed by trained doctors or nurses from local community clinics. Data on the following information was collected using the questionnaire: age, gender, marital status, family history of diabetes,

education attained, work status, smoking status, alcohol consumption, tea consumption, and personal monthly income. In regard to marital status, subjects were classified as married/cohabiting and unmarried (single, divorced, or widowed). Family history of diabetes was defined as positive if at least one first-degree relative (parents, siblings or offspring) had diabetes. The level of education attained was categorized as illiterate/elementary school, junior high school, and senior high school or higher. The level of occupational physical activity (PA) was classified as light (housewife, retired, or unemployed), moderate (teacher, doctor, or nurse), or heavy (worker, farmer, or fisher). With regard to smoking status, subjects were classified as smokers (smoking every day) and nonsmokers (including ex-smokers, opportunity smokers, and nonsmokers). The alcohol consumption level was categorized as drinkers and nondrinkers (including ex-drinkers, rare drinkers, and nondrinkers). Similarly, subjects were classified as tea drinkers and those who do not drink tea, depending on their history of tea drinking. Personal monthly income was classified as income levels of ≤ 599 Chinese Yuan (CNY), 600–1999 CNY, and ≥ 2000 CNY.

Height and weight were measured with the participants wearing only light clothes and no shoes. BMI was calculated as the weight in kilograms divided by the height in meters squared (kg/m^2). WC was measured at the midpoint between the lower rib margin and the superior border of the iliac crest. Hip circumference (HC) was measured at the maximal horizontal girth between the waist and the thigh. Blood pressure was measured while patients were seated using a mercury sphygmomanometer in the right arm. Measurements were taken three times at intervals of 5 min. The mean of the three readings was recorded for data analysis.

Blood samples were preserved in ice-cooled containers and transported immediately to the central laboratory of Qingdao Endocrine and Diabetes Hospital. All subjects without diagnosed diabetes underwent a standard 2-h 75-g oral glucose tolerance test (OGTT). The plasma glucose levels were determined by the glucose oxidase method.

Qingdao Diabetes Risk Score

Qingdao Diabetes Risk Score (QDRS), a diabetes risk assessment tool for laypersons, was originally developed using the data from the Qingdao Diabetes Prevention Program (QDDPP) [7]. QDRS was calculated using a simple questionnaire, which contained three questions including WC (in Chinese chi, 1 Chinese chi ≈ 33 cm), age (years), and family history of diabetes. Each question had been scored according to the previously described values [7], with the total risk scores ranging from 3 to 32. The scores were recorded as follows: (1) WC: for men, measurements of ≤ 2.3, 2.4–2.6, 2.7–2.9, and ≥ 3.0Chinese chi were scored as 1, 4, 8, and 12; for women, measurements of ≤ 2.0, 2.1–2.3, 2.4–2.6, ≥ 2.7 Chinese chi were scored as 1, 3, 6, and 9. (2) Age: for age groups ≤ 35 years, 36–45 years, 46–55 years, 56–65 years, and ≥ 65 years, the scores were recorded as 1, 3, 6, 9, and 12. (3) For family history of diabetes, the score was recorded as 1 and 8 for a positive family history. Participants with a risk score of ≥ 14 were classified as individuals at high risk for diabetes.

Criteria for overweight/obese

The cutoff values for classifying BMI were based on the criteria defined by the Working Group on Obesity in China [19]. According to BMI, individuals were classified into normal weight (BMI: 18.5–23.9 kg/m^2), overweight (BMI: 24.0–27.9 kg/m^2), and obese (BMI ≥ 28.0 kg/m^2). In this study, the participants were divided into two BMI categorical groups, normal weight, and overweight/obese, according their BMI in baseline.

Identification of diabetes

During follow-up, diabetes was diagnosed on the basis of the World Health Organization (WHO)/International Diabetes Federation (IDF) criteria [20]. Participants were diagnosed with diabetes if they met at least one of the following criteria at follow-up: (1) fasting plasma glucose (FPG) level of ≥ 7.0 mmol/l, (2) 2-h post-load plasma glucose (2-hPG) level of ≥ 11.1 mmol/l, or (3) a history of diabetes. The subject was classified as non-diabetic if FPG was < 7.0 mmol/l and 2-h PG < 11.1 mmol/l during follow-up.

Criteria for hypertension

Hypertension was defined according to the WHO criteria [21]. Hypertension was defined by a mean systolic blood pressure (SBP) of ≥ 140 mmHg and/or a mean diastolic blood pressure (DBP) of ≥ 90 mmHg and/or an established diagnosis of hypertension at baseline.

Depression measurement

The Zung Depression Rating Scale (ZDRS) [22] was used to assess the presence or absence of depression. The ZDRS questionnaire included 20 questions, including 10 of each positively and negatively phrased questions. Responses to each question were scored 1 through 4, and the total scores for the questionnaire ranged from

20 to 80. Participants were classified as normal or depressed depending on whether their ZDRS scores at baseline were 20–44 and ≥ 45, respectively.

Statistical analysis

We compared the baseline characteristics of participants using *t* test analysis for continuous variables and chi-square test for categorical variables. Using data from the 2010 census in Qingdao, the age-standardized cumulative incidence of diabetes was calculated according to the QDRS and BMI categories for the age group of 35–74 years. To examine the effects of QDRS and BMI on the incidence of diabetes among the urban and rural populations, we utilized Cox regression models to calculate the hazard ratio (HR) and 95% confidence intervals (CI). Subsequently, multivariate Cox regression models were adjusted for age and/or gender. Furthermore, to assess the combined effect of QDRS and BMI on the incidence of diabetes, interaction tests were used on additive scale in the model. Using previously described methods for statistical interaction between risk factors after multiple Cox regression, the relative excess risks due to interaction (RERI), synergy index (S), and attributable proportion due to interaction (AP) were calculated. IBM SPSS Statistics 20.0 was used for all the statistical analyses. $p < 0.05$ was considered to indicate statistical significance.

Results

The baseline characteristics of the participants have been shown in Table 1. A total of 3033 participants were enrolled. The mean age of the participants in QDRS < 14 and QDRS ≥ 14 was 45.5 ± 7.1 years and 57.2 ± 9.4 years, and the prevalence was 52.1% and 47.9%, respectively. All the variables showed significant differences in the distribution between QDRS < 14 and QDRS ≥ 14, excluding FPG, monthly income, and depression. The mean age of the participants in normal weight and overweight/obese was 50.9 ± 10.5 years and 51.3 ± 10.0 years, and the prevalence was 39.0% and 61.0%, respectively. All the variables showed significant differences in the distribution between normal weight and overweight/obese, excluding FPG, regional distribution, marital status, education attainment, and depression.

Table 1 Baseline characteristics of the study population

Characteristic	QDRS <14	QDRS ≥14	*p* value	Normal weight	Overweight/ obese	*p* value
N (%)	1557(52.1)	1447(47.9)	*0.018*	1184(39.0)	1849(61.0)	*< 0.001*
Female, *n* (%)	1098(69.6)	849 (58.7)	*< 0.001*	713(60.2)	1239(67.0)	*< 0.001*
Age, years (mean ± SD)	45.5 ± 7.1	57.2 ± 9.4	*< 0.001*	50.9 ± 10.5	51.3 ± 10.0	*0.014*
FPG (mmol/L, mean ± SD)	5.4 ± 0.7	5.6 ± 0.6	0.055	5.4 ± 0.6	5.5 ± 0.7	0.330
2-hPG (mmol/L, mean ± SD)	6.2 ± 1.5	6.9 ± 1.7	*< 0.001*	6.2 ± 1.6	6.8 ± 1.7	*0.047*
Rural	1256 (79.6)	1029(71.1)	*< 0.001*	907(76.6)	1387(75.0)	0.319
Married, *n* (%)	1523(96.6)	1337(92.4)	*< 0.001*	1111(93.8)	1758(95.1)	0.139
Education attainment, *n* (%)			*< 0.001*			0.434
Illiterate/elementary school	514(32.6)	721(49.8)		467(39.4)	773(41.8)	
Junior high school	715(45.3)	419(29.0)		455(38.4)	683(36.9)	
Senior high school or higher	348(22.1)	307(21.2)		262(22.1)	393(21.3)	
Occupational PA, *n* (%)			*< 0.001*			*0.002*
Light	589(37.3)	702(48.5)		461(38.9)	835(45.2)	
Moderate	306(19.4)	168(11.6)		190(16.0)	285(15.4)	
Heavy	682(43.2)	577(39.9)		533(45.0)	729(39.4)	
Smoker, *n* (%)	322(21.1)	362(25.1)	*0.009*	343(29.0)	352(19.1)	*< 0.001*
Drinker, *n* (%)	460(29.5)	496(34.6)	*0.003*	408(34.7)	551(30.2)	*0.009*
Income (CNY/month), *n* (%)			0.226			*0.017*
≤ 599	910(57.7)	790(54.6)		704(59.5)	1002(54.2)	
600–1999	585(37.1)	575(39.7)		422(35.6)	741(40.1)	
≥ 2000	82(5.2)	82(5.7)		58(4.9)	106(5.7)	
Depression, *n* (%)	57(4.0)	68(5.2)	0.143	40(3.7)	85(5.2)	0.080
Hypertension	554 (35.2)	902(62.5)	*< 0.001*	413(34.9)	1047(56.7)	*< 0.001*

BMI body mass index, *WC* waist circumference, *HC* hip circumference, *DRS* diabetes risk score, *FPG* fasting plasma glucose, *2-hPG* 2-h post-load plasma glucose, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PA* physical activity, *CNY* Chinese Yuan

During a mean follow-up period of 4.1 years, 87 (11.8%) urban participants and 199 (8.7%) rural participants developed diabetes. The age-standardized cumulative incidence of diabetes in urban and rural settings was higher in the group with QDRS of ≥ 14 than in the group with QDRS of < 14($p < 0.001$); similar results were obtained for BMI categories. Age-standardized cumulative incidence of diabetes was 16.9% (Fig. 1a) and 14.1% (Fig. 1b) in patients with QDRS ≥ 14 and in the overweight/obese group in urban settings, and 10.8% (Fig. 1a) and 9.1% (Fig. 1b) in rural settings, respectively.

Univariate Cox regression analysis revealed that compared to subjects with QDRS < 14, those with QDRS ≥ 14 showed a significantly higher risk for incidence of diabetes in both urban (HR 3.01; 95% CI 1.86–4.90) and rural (HR 1.91; 95% CI 1.44–2.54) settings. Compared with the normal weight group, overweight/obese individuals showed a significantly higher risk for diabetes in urban (HR 2.76, 95%CI 1.62–4.71) settings, but not in rural settings (HR 1.12, 95%CI 0.84–1.50). A significantly increased incidence of diabetes was noted for unmarried status, positive family history of diabetes, personal income levels of 1000–2999 CNY or ≥ 3000 CNY, and hypertension in urban settings and depression and hypertension in rural settings. However, education levels of junior high school and senior high school or higher and income of 600–1999CNY in rural settings showed a significant association with a lower risk of diabetes. Univariate HR and 95% CI for incidence of diabetes in urban and rural populations are presented in Table 2.

As shown in Table 3, a multivariate Cox regression analysis was performed to determine the association of QDRS and BMI with the incidence of diabetes. In model 1, compared with participants with QDRS of < 14, those with QDRS of ≥ 14 showed a significantly higher risk for diabetes after adjustment for age, in both urban (HR 2.37, 95% CI 1.35–4.15) and rural (HR 1.49, 95% CI 1.09–2.04) settings. In model 2, after controlling for both age and gender, overweight/obese participants had a significantly higher risk for diabetes than normal weight participants in urban settings (HR 2.50, 95% CI 1.33–4.69); however, no such association was noted in the rural settings (HR 1.15, 95%CI 0.84–1.59).

Finally, the synergistic effects of QDRS and BMI on the risk of diabetes were assessed, and the results are shown in Table 4. The risk for incidence of diabetes was higher for individuals with a QDRS ≥ 14 combined with being overweight/obese, than individuals with a QDRS < 14and normal weight in both urban (HR 3.78, 95% CI 1.64–8.71) and rural (HR 1.53, 95%CI 1.01–2.31) settings. The RERI, S, and AP for the combinations were 1.59, 2.34, and 42.06% in urban settings and 0.07, 0.89, and 4.55% in rural settings, respectively.

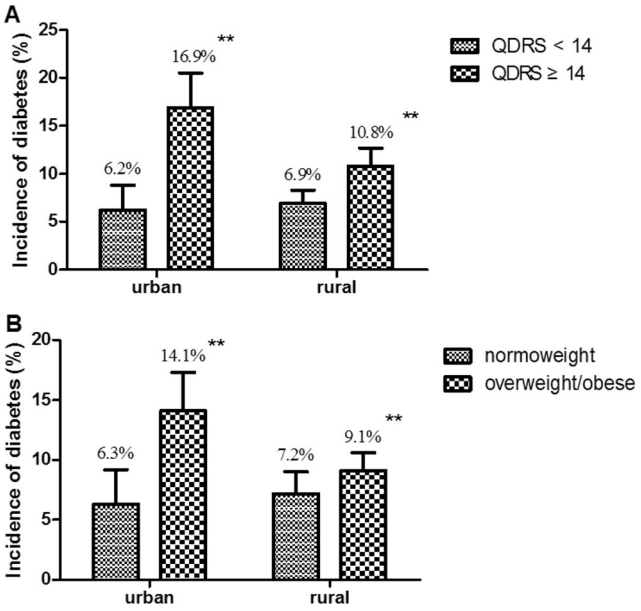

Fig. 1 The age-standardized cumulative incidence (%) of diabetes in urban and rural settings by QDRS (**a**) and BMI (**b**). **$p < 0.001$ between two group in urban and rural setting

Discussion

In the present study, we found that both elevated QDRS and BMI increase the risk for diabetes. Despite being a predominant risk factor for diabetes, BMI is not included in QDRS. QDRS is as a useful screening tool for diabetes; besides identifying individuals at high risk of diabetes, it also increases public awareness regarding the risk of diabetes.

The value of using a risk-assessment questionnaire as a screening tool for diabetes has been assessed in many studies [8, 9]. In a previous study, QDRS for a cutoff value of ≥ 14 showed comparative high sensitivity and specificity in detecting individuals at high risk for diabetes [7]. In our study, the age-standardized cumulative incidence of diabetes of participants with a QDRS of ≥ 14 at the baseline was significantly higher than that with a QDRS of < 14 in both urban and rural settings, with a QDRS of ≥ 14 being strongly associated with the risk for diabetes. Further, a large proportion of diabetics in China has been shown to be asymptomatic [23, 24].. QDRS, which was developed for the Chinese population, is a simple, self-measurable questionnaire and is well understood by laypersons [7]. It can be widely applied in the asymptomatic diabetes population and can enable the detection of individuals who are at a high risk for diabetes. Further, the present study confirms that QDRS can be accurately used in predicting the incidence of diabetes, as reported previously [7].

In the present study, the age-standardized cumulative incidence of diabetes was significantly higher in the overweight/obese population than that in the normoweight

Table 2 Univariate hazard ratio (HR) and 95% confidence intervals (95%CI) for incidence of diabetes in urban and rural settings

	Urban		Rural	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value
QDRS				
≥ 14	*3.01 (1.86–4.90)*	*< 0.001*	*1.91 (1.44–2.54)*	*< 0.001*
Weight category				
Overweight/obese	*2.76 (1.62–4.71)*	*< 0.001*	1.12 (0.84–1.50)	0.442
Female	1.37 (0.84–2.25)	0.206	0.80 (0.60–1.05)	0.110
Unmarried	*1.90 (1.01–3.59)*	*0.047*	1.36 (0.74–2.50)	0.319
Education attained		0.552		*< 0.001*
Illiterate /elementary school	1.00		1.00	
Junior high school	0.69 (0.33–1.45)	0.322	*0.52 (0.38–0.72)*	*< 0.001*
Senior high school or higher	0.68 (0.33–1.38)	0.284	*0.56 (0.35–0.88)*	*0.013*
Occupational PA		0.265		0.942
Light	1.00		1.00	
Moderate	0.46 (0.14–1.45)	0.183	0.94 (0.62–1.42)	0.756
Heavy	0.65 (0.28–1.50)	0.313	0.99 (0.72–1.37)	0.984
Smoker	1.22 (0.74–2.01)	0.427	0.94 (0.68–1.30)	0.716
Drinker	0.72 (0.46–1.12)	0.140	0.93 (0.68–1.25)	0.620
Income (CNY/month)		*0.018*		0.016
≤ 599	1.00		1.00	
600–1999	*2.26 (1.21–4.22)*	*0.010*	*0.62 (0.43–0.89)*	*0.008*
≥ 2000	*2.79 (1.30–5.96)*	*0.008*	1.36 (0.67–2.78)	0.398
Depression	0.58 (0.18–1.83)	0.351	*1.97 (1.12–3.47)*	*0.019*
Hypertension	*2.33 (1.48–3.65)*	*< 0.001*	*1.56 (1.17–2.08)*	*0.002*

Table 3 Multivariate HR and 95% CI of the possible risk factors for diabetes in urban and rural settings

	Model 1		Model 2	
	Urban	Rural	Urban	Rural
QDRS				
≥ 14	*2.37 (1.35–4.15)*	*1.49 (1.09–2.04)*		
BMI category				
Overweight/obese			*2.50 (1.33–4.69)*	1.15 (0.84–1.59)
Unmarried	1.55 (0.71–3.39)	0.92 (0.46–1.81)	1.55 (0.69–3.48)	0.90 (0.45–1.77)
Family history of diabetes			1.53 (0.95–2.44)	1.30 (0.90–1.89)
Educational attainment				
Illiterate/elementary school	1.00	1.00	1.00	1.00
Junior high school	0.69 (0.31–1.55)	*0.57 (0.40–0.83)*	0.78 (0.34–1.79)	0.70 (0.46–1.05)
Senior high school or higher	0.80 (0.37–1.76)	*0.57 (0.33–0.97)*	0.94 (0.42–2.10)	0.69 (0.39–1.21)
Income (CNY/month)				
≤ 599	1.00	1.00	1.00	1.00
600–1999	1.34 (0.66–2.73)	0.77 (0.52–1.13)	1.41 (0.67–2.93)	0.83 (0.56–1.24)
≥ 2000	2.00 (0.82–4.88)	1.48 (0.63–3.45)	1.85 (0.73–4.66)	1.54 (0.66–3.63)
Depression	0.63 (0.20–2.03)	*1.92 (1.08–3.40)*	0.70 (0.22–2.25)	*1.79 (1.00–3.19)*
Hypertension	*1.78 (1.08–2.93)*	1.35 (0.99–1.83)	*1.58 (0.95–2.63)*	*1.25 (0.91–1.72)*

Model 1 was adjusted for gender. Model 2 was adjusted for age and gender

Table 4 Interaction between QDRS and BMI in the possible risk factors for diabetes in urban and rural settings

		Urban				Rural			
Risk score	Weight category	HR (95%CI)	RERI	S	AP	HR (95%CI)	RERI	S	AP
< 14	Normal weight	1.00				1.00			
< 14	Overweight/obese	1.62 (0.62–4.26)				1.06 (0.66–1.67)			
≥ 14	Normal weight	1.57 (0.54–4.57)				1.55 (0.93–2.59)			
≥ 14	Overweight/obese	*3.78 (1.64–8.71)*	1.59	2.34	42.06	*1.54 (1.02–2.32)*	0.07	0.89	4.55

Cox regression analysis was adjusted for gender, marital status, education attained, personal monthly income, depression, and hypertension. RERI > 0 and S > 1.00 indicate a synergistic effect between DRS ≥ 14and overweight/obese

population in both urban and rural settings, as observed in previous studies [25]. In parallel, the present study found that the cumulative incidence of diabetes was higher in urban than in rural settings, which is consistent with the findings of Yang et al. [3] and our previous research on the prevalence of diabetes [18]. In this study, we also found that being overweight/obese was strongly associated with an increased risk for diabetes in urban but not in rural settings. Although considerable changes have taken place in China in the socio-economic status and lifestyle, rural settings continue to offer more opportunities for exercise in the form of traditional manual work and outdoor activities than urban settings. Yang et al. also reported a higher rate of diabetes as a result of economic development, lifestyle, and diet changes [3]. Unhealthy lifestyle and diet may lead to being overweight and/or obese, which is a crucial risk factor for diabetes [15–17, 25]. Hence, education and lifestyle interventions are imperative in Qingdao to prevent the increase in the incidence of diabetes [18].

In epidemiology, "interaction" refers to the biologic interaction and statistical interaction. Biologic interaction is used to assert effects of disease risk by two or more factors of disease. And statistical interaction, assessing biological interaction, included additive and multiplicative models [26]. In the present study of additive models, interaction effect was evaluated according to parameters of RETI > 0, AP > 0, and S > 1 in urban, however, RETI > 0, AP > 0, and S < 1 in rural. So, we found a strong synergistic effect between a QDRS ≥ 14 and being overweight/obese in relation to an increased risk of diabetes in urban settings, but such a phenomenon was not observed in the rural settings. And, QDRS has been developed according to Chinese population [7] and validated in Chinese population [27]. At present, QDRS, as a first-line screening tool, followed by a capillary blood glucose testing has identified a huge number of individual at high risk for diabetes. These individuals were referred by the primary care clinics to higher-level hospitals for confirmative diagnostic test and treatment. As thus, QDRS can be used to prevent diabetes and enhance the quality of life.

In a previous study on risk-assessment questionnaires for diabetes from other countries [8, 9], BMI was accounted for in the evaluation of health risk. However, the QDRS was designed with the waist circumference only and did not include BMI. The reasoning for doing this was threefold: first, screening tools for application in large populations must be simple, since complicated methods of measuring BMI are rarely acceptable by the general public. Second, previous risk-assessment tools, which are based on demographic information and environmental factors in different ethnic populations, may not be suitable for the Chinese population. The efficiency of risk-assessment tools should vary according to real-life settings. Third, the QDRS was developed in China and has already been demonstrated as a reasonable screening tool for individuals at high risk for diabetes [7]. Furthermore, QDRS is a simple, fast, cost-effective, and feasible sensitization screening tool [7, 10, 27] that can be widely distributed among populations residing in the study areas through primary care clinics, schools, various public health activities, booklets, and other measures. The widespread use of the QDRS as an effective health promotion tool [27] has been shown to greatly contribute towards raising public awareness, which may lead to early diagnosis of diabetes.

Nevertheless, this study does have a few limitations. First, the percentage of subjects lost to follow-up is high in this study. Responders (6.7%) did not provide useful information, which maybe a potential source of selection bias. Compared to the baseline characteristics of non-participants, there were no differences in years, genders, BMI, and QDRS of participants in baseline. The dominant reasons recorded for loss to follow-up were subject illness or demise, loss of contact due to urbanization, and the subject was unable to attend follow-up due to a busy schedule. Second, this study was conducted on a relatively small sample size of the adult community in Qingdao [14]. Although QDRS is a simple and efficient tool, some participants, especially rural participants, failed to provide details regarding their family history of diabetes. Ideally, QDRS is only a first-line screening and informational tool.

Despite the aforementioned limitations, our study provided population-based cohort data, which indicated that QDRS is a suitable screening tool for diabetes with a low risk of bias due to self-reporting. Further investigation as a large-scale multi-center study in China is warranted to further assess the performance of the QDRS.

Conclusion

In conclusion, the QDRS showed a strong positive association with the incidence of diabetes. Additionally, a QDRS of ≥ 14 in addition to being overweight/obese had a highly detrimental effect on the incidence of diabetes in urban but not in rural settings. Our results suggest that diabetes management in a clinical setting should be conducted so that QDRS is maintained at < 14; preventing of abdominal obesity and being overweight/obese is addressed through lifestyle intervention in a clinical setting.

Acknowledgments We are grateful to the participants, primary care doctors, and nurses who participated in this survey. Working spaces, facilities, and staff were provided by Qingdao Municipal Health Bureau and Qingdao CDC. Finally, we thank Medjaden Bioscience Limited [http://www.medjaden.com/index.html] for providing English language editing services. We are thankful to Prof. Qing qiao for helping us in the experimental designing and manuscript preparation.

Availability of data and materials The datasets generated or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions Jianping Sun, Zulqarnain Baloch, and Peng Fu wrote and revised the draft manuscript and subsequent manuscripts and analyzed participant samples. Zulqarnain Baloch and Jing Cui designed the study and revised the draft manuscript. Nafeesa Yasmeen, Guorong Bao, Peng Fu, Hualei Xin, and Li Shanshan assisted with sample analysis. Jing Cui and Jianping Sun conceived and designed the study, appraised relevant studies, and assisted with drafting and revising the manuscript. All the authors read and approved the final manuscript.

Funding This study was supported by the World Diabetes Foundation (WDF05-108 and WDF07-308), Qingdao Outstanding Health Professional Development Fund, Qingdao Medical Research Guidance Program in 2017 (2017-WJZD129 and 2017-WJZD134).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest..

Consent for publication Not applicable.

Ethics approval and consent to participate The study was approved by the ethics committees of the University of Helsinki, Finland, Qingdao Municipal Center for Disease Control and Prevention, Qingdao, China. Informed consent was obtained from all individual participants included in the study.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):739–748
https://doi.org/10.1007/s13410-019-00730-5

ORIGINAL ARTICLE

What makes patients with diabetes adopt physical activity behaviors?—a transtheoretical model approach

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Received: 19 November 2018 / Accepted: 17 February 2019 / Published online: 2 April 2019

Abstract

Background Physical activity is an essential health behavior in patients with diabetes and is the one which is least adapted in the Indian context. There is a need to understand the motivators and demotivators of this behavior. This study was conducted to evaluate the stages of physical activity behavior change, process of change, decisional balance that influences the change and situational self-efficacy in patients with diabetes attending a tertiary care health facility in Chennai, India.

Methods Among 150 patients with diabetes attending the tertiary care hospital, selected in a non-random consecutive manner, a questionnaire-based survey was administered covering the domains of stage of change, process of change, decisional balance and situational self-efficacy.

Results About 50% of the sample were not physically active belonging to the precontemplation or the reversal phase. About 23% were in the maintenance phase of physical activity and remaining 27% were in various intermediate stages of contemplation, preparation and action. The dominant dimensions of process of change were dramatic relief, self-re-evaluation and positive reinforcement. There was a high level of perceived pros of physical activity as well as cons and so there was a decisional balance not favouring either end of the behavior change spectrum. Situational self-efficacy levels were low. The perceived pros (OR 1.042; 95% CI 1.005–1.080) and cons (OR 0.929; 95% CI 0.877–0.985) influenced the behavior change in a statistically significant manner in a multivariate adjusted model.

Conclusion A very low proportion of patients with diabetes are in maintenance phase of physical activity with a majority in various stages of change. The patients show various processes of change which all help in moving them through the early stages of change. Perceived pros and cons influence the physical activity behavior change and measures taken to address them are likely to positively influence physical activity behavior.

Keywords Physical activity · Diabetes · Transtheoretical model · Stages of change · Process of change · Decisional balance · Situational self-efficacy

Background

India has a huge burden of diabetes and it is a major public health problem in the country [1]. Effective management of diabetes requires a healthy diet, adequate physical activity and intake of appropriate medications. Previous studies of diabetes self-management from India have shown that communities have good levels of medication intake and diet regulation, but have poor levels of physical activity [2]. Physical activity has many advantages in the control of diabetes [3, 4]. Therefore, motivating patients with diabetes to engage in physical activity is an essential intervention.

Several factors have been reported to influence exercise behaviors of patients with diabetes. The most significant factor was motivation, and support from friends, relatives and neighbours. Presence of co-morbid conditions such as osteoarthritis of knees and obstructive lung disease discouraged patients from exercising [5].

Many behavioral health models have been studied in relation to factors that motivate and discourage patients from

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adopting health-promoting behaviors. Three of the most commonly studied behavioral health models are the Health Belief Model, the Theory of Planned behavior and the Transtheoretical Model [6]. The transtheoretical model has been applied in understanding the motivators and detractors of physical activity among patients with diabetes in previous studies [7]. A study which used the transtheoretical model to design interventions to promote physical activity among diabetic patients showed that the model is very effective in influencing behavior related to physical activity [8].

The Transtheoretical Model of behavior change was first introduced by Prochaska and DiClemente in 1982 and since then has been applied to various health-related behaviors [9]. The transtheoretical model states that people are at five different stages of change or stages of adopting a new behavior namely, precontemplation, contemplation, preparation, action and maintenance. Later, a sixth stage called the stage of reversal was added, which indicated fall back from the newly adopted behavior. In the precontemplation phase, people do not intend to adopt the new behavior in the near future. Usually, people who are poorly informed about the advantages of the behavior are in the precontemplation stage. Contemplators are people who intend to change in the next 6 months. Contemplators tend to remain for prolonged periods of time in this phase without much change. People in the preparation phase are those who intend to act within the immediate next 1 month. There is usually a concrete plan of action such as joining a gym, talking to a fitness consultant etc. Action is the stage where people have incorporated a specific overt modification in their lifestyle. People in the maintenance phase take specific actions to prevent relapse and continue to maintain the behavior. Usually, people remain in the maintenance phase from 6 months to 5 years after which they relapse. The movement of people across these stages of change is influenced mainly by the process of change which comprises of behavioral and experiential factors, decisional balance which is the assessment of pros and cons of the new behavior and situational self-efficacy, which comprises of response to social situations, habits, cravings and negative affect states. The experiential and behavioral processes of change include consciousness raising or gathering facts and information about exercise, dramatic relief or paying attention to feelings related to exercise, self-re-evaluation or seeing oneself as a new person because of exercise, environmental re-evaluation or noticing that one's behavior change will influence others, social liberation or observing that there are social supports for regular exercise, self-liberation or believing in one's ability to start exercising, helping relationships who can provide support, counter conditioning or substituting physical activity to sedentary life in everyday living, reinforcement management or using positive reinforcement, and stimulus control or managing the environment to promote exercise [10]. These factors such as experiential and behavioral processes of change, decisional balance between pros and cons and situational self-efficacy motivate people to move from one stage of change to the other. Consciousness raising, environmental re-evaluation, dramatic relief and social liberation help people move from precontemplation to contemplation stage. In this process of movement, the perceptions of pros dominate the decisional balance. People move from contemplation to preparation after self-re-evaluation and when the decisional balance tips towards the side of pros. Helping relationships, self-liberation and counter conditioning help move from preparation to action stage. Strongly positive decisional balance and increased self-efficacy also support this movement. Finally, reinforcement management, stimulus control and self-efficacy help move people from action to maintenance stage of behavior. This theoretical explanation is provided in Fig. 1.

A thorough understanding of the behavior of physical activity, the level of motivation to practice regular physical activity and the various factors that influence this is essential for promoting healthy physical activity among patients with diabetes. This study was conducted to understand the stage of change with respect to adoption of regular physical activity, the process of change, the decisional balance that influences this change and the level of self-efficacy of patients with type 2 diabetes in a typical urban tertiary hospital setting in Chennai, India, using the transtheoretical model.

Methods

Study setting

The study was conducted among patients with diabetes attending a tertiary care hospital in Chennai, the capital city of Tamil Nadu, a coastal state in the southern part of India. The prevalence of diabetes in Chennai has been studied extensively and one of the studies in 2006 reported a prevalence of about 15% with a trend of about 72% increase in prevalence over 14 years [11]. The patients served in this hospital are covered by a government run contributory social insurance scheme of employees of companies drawing a monthly wage of less than Rs 2100 [12].

Study participants

The sample size was calculated to detect a difference of at least 15% in decisional balance scores between patients who are in the maintenance phase and those who are in the precontemplation phase of adopting physical activity. The proportion of patients who are in the maintenance phase with a favourable decisional balance was conservatively assumed to be 5%. For a 95% confidence level and 80% power, the sample size was calculated to be 150. Participants in the

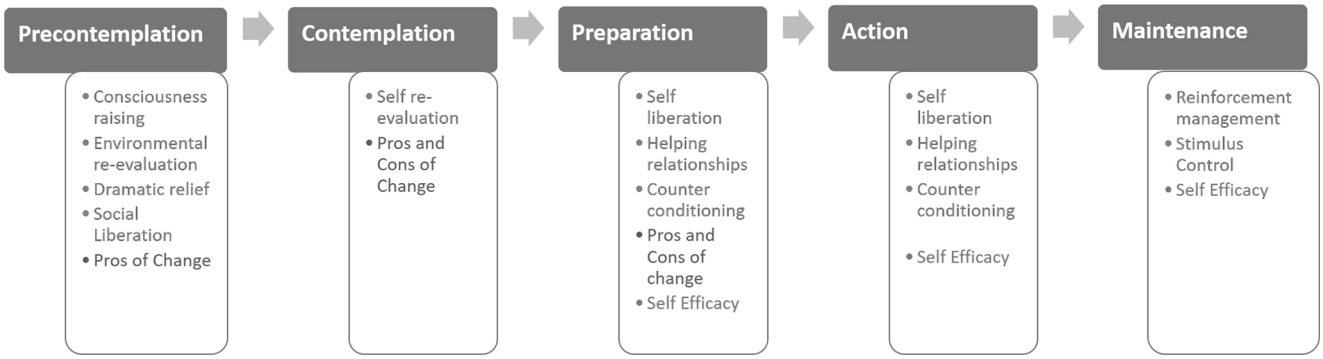

Fig. 1 This figure shows the transtheoretical model. The various stages of change namely, precontemplation, contemplation, preparation, action and maintenance are depicted. The processes of change that influence the transition from one stage to the other are depicted in the white boxes

diabetes out-patient department and patients admitted in the wards with diabetes were selected in a non-probabilistic manner and interviewed with the help of a structured, pretested questionnaire.

Study instruments

The study questionnaire contained two parts namely sociodemographic variables and the various items relating to the transtheoretical model for adoption of regular physical exercise. The main constructs in the transtheoretical model include stages of change in adoption of the physical activity behavior, process of change in behavior including behavioral and experiential processes, decisional balance including pros and cons of adopting regular physical activity and situational self-efficacy including factors which influence giving up or not adopting the behavior. The items of the scale were adapted and modified from a previous similar study using the transtheoretical model [13]. The modified and adapted scale was given to five experts in public health and health promotion and content validation performed. Their suggestions for modifying the questionnaire were incorporated and the scale translated in Tamil, the local language. The validity of translation was checked by an uninvolved third person, being an expert in Tamil. Detailed construct validation and reliability testing was not felt to be necessary, as the scale has previously been thoroughly validated for its construct and very minor changes were made to the scale to adapt to local context.

Data collection and management

The questionnaire was printed and administered in a pen and paper format, by the principal investigator after obtaining an informed consent from the participants. The principal investigator interviewed the participants in a private space and asked each question and marked their responses on a Likert type scale ranging between strongly agree–agree–neither agree nor disagree–disagree–strongly disagree. The data were then entered in a MS Excel spreadsheet.

Statistical analysis

The data were analysed using SPSS Statistical Software version 21. All the Likert type responses were scored from 1 to 5, the positively worded items scoring 5 for strongly agree, 4 for agree and so on and negatively worded items scored in a reverse manner. The scores of the items belonging to specific domains such as process of change, pros of change, cons of change and situational self-efficacy were added up to give cumulative domain scores. The difference in the scores on all these four domains was studied across the six stages of change namely precontemplation, contemplation, preparation, action, maintenance and reversal using the ANOVA test. The magnitude of influence that each of these domain scores had on the stage of change was studied using a multiple logistic regression analysis after converting the stages of change into two groups namely those who had adopted regular physical activity (action and maintenance) and those who had not (precontemplation, contemplation, preparation, reversal). The p values that were less than 0.05 were considered as indicating statistical significance.

Ethical considerations

The study was approved by the Institutional Ethical Committee of the ESIC Medical College & PGIMSR, Chennai, through an expedited review process. Verbal informed consent was obtained from all participants before the interview. The study was classified as having very low ethical risk. In the context of Tamil Nadu, the process of obtaining a written informed consent is associated with important medical procedures and important medical decisions. Therefore, to allay any anxieties that obtaining a written informed consent would produce, the ethics committee permitted the researchers to obtain a thorough verbal informed consent and document it in the questionnaires. Adequate privacy was provided to the participants during the interview. Their private information was kept confidential.

Results

Out of total 156 participants approached for the study, 151 consented to participate and provided the data (response rate of 96.8%). Out of the 151 who responded, 150 data were complete and used for analysis. The data of one woman was incomplete and so was excluded. The study sample included equal number of men and women, about 75% above the age of 50 years, and more than 65% with a duration of diabetes of more than 5 years. The characteristics of the study sample are shown in Table 1.

Stages of change

The proportion of respondents in each stage of change with respect to adopting the regular physical activity behavior is shown in Fig. 2. It is seen that the distribution is peaked at both extremes of the stages of change, about 29% in the precontemplation phase, and 20% in the reversal phase. There were about 23% of the patients in the maintenance phase of physical activity. This bimodality of presentation shows that about 50% of the participants were in the no physical activity phase including precontemplation and reversal.

Domains of the transtheoretical model

The responses of the participants to the various items on the transtheoretical model questionnaire are shown in Tables 2, 3, 4, and 5. The processes of change comprising of behavioral and experiential factors is shown in Table 2. It is seen that self-re-evaluation, self-liberation and positive reinforcement are dominant domains with high scores. While self-re-evaluation helps a contemplator to move to preparation, self-liberation helps move from preparation phase to action. Positive reinforcement helps the actors to move to maintenance.

Table 3 shows the responses to perceived pros of adopting regular exercise behavior. It is seen clearly that most of the participants strongly perceived the pros of the physical exercise. The responses were 'strongly agree' in more than 70% of the participants for all the statements.

Table 4 shows the responses to the perceived cons of adopting regular physical activity. It is seen that for many items, especially the ones on body aches and pain, difficulty in waking up early and adopting exercises, and lack of immediate perceived benefits had strong agreement.

Table 5 shows the situational self-efficacy variables. This also indicates majority of the participants lack the situational self-efficacy to continue to practice regular physical activity during times of negative emotional affect, positive social situations and habits and cravings.

Table 1 Characteristics of the study sample

S. No.	Characteristic	Categories	Number	%
1	Age	31–40 years	7	4.6
		41–50 years	30	20
		51–60 years	52	34.6
		61–70 years	51	34
		> 70	10	6.8
2	Sex	Male	75	50
		Female	75	50
3	Duration of diabetes	< 5 years	53	35.3
		5–10 years	70	46.6
		11–15	13	8.6
		> 15 years	14	9.5
4	Educational qualification	No schooling	55	36.6
		Up to high school	91	60.6
		Undergraduate	4	2.7

Comparison of the scores on the transtheoretical model domains across the stages of change

Figure 3 shows the comparison of the scores on the four major domains of the transtheoretical model across the stages of change that the patients belong to. The ANOVA revealed that there was an increase in the scores on process of change domain from precontemplation stage to maintenance stage (F value = 2.226 and p value = 0.05). There was a dip in the score in the reversal stage. It was seen that there was no difference with respect to scores on perceived pros of change across the groups. However, there was a small reduction in the perceived cons of change score between precontemplation and contemplation phase and a significant increase in cons score in the maintenance phase which was statistically significant (F value = 6.034 and p value < 0.001). There was also a significant increase in situational self-efficacy in the contemplation stage compared to precontemplation stage and another substantial increase between action and maintenance stage (F value = 2.642 and p value = 0.026).

Association between transtheoretical model domains and adoption of physical activity behavior

The multivariate logistic regression analysis showed that pros of change and cons of change significantly influenced the stage of change that the participants were in. None of the other factors influenced the stage of change. This is shown in Table 6.

Analysis performed using multiple logistic regression with stage of change as binary-dependent variable (change adapted/not adapted) and the factors influencing the stage of change as continuous scores.

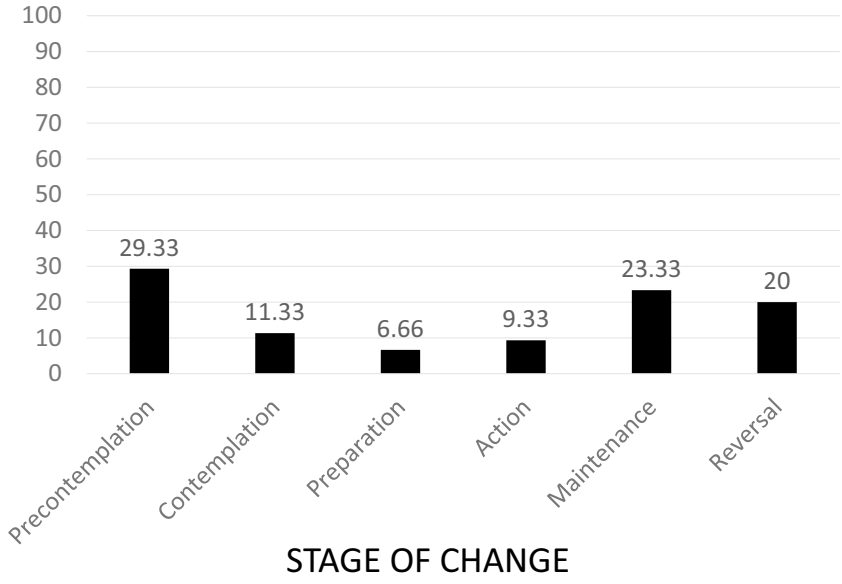

Fig. 2 This figure shows that about 29% of the participants were in the precontemplation phase, about 23% in the maintenance phase and 20% in the reversal phase

Table 2 Process of change

S. No.	Domain	Statement	Strongly agree (%)	Agree (%)	Neither agree nor disagree (%)	Disagree (%)	Strongly disagree (%)
1	Consciousness raising	I look out for information about benefits of reg. exercise for people with diabetes	19 (12.7)	28 (18.7)	15 (10)	12 (8)	76 (50.7)
2	Consciousness raising	I talk with others with type 2 diabetes about their experience of doing regular exercise	19 (12.7)	22 (14.7)	15 (10)	10 (6.7)	84 (56)
3	Dramatic relief	I feel worried about my prolonged periods of inactivity	43 (28.7)	6 (4)	8 (5.3)	1 (0.7)	92 (61.3)
4	Dramatic relief	I am inspired by people with diabetes, who do regular exercise	93 (62)	12 (8)	17 (11.3)	7 (4.7)	21 (14)
5	Self-re-evaluation	I feel if I do reg exercise I am a whole new man/woman	113 (75.3)	8 (5.3)	10 (6.7)	2 (1.3)	17 (11.3)
6	Environmental re-evaluation	I feel if I start to regular exercise I can inspire others to do the same	99 (66)	11 (7.3)	13 (8.7)	3 (2)	24 (16)
7	Environmental re-evaluation	I feel my prolonged inactivity demotivates others with type 2 diabetes to do regular exercise	102 (68)	9 (6)	10 (6.7)	4 (2.7)	25 (16.7)
8	Social liberation	I notice that there are walking or exercise clubs	36 (24)	40 (26.7)	7 (4.7)	8 (5.3)	59 (39.3)
9	Social liberation	I notice that there are pavements or parks to do walking	64 (42.7)	23 (15.3)	2 (1.3)	6 (4)	55 (36.7)
10	Self-liberation	I believe I can start walking or exercise regularly	105 (70)	5 (3.3)	5 (3.3)	4 (2.7)	31 (20.7)
11	Helping relationships	I have friends who will accompany me in doing regular exercise	31 (20.7)	6 (4)	6 (4)	1 (0.7)	106 (70.7)
12	Helping relationships	I have family members who will accompany me in doing regular exercise	24 (16)	19 (12.7)	2 (1.3)	8 (5.3)	97 (64.7)
13	Counter conditioning	I can walk to nearby places instead of using motor vehicle	90 (60)	4 (2.7)	15 (10)	4 (2.7)	37 (24.7)
14	Counter conditioning	I can keep walking in my house instead of sitting for long periods of time	87 (58)	10 (6.7)	12 (8)	4 (2.7)	37 (24.7)
15	Reinforcement management	If I do regular exercise or walking it reduces my body pain	90 (60)	8 (5.3)	16 (10.7)	9 (6)	27 (18)
16	Reinforcement management	If I do regular exercise I become energetic	116 (77.3)	13 (8.7)	6 (4)	4 (2.7)	11 (7.3)
17	Stimulus control	My walking or exercise clothes remind me to do exercise or walking	20 (13.3)	18 (12)	38 (25.3)	7 (4.7)	67 (44.7)
18	Stimulus control	My walking or exercise footwear remind me to do exercise or walking	17 (11.3)	22 (14.7)	38 (25.3)	7 (4.7)	66 (44)

Table 3 Decisional balance—perceived pros of exercise

S. No.	Statement	Strongly agree (%)	Agree (%)	Neither agree nor disagree (%)	Disagree (%)	Strongly disagree (%)
1	Exercise could help me improve my strength	107 (71.3)	14 (9.3)	20 (13.3)	3 (2)	6 (4)
2	Exercise is good for my body	110 (73.3)	15 (10)	18 (12)	1 (0.7)	6 (4)
3	Exercise will help me have a better overall health	110 (73.3)	15 (10)	18 (12)	1 (0.7)	6 (4)
4	Regular walking or exercise will help me live a longer life	107 (71.3)	18 (12)	18 (12)	1 (0.7)	6 (4)
5	Regular walking or exercise make me feel energetic	105 (70)	18 (12)	19 (12.7)	1 (0.7)	7 (4.7)
6	Regular walking or exercise helps prevent heart attack	108 (72)	16 (10.7)	19 (12.7)	1 (0.7)	6 (4)
7	Regular walking or exercise helps prevent stroke	107 (71.3)	16 (10.7)	20 (13.3)	1 (0.7)	6 (4)
8	Regular walking or exercise helps lose weight	108 (72)	12 (8)	21 (14)	1 (0.7)	8 (5.3)
9	Regular walking or exercise is a good substitute to lazy life	114 (76)	9 (6)	20 (13.3)	3 (2)	4 (2.7)
10	Regular walking or exercise can be enjoyable	107 (71.3)	9 (6)	24 (16)	1 (0.7)	8 (5.3)
11	Regular walking or exercise reduces blood pleasure	107 (71.3)	13 (8.7)	24 (16)	1 (0.7)	5 (3.3)
12	Regular walking or exercise helps in building better relationship with companion	104 (69.3)	13 (8.7)	28 (18.7)	1 (0.7)	4 (2.7)
13	Regular walking or exercise gives access to fresh air	124 (82.7)	8 (5.3)	12 (8)	1 (0.7)	5 (3.3)

Discussion

This study evaluated the behavior of regular physical activity among patients with diabetes using the transtheoretical model. It was found that about half the patients were either in precontemplation or reversal stage, thus without any type of physical activity. About 23% were in a regular maintenance stage and the remaining were in contemplation or preparation phase. It was further found that self-re-evaluation, self-liberation and positive reinforcement were the main processes adopted by the patients across the stages of change. The perceived pros of adopting the behavior were high in most participants and perceived cons were also moderately high. Situational self-efficacy levels were low. On evaluation of the differences in the scores on various domains across the stages of change, it was seen that perceived cons were highest among those in maintenance phase and there were significant differences in the process of change as well as situational self-efficacy across the stages. On multivariate analysis, it was clear that only perceived pros and cons influenced the decision to adopt the behaviors and neither the processes of change nor situational self-efficacy had any significant influence. The following paragraphs will discuss these important findings.

Physical activity levels among patients with diabetes

The study clearly showed that a very small proportion (23%) of the patients were in the maintenance stage of physical

Table 4 Decisional balance—perceived cons of exercise

S. No.	Statement	Strongly agree (%)	Agree (%)	Neither agree nor disagree (%)	Disagree (%)	Strongly disagree (%)
1	It takes time to do regular exercise	41 (27.3)	12 (8)	4 (2.7)	1 (0.7)	92 (61.3)
2	I dont know how to do exercise	74 (49.3)	6 (4)	8 (5.3)	5 (3.3)	57 (38)
3	I have no time for walking or exercise	56 (37.3)	4 (2.7)	7 (4.7)	7 (4.7)	76 (50.7)
4	I dont enjoy doing regular exercise	57 (38)	2 (1.3)	11 (7.3)	8 (5.3)	72 (48)
5	I feel shy to go outside on road and do regular exercise and walking	17 (11.3)	1 (0.7)	4 (2.7)	8 (5.3)	120 (80)
6	I have body aches and pains and cannot do regular exercise or walking	94 (62.7)	6 (4)	6 (4)	4 (2.7)	40 (26.7)
7	I hate to wake up early in the morning to do regular exercise or walking	94 (62.7)	11 (7.3)	4 (2.7)	4 (2.7)	37 (24.7)
8	I hate feeling sweaty while doing regular exercise or walking	87 (58)	8 (5.3)	18 (12)	4 (2.7)	33 (22)
9	I feel that exercise is expensive to follow	45 (30)	4 (2.7)	10 (6.7)	17 (11.3)	74 (49.3)
10	I feel that exercise do not give immediate relief	119 (79.3)	3 (2)	11 (7.3)	4 (2.7)	13 (8.7)

Table 5 Situational self-efficacy

S. No.	Statement	Strongly agree (%)	Agree (%)	Neither agree nor disagree (%)	Disagree (%)	Strongly disagree (%)
1	When my relatives are gathered I am not able to do my regular exercise or walking	97 (64.7)	11 (7.3)	15 (10)	0	27 (18)
2	When I am travelling out of town I am not able to do my regular exercise or exercise	89 (59.3)	16 (10.7)	15 (10)	3 (2)	27 (18)
3	When I am sad or low I am unable to do my regular exercise or walking	90 (60)	8 (5.3)	15 (10)	3 (2)	34 (22.7)
4	When I have an argument with a close one and feel upset about it I am unable to do my regular exercise or walking	85 (56.7)	7 (4.7)	14 (9.3)	12 (8)	32 (21.3)
5	When I am nervous about something I am unable to do my regular exercise or walking	84 (56)	10 (6.7)	16 (10.7)	6 (4)	34 (22.7)
6	When I am sick I do not feel like doing regular exercise or walking	111 (74)	9 (6)	7 (4.7)	11 (7.3)	12 (8)

activity. This is consistent with a national-wide study that reported about 35% physical activity levels among urban Indians [14]. Another study from Kerala, a neighboring state, showed a similar low prevalence of physical activity [15]. In addition, this study also showed that about 27% of the patients were in a stage of contemplation, preparation or action. This group indicates the potential group that can be effectively converted to the action or maintenance phase. Therefore, this gives a clear picture that there are three distinct groups of people, one who have never thought of physical activity or have given up, one who are hesitating or preparing and one who are already physically active. This will help plan for

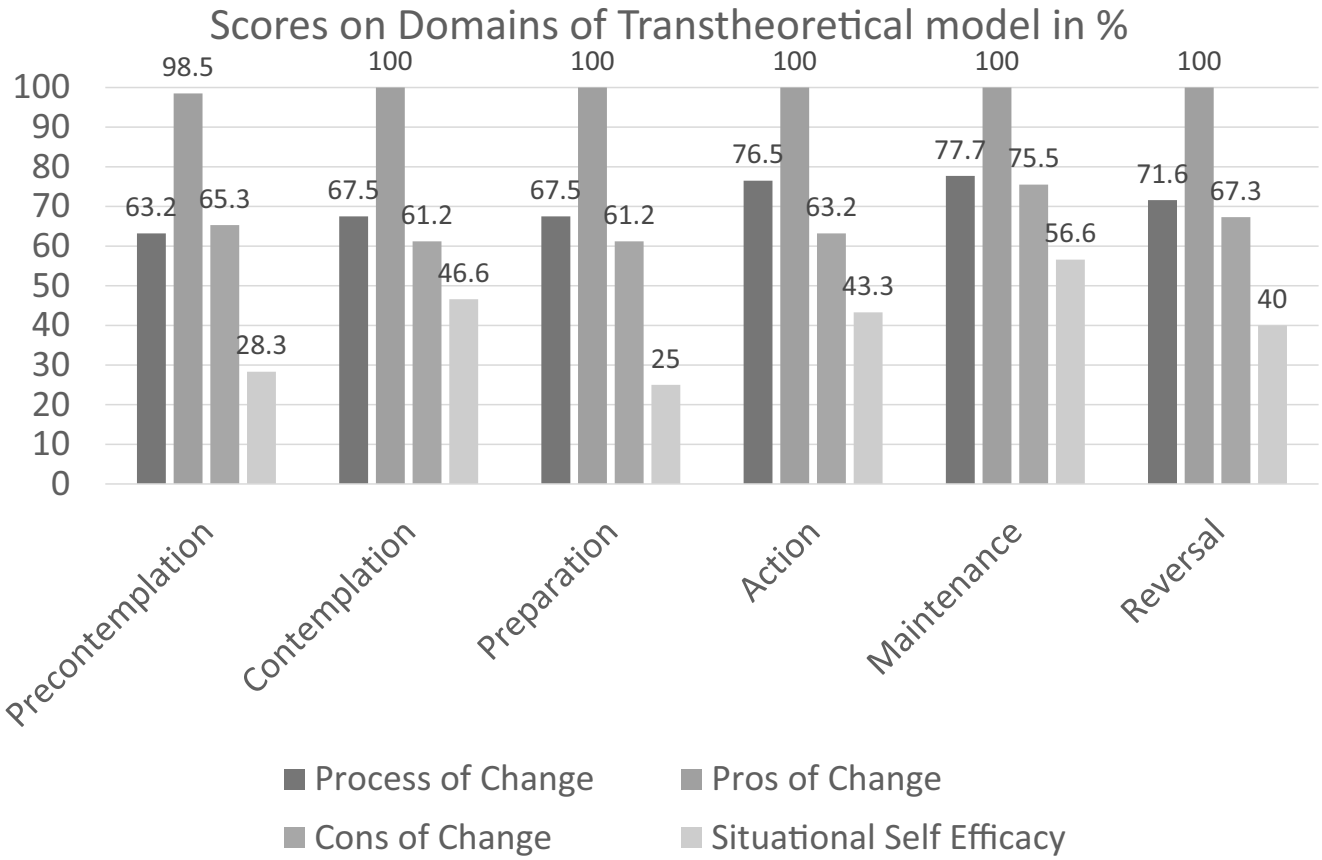

Fig. 3 The scores obtained by the participants in the four domains of process of change, pros of change, cons of change and situational self-efficacy are shown in this figure. It is seen that there is a significant difference in the process of change, cons of change and situational self-efficacy scores among the different stages of change.

Table 6 Factors influencing the stages of change

S. No.	Factor influencing the stage of change	Adjusted OR	95% CI	*p* value
1	Process of change	1.017	0.984–1.052	0.313
2	Situational self-efficacy	1.054	0.990–1.123	0.101
3	Decisional balance—pros of change	1.042	1.005–1.080	0.025*
4	Decisional balance—cons of change	0.929	0.877–0.985	0.014*
5	Age	0.965	0.926–1.005	0.089
6	Sex	0.633	0.307–1.305	0.215
7	Duration of diabetes	1.038	0.977–1.103	0.224

*Statistically significant at $p < 0.05$

interventions to promote physical activity among patients with diabetes.

Factors that influence adoption of physical activity

The process of change domain includes the various activities, behavioral and experiential that make people move across the stages. In the movement from precontemplation to contemplation and preparation phase, people mostly adapt consciousness raising, environmental re-evaluation, dramatic relief and social liberation as their strategies. Helping relationships, conditioning, reinforcement and stimulus control are used by people while moving from preparation to action and maintenance phases [10]. In this study, it was found that self-re-evaluation, self-liberation and positive reinforcement were high in this population. This is consistent with the fact that there were many people in the precontemplation phase and preparatory phases. There were very few in the stage of movement between action and maintenance, which is the stage in which the other key processes of change would be dominant. Previous studies on applying the transtheoretical model to study physical behavior have shown that stage-matched interventions are very effective in bringing about behavior change with respect to physical activity. Here, stage-matched intervention refers to understanding the stage of change that the individual patient is in and adopting the appropriate process of change measures to help them move across the stages [16]. Further, it was seen that the perceived pros of adopting physical activity was high among most participants. Similarly, the perception of cons was also moderately high. Janis and Mann in their pioneering work on decisional balance sheet mention that people adopt an action when the pros outweigh the cons in the analysis [17]. In the precontemplation and the reversal phase, the cons outweigh the pros. However, in the preparation, action and maintenance phases, the pros outweigh the cons. Interventions should focus on tipping the balance towards the perceived pros of physical activity. Further, the study also found low levels of situational self-efficacy. Bandura proposed that increases in self-efficacy will predict sustainable behavior change [18]. Therefore, the low levels of self-efficacy should be carefully considered for modification if a sustained behavior change is intended.

Understanding differences in influence across the stages of change of physical activity behavior

It was seen that there was no difference in the perception of pros across the stages. The perception of cons was highest in the patients in maintenance phase. This could mean two important things. Firstly, the people in the maintenance phase are the ones who are actively practicing physical activity and so likely to experience and perceive the cons. Secondly, these people are at risk of reversal from their maintenance phase as they are perceiving the cons. This is very important, as interventions must be planned to overcome their perceived cons so that they can continue in the maintenance phase. A graded increase in the overall process of change scores as one moves across the stages of change was clearly seen. It was also seen that the people in the contemplation phase had a significantly higher situational self-efficacy than those in the precontemplation phase and people in the maintenance phase had a substantially higher self-efficacy compared to those in the action phase. This is consistent with the fact that situational self-efficacy is an important determinant of change in behavior.

The multivariate analysis showed that perceived pros and perceived cons had a significant influence on whether a person belonged to action and maintenance phase or in one of the other non-action phases. This was true even after adjusting for confounding variables such as age, sex and duration of diabetes. Though the measures of association are very small, they show an indication towards a relationship, which remains statistically significant even after adjustment of other factors.

Implications of the findings and potential interventions

The study has shown that the factors of self-re-evaluation, self-liberation and positive reinforcement are the major influences on adopting physical activity behavior among

Table 7 Clinical implications of findings of this study

S. No.	Domain	Main finding	Clinical implications
1	Stages of change	About 29% of the patients were in the precontemplation phase and 20% in the reversal phase. Remaining 51% were in the contemplation, action and maintenance phases	Given the very low proportion of people in the maintenance phase (23%), and the high proportion (49%) not on any physical activity, there is a need to actively promote movement of people across the precontemplation, contemplation, action and maintenance phases
2	Process of change	There is a high level of self-re-evaluation, self-liberation and positive reinforcement. Low levels of helping relationships, stimulus control were observed	behavior change interventions should use the strategies of self-re-evaluation, self-liberation, positive reinforcement, stimulus control and helping relationships. This can be done by peer role modelling, formation of peer support groups
4	Decisional balance—pros and cons	The perception of pros of exercise are very high and cons of exercise are moderate. The cons of exercise are perceived more by people who are in maintenance phase	Patients in the maintenance phase of physical activity should be provided support to overcome the perception of cons, so that they can remain in the maintenance phase
5	Situational self-efficacy	The situational self-efficacy levels are low	Patients should be provided behavior change communication to improve self-efficacy through activities like medium intensity physical activity that will increase a sense of achievement, discussions with peer role models who demonstrate the ability to maintain the physical activity levels, promoting positive mood

patients with diabetes. Therefore, interventions should focus on improving self-re-evaluation, self-liberation and positive reinforcement. behavior change communication programs should work on encouraging the patients to see themselves as new, healthy and positive individuals after adopting physical activity. This can be done with the help of role models or "diabetes physical activity champions." Interactions with role models who adopt physical activity and feel healthy and positive can make patients re-evaluate themselves and see themselves as positive and new people after adapting physical activity. The other strategy is to help patients believe that they can start and maintain a physical activity regimen. This aspect of self-liberation can be encouraged by breaking down physical activity levels into small and simple steps, incorporating them into everyday life and making the patients feel that they can do this. Positive reinforcement with the help of rewards, social acknowledgment of achievement in physical activity levels can also help adopting the physical activity behavior.

Moreover, it was also seen that those in maintenance phase of physical activity started perceiving greater levels of cons. They should be provided intensive behavioral change communication to increase their situational self-efficacy. Activities like medium intensity physical activity that will increase a sense of achievement, discussions with peer role models who demonstrate the ability to maintain the physical activity levels, promoting positive mood, can all support increase in self-efficacy. The assessment of stage of change, processes of change, assessment of pros and cons and self-efficacy can be performed for individual patients with diabetes and the finding used to tailor-make the behavior change intervention for them (Table 7).

Strengths and limitations of this study

This study has systematically applied a robust theoretical behavioral model to the process of adoption of physical activity among patients with diabetes. There are several limitations of this study which should be borne in mind while interpreting the findings. The sampling method is non-probabilistic. But the sample is representative with respect to the age-sex profile of a typical diabetic population and hence can still give some indication to the true picture in the community. The instrument used to measure the transtheoretical model variables has undergone content validation for the purpose of this study; however, its construct validity is not known. Therefore, it is important to rigorously validate the scale for future applications. The cross-sectional nature of the study introduces the temporal bias, thus precluding any conclusion regarding causal association between the process of change, situational self-efficacy, decisional balance and the stages of change. Longitudinal studies which look at the variation of these constructs with temporal variation of the stages of change should be conducted to clearly understand the behavior change process. The effect sizes of the association between the stages of change and the factors influencing it are very small, thus raising important questions of its clinical and public health significance. However, it is to be kept in mind that small effect sizes are the norm in some areas of research such as social and psychological research [19].

Conclusions

This study has demonstrated that patients with diabetes tend to be in various stages of adoption of physical activity behavior. The patients tend to adopt various processes of change, majority of which are those that help in the early stages of adoption of the behavior. Any intervention to promote physical activity in this population should consider influencing the perceived pros and cons of physical activity by counselling, health promotion interventions and support. Though these findings cannot be directly extrapolated to other lifestyle behaviors such as diet and foot care, similar transtheoretical model approach can be followed to understand the stages, processes of change, decisional balance and situational self-efficacy to influence those behaviors as well.

Compliance with ethical standards

Conflict of interest The questionnaire was printed and administered in a pen and paper format, by the principal investigator after obtaining an informed consent from the participants.

Ethical approval The study was approved by the Institutional Ethical Committee of the ESIC Medical College & PGIMSR, Chennai, through an expedited review process. Verbal informed consent was obtained from all participants before the interview.

Abbreviations ANOVA, Analysis of variance; SPSS, Statistical Package for Social Sciences

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):749–755
https://doi.org/10.1007/s13410-019-00716-3

ORIGINAL ARTICLE

A community-based cross-sectional study of magnitude of dysglycemia and associated factors in Southwest Ethiopia

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Received: 4 October 2018 / Accepted: 13 January 2019 / Published online: 5 February 2019

Abstract

Background Diabetes, one of the non-communicable diseases becoming major public health problems in the country, is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. This study aimed at assessing the prevalence of dysglycemia (type 2 diabetes and impaired fasting glucose) and associated factors for adults older than 40 years living in Southwest Ethiopia.

Methods A community-based cross-sectional study was conducted using the WHO STEPwise tool for surveillance of non-communicable diseases. Data was collected by face-to-face interview and measurement of anthropometry, blood pressure, and fasting blood sugar using pretested questionnaire, and it was analyzed using SPSS version 20. Logistic regression was used to identify associated factors with the outcome variable.

Results The overall prevalence of dysglycemia was 18.6% among adults older than 40 years. Type 2 diabetes accounts for 5.7%, and impaired fasting glucose accounts for 12.9%. Presence of family history of diabetes [AOR = 2.45, 95% CI (1.08, 5.52)], being overweight [AOR = 3.8, 95% CI (1.84, 7.95)], and being obese [AOR = 7.78, 95% CI (2.90, 20.91)] were significantly and independently associated with dysglycemia.

Conclusion In this study, the prevalence of dysglycemia was high. Having a family history of diabetes mellitus and higher body mass index (overweight or obese) were risk factors for dysglycemia.

Keywords Dysglycemia · Fasting blood sugar · Associated factors · Jimma

Background

Type 2 diabetes which is a group of metabolic diseases is one of the major non-communicable diseases in the world. It is a public health problem due to its high prevalence, and association with cardiovascular diseases is characterized by chronic hyperglycemia. And also, the chronic hyperglycemia is associated with long-term damage and dysfunction of different organs. In the development of diabetes, several pathogenic processes are involved with consequent insulin deficiency to abnormalities that result in resistance to insulin action [1, 2].

Type 2 diabetes is a non-communicable disease of major importance as the prevalence has increased globally over the last decades [3]. Even though diabetes mellitus was previously considered as a rare condition in sub-Saharan Africa, currently, many studies revealed that the magnitude is rising which indicates that, as compared to developed region, developing countries are losing productive age groups. Type 2 diabetes, previously called non-insulin-dependent diabetes or adult-onset diabetes, accounts approximately 90–95% of those with diabetes, and most patients with this form of diabetes are obese [4, 5]. Majority of the people with diabetes in developing countries are typically older than 40 years while those in developed country areas aged 65 years and above, type 2 DM diagnosis remains undetected for a long time and many patients with newly detected diabetes have complication at the time of diagnosis. This underlines the importance of detecting

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undiagnosed diabetes, and early detection of individuals at risk of diabetes could be extremely beneficial [6, 7]. The difficulty in treating type 2 DM once it has developed and its human and substantial burden makes it an appropriate for early prevention. Further, the existence of a defined state of increased risk allows identification of patients who are most likely to benefit [1, 2].

Undiagnosed type 2 DM and who are at risk of its development are significantly at increased risk for the development of heart diseases, stroke, and peripheral vascular diseases. On the other hand, affected individuals have a greater likelihood of having dyslipidemia, hypertension, and obesity. Therefore, it is important for the clinician to screen for diabetes in a cost-effective manner in subjects who demonstrate major risk factors for diabetes [8].

In Ethiopia, the magnitude of undiagnosed DM is high when compared with many African countries and is responsible for a number of serious health problems and complications. Thus, due attention should be given to it through increasing public awareness on the diseases and even plan mass screening programs. Therefore, the aim of this study was to determine the magnitude of dysglycemia (type 2 diabetes and impaired fasting glucose) and associated factors for adults older than 40 years living in Jimma Town, Southwest Ethiopia.

Methods and materials

A community-based cross-sectional study was conducted from September 2016 to August 30, 2017 in Jimma Town, Southwest Ethiopia. Jimma Town is located 356 km southwest of Addis Ababa, capital city of Ethiopia, and it is divided into 17 administrative units. The town is one of the larger cities located in Oromia regional state with estimated population of 177,900 in 2015 [9]. From this total population, adults older than 40 years constitute 12.5%.

The source population for this study was the adult population living in Jimma Town, and the study population for this study were adults aged 40 years and above. All adults aged 40 years and above and permanent residents of the town were included in the study, but individuals who were known diabetic on treatment or follow-up, individuals who were taking any drugs with possible impact on glucose metabolism (ART drugs, oral contraceptives, steroids) during the study period, pregnant women (by LMP), and individuals who could not give consent due to mental illnesses or other debilitating conditions were excluded from the study.

Sample size and sampling procedure

Sample was calculated using a formula for estimation of single population proportion taking prevalence of hyperglycemia (DM, IFG) from the previous study [10] to be 20%, margin of error 5%, and using 95% confidence level. Then, after considering non-response rate of 10%, the final sample size became 269. Multi-staged sampling procedures were applied to select study participants. Out of 17 kebeles (smallest administrative units in Ethiopia) in the town, eight kebeles were included in the study. From each kebele, households were selected using systematic sampling techniques with specified sampling interval; every 50th household in the kebele was selected using an estimated 1700 households per kebele, and giving about 34 participants per kebele. Then, eligible individuals from the households were enrolled in the study. In cases where there was more than one eligible individual in the household, a lottery method was used to choose among them, and if there was no eligible individual in a household, the next house was visited.

Data collection, processing, and analysis

As recommended in the WHO STEPwise Approach guidelines on NCD risk factor surveillance [11], the survey consists of the use of interviewer-administered structured questionnaires, to assess the socioeconomic, sociodemographic, and behavioral characteristics of the study subjects. One day prior to the interview, the study participants were told to have overnight fasting till late morning hours (nothing per os except water). Then, the participants were interviewed after verbal consent is obtained. Physical measurements (BP, height, weight, waist circumference) were measured using standard calibrated instruments. A venous blood sample was taken from the interviewed and assessed subjects, and the sample was transported to Jimma University Specialized Hospital Laboratory. Plasma glucose determination was done using glucose oxidase method, and the result was registered.

The questionnaires and checklists were prepared in English by the principal investigator by reviewing different related literature and were translated to local languages (Amharic and Afan Oromo) by a health professional who is fluent in English, Afan Oromo, and Amharic languages and were checked for consistency by a third independent person competent in all the mentioned languages. The questionnaires were precoded and pretested to minimize errors. Then, data were collected by trained clinical nurses and laboratory technician. Instructional manual on the procedures of data collection, handling, operational definitions, roles of data collectors, and ethical issues was prepared. The data collectors and assistant were trained with demonstrations on the questionnaires/checklists by principal investigator for 1 day on the instruction manual of data collection ahead of the data collection schedule. The necessary tools for the data collections were given to the data collectors ahead of time, and data collection was supervised daily. During data collection, the collected data

were checked daily for completeness by the supervisor. The data collection assistant was arranging the equipment needed for the data collection and cross-checked the collected data for completeness and finally by principal investigator before entry in to the computer. The collected data was rechecked for completeness and cleaned by principal investigator. Finally, data was entered and analyzed by using SPSS version 20. Appropriate coding and re-coding were done at each step for the variables as necessary. Descriptive statistics like frequencies, percentages, means, medians, standard deviations, and ranges were used to describe the findings. A binary logistic regression analysis was done to sort variables candidate for multiple logistic regression having a value less than or equal to 0.25. Multivariate logistic regression analysis was conducted to generate factors strongly associated with dysglycemia. Finally, the association was declared with a p value less than 0.05 with an adjusted odds ratio (AOR) at 95% confidence level. Additionally, data from sociodemographic factors, behavioral and medical risk factors, and measurable variables were described based on their categories and the identified themes across dysglycemia.

Results

Sociodemographic characteristics

Out of 269 study populations, a total of 264 participated in the study giving a response rate of 98.1%. Of the total respondents, 150 (56.8%) were females and 114 (43.2%) were males. The age of the respondents ranged from 40 to 90 years, with a mean age of 54 (SD = 13) years. The age group 40–64 years, with a total of 194 study subjects (73.5%), constituted the majority of respondents. Majority, 75.8% of the respondents were married, and 37.5% of the respondents were housewives (Table 1).

Table 1 Socio-demographic characteristics of the respondents in Jimma Town, Southwest Ethiopia, 2017 ($n = 264$)

Variables	Category	Frequency	Percentage
Age	40–64 years	194	73.5
	65–79 years	57	21.6
	More than 80 years	13	4.9
Sex	Male	114	43.2
	Female	150	56.8
Marital status	Married	200	75.8
	Single	10	3.8
	Divorced	41	15.5
	Widowed	13	4.5
Religion	Orthodox	106	40.1
	Muslim	110	41.7
	Protestant	47	17.8
	Others	1	0.4
Ethnic group	Oromo	118	44.7
	Amhara	57	21.6
	Dawro	28	10.6
	Gurage	22	8.3
	Others*	39	14.8
Educational status	Illiterate	22	8.3
	Read and write	48	18.3
	Grades 1–8	79	29.9
	Grades 9–12	51	19.3
	Higher education	64	24.3
Occupation	Housewives	99	37.5
	Government employees	70	26.5
	Merchants	60	22.7
	Others**	35	13.3
HH monthly income	Low	79	29.9
	Intermediate	154	58.3
	High	31	11.7

*Hadiyya, kaffa

**Students, farmers

Medical and behavioral risk factors

Family history of DM was presented in 37 (14%) of participants and gestational DM in 18 (12%) female respondents and personal history of hypertension in 53 (20%). Regarding the level of physical activity, 120 (45.5%) of the respondents reported to have insufficient physical activity, 75 (28.4%) were inactive, and 69 (26.1%) had sufficient physical activity, according to the WHO definitions. History of alcohol consumption was reported by 64 (24.2%) of the study participants, 8 (3%) reported heavy drinking, 16 (6%) moderate drinking, and 40 (15%) reported light drinking. In this study, 18% participants had hypertension. About 15 (30.6%) of participants who had hypertension with our measurement were either told to have hypertension previously or are taking antihypertensive medications. The mean systolic blood pressure of the study population was 118 ± 14 mmHg, while the diastolic mean was 75 ± 10.2 mmHg. There was no statistically significant difference in the mean value of blood pressure either between males and females ($p = 0.44$) or among respondents with normal FBS or dysglycemia ($p = 0.47$).

The BMI of the respondents ranged from 16.65 to 36.40 kg/m^2, with a mean of 24.16 kg/m^2. The mean BMI of the female respondents was 24.5 ± 3.4 kg m^2 and of the males was 23.6 ± 3.8 kg m^2. Females constitute larger frequency of overweight or obese individuals, but there is no statistically significant difference between the two means. The difference between the means of BMI of respondents with normal FBS and dysglycemia is statistically significant ($p = 0.00$).

Table 2 Summary of medical and behavioral risk factors of the study participants in Jimma Town, Southwest Ethiopia, 2017

Variable		Male, *N* (%)	Female, *N* (%)	Total, *N* (%)
Gestational DM		–	18 (12)	18 (12)
Family history of DM		17 (14.9)	20 (13.3)	37 (14)
History of HTN		17 (14.9)	36 (24)	53 (20)
Smoking history		15 (13)	3 (2)	18 (6.8)
Physical activity	Inactive	24 (21)	51 (34)	75 (28.4)
	Insufficiently active	48 (42)	72 (48)	120 (45.5)
Diet (fruit and veg)	Four times or less/day	32 (28)	75 (50)	107 (40.5)
Alcohol consumption		30 (26.3)	34 (22.7)	64 (24.2)
Alcohol amount	Regular daily	6 (5.2)	2 (1.3)	8 (3)
	Moderate	9 (8)	7 (4.7)	16 (6)
	Light	15 (13)	25 (16.7)	40 (15.2)
Hypertension		21 (18.4)	28 (18.7)	49 (18.5)
BMI	Overweight	32 (28)	53 (35.3)	85 (32.2)
	Obese	9 (8)	15 (10)	24 (9.1)
Waist circumference (central obesity)		18 (15.8)	35 (23.3)	53 (20.1)

Waist circumference was (using the European cutoff points) 23.3% for females, and 15.8% of male respondents had central obesity. It ranges from 70 to 105 cm with a mean of 83.2 cm for males and 73 to 104 cm with a mean of 83 cm for females. There was no statistically significant difference between the mean WC of male and female ($p = 0.16$), but there was statistically significant difference between the mean of WC in normal FBS and dysglycemia ($p = 0.00$). The fasting blood sugar in the surveyed population ranges from 70 to 210 mg/dl, and its mean (SD) was 96 ± 17 mg/dl (Tables 2 and 3).

Prevalence of dysglycemia

Of the total 264 subjects who were tested, 15 (5.7%) had diabetes (with a single test for the survey), while 34 (12.9%) had impaired fasting glucose. Overall, dysglycemia was present in 48 (18.6%) of the respondents (10.6% males and 8% females). Highest frequency by age group was seen in greater than 80-year-old age group, although this is not statistically significant ($p = 0.49$). This study revealed that 35% of participants with family history of DM and 22.6% of participants with history of hypertension had dysglycemia.

Factors associated with dysglycemia

Bivariate logistic regression analysis showed that family history of DM, BMI, waist circumference, and Physical inactivity had positive association with dysglycemia. Stepwise multiple logistic regression showed that the likelihood of dysglycemia for study subjects who had family history of DM was about 2.5 times higher than those who had no family history of DM [AOR = 2.45, 95% CI (1.08, 5.52)]. Similarly, body habitus (overweight or obese) was also associated with increased risk of dysglycemia compared to respondents who had a normal BMI (overweight [AOR = 3.8, 95% CI (1.84, 7.95)], obese [AOR = 7.78, 95% CI (2.90, 20.91)] (Table 4).

Discussion

In this study, the prevalence of DM was 5.7%, which is comparable with the findings from Northwest Ethiopia, 5.1% [12]; Bishoftu, Central Ethiopia, 5% [13]; and sub-Saharan Africa, 6.5% [14]. Similarly, the prevalence was in line with the finding from Gilgel Gibe research project, Southwest Ethiopia (4.4%) [15], which may be explained by the younger age group it involved (15–64) and inclusion of rural areas as well. However, this finding is in contrast with the estimated magnitude 2% by IDF for Ethiopia overall urban and rural in 2013. Since this estimate is an overall for rural and urban areas, the reason for this difference may be that the prevalence of DM is higher in urban than in rural area.

This study revealed that the prevalence of IFG was 12.9% and that of dysglycemia was 18.6%. When compared with the Gilgel Gibe research project report [15] which used the WHO cutoff point, both IFG (9.7%) and dysglycemia (14.4%) were slightly lower in this study. The study done in Jimma Town, Ethiopia, in 2006 used 100–125 mg/dl to define IFG, and by then, the prevalence was 15.4%. Using this cutoff point and calculating the prevalence to compare and see the trend, the IFG in our study was 26.7%, which may be interpreted as an increase in IFG by about 11% over 10 years (i.e., we used the WHO definition of impaired fasting glucose > 110 mg/dl, and

Table 3 Summary of mean and standard deviation of continuous variables in study subjects in Jimma Town, 2017 ($n = 264$)

Parameter [mean (SD)]	Sex		p value	FBS		p value
	M	F		Normal	Dysglycemia	
Systolic BP	118 (13.76)	119 (14.04)	0.44	119 (13.82)	118.8 (14.4)	0.97
Diastolic BP	75 (10.40)	75 (10.04)	0.70	75 (9.82)	76 (11.7)	0.47
BMI	23.67 (3.83)	25.52 (3.89)	0.07	23.5 (3.55)	26.9 (4.08)	0.00
Waist circ.	83 (8.67)	81.6 (8.98)	0.16	81 (8.26)	86.3 (10.29)	0.00
FBS	96 (16.64)	95 (17.88)	0.58	89.96 (10.35)	122 (17.47)	0.00

they used > 100 mg/dl of American Diabetic Association, which accounts for the difference). Studies in Ethiopia and other African countries showed that, in general, the prevalence of IFG or DM is higher in urban than rural areas. The urban prevalence and rural prevalence of those studies were 5.1% versus 2.1% [12], 8.4% versus 1.1% [16], and 15.9% versus 12.9% [17]. This difference has been ascribed to body habitus, dietary habit, and sedentary lifestyle seen in urban settings.

Among the medical and behavioral risk factors, having a first-degree family history of DM was an independent predictor of dysglycemia. Study participants who had a family history of DM were about 2.5 times more likely to have dysglycemia than those who had no family history of DM. How genetic predisposition alone causes DM is not known, but it is thought to be the result of a combination of genetic and environmental factors [18]. There are only few studies which are specifically designed to assess independent predictors of dysglycemia, as most are focused on type 2 DM rather than prediabetic states. On the other hand, there are many studies which showed that having a family history is an independent predictor of T2DM [19–23]. One study in Ethiopia showed that a family history of DM is an independent predictor of dysglycemia, other determinants being hypertension and age more than 45 years [20]. The other independent predictor of dysglycemia in our study is body mass index. Participants who were overweight were about four times more likely to have dysglycemia compared to those with normal BMI. Similarly, obese individuals as defined by BMI were about eight times more likely to have dysglycemia compared to those with normal BMI. A study in Addis done to assess the trend of overweight and obesity over one decade (2000–2011) has shown that overweight increased by 24.5% and obesity by 40.2% [14]. In a cross-sectional study done in Gonder, North Ethiopia, to assess the prevalence of hypertension and body habitus, 32.4% of individuals were overweight and 16% were obese [24]. Closely related to overweight and obesity is the presence of sedentary lifestyle especially among the urban population. In this study, about 74% of the participants reported to have either inactive or insufficiently active level of physical activity. This may be because of the less physically demanding nature of occupation in towns compared to rural areas. The largest proportion of dysglycemia, 36.4%, was seen in the physically inactive group. The bivariate analysis revealed that physical inactivity and central obesity were positively associated with dysglycemia in this study, although after adjustment for other variables, their effect was not statistically significant. Studies in African countries, including Ethiopia, showed that physical inactivity and central obesity were independent predictors of DM [13, 19, 25].

This study revealed that hypertension was presented in 18.5% of the study participants in which only 30% of those were told to have elevated BP before or are taking

Table 4 Multiple logistic regression of independent variables with dysglycemia in study subjects of Jimma Town, 2017

Variable		COR (95% CI)	p value	AOR (95% CI)	p value
Family history of DM	No	1	0.007	1	*0.031**
	Yes	2.87 (1.34, 6.16)		2.45 (1.08, 5.52)	
Physical inactivity	Inactive	2.5 (1.21, 5.36)	0.054		
	Insufficiently active	1			
	Active	1.7 (0.8, 3.95)	0.047		
Waist circ.	Normal	1	0.002		
	Obese	2.9 (1.5, 5.92)			
Body habitus (BMI)	Normal	1		1	0.00*
	Overweight	3.96 (1.92, 8.17)	0.00	3.8 (1.84, 7.95)	
	Obese	8.5 (3.22, 22.54)		7.78 (2.90, 20.91)	

*Statistically significant at $p < 0.05$

antihypertensive, which means that hypertension remains undiagnosed. This is comparable with the finding from Addis Ababa, 19%, and Gondar, 14.4% [14, 25]. In our study, 22.6% of respondents who reported a history of hypertension had dysglycemia and 24.5% of those with measured high BP had dysglycemia. There is no statistically significant difference between the mean blood pressure between males or females ($p = 0.44$) or between participants with normal FBS or dysglycemia ($p = 0.47$). In both bivariate and multiple logistic regression, there is no significant association between hypertension and dysglycemia in this study. But, literatures show that hypertension remains an important comorbid condition with diabetes or prediabetic conditions [14, 20, 21] and hypertension is considered as a risk factor for insulin resistance and ADA recommends screening for patients with hypertension [8].

Lastly, this study did not show any statistically significant association between the sociodemographic variables (religion, ethnicity, occupation, income category) and dysglycemia. Similarly, even though physical activity was statistically significant in bivariate analyses, it was not statistically significant in multivariable analysis. However, previous meta-analysis [26] showed that there was an association between physical activity and type 2 diabetes. The difference might be due to the fact that different study designs were employed.

This study has its own strength in that it was done using a validated WHO STEPwise Approach and the study used a modified version of the standard WHO risk factor questionnaire that had been pretested for its suitability in the Ethiopian population. However, this study has some limitations: factor like dyslipidemia was not assessed, and OGTT was not done (full picture of prediabetic may not be seen with fasting blood sugar alone).

Conclusions

This study has found a prevalence of dysglycemia higher than previously reported in urban populations, but comparable prevalence of DM. Hypertension was found to be prevalent and remains largely undiagnosed although not associated with dysglycemia in this study. Family history of DM and body habitus (overweight and obesity) were found to be independent predictors for dysglycemia. The proportion of respondents with lower level of physical activity could in part may account for the high prevalence of overweight, obesity, and dysglycemia among the study subjects. Therefore, given the high prevalence of impaired glucose hemostasis in the study area, 40 years and more adults with overweight or obese body habitus, family history of DM, and hypertension need to be screened for dysglycemia. Moreover, further specific studies are needed on the predictor of DM and hypertension, and large-scale studies that also include the rural population, as the population profile may not be similar to the town population, are needed to develop local protocols for screening.

Acknowledgments We are especially grateful to all participants who participated in this study. This would not have been possible without their involvement and contribution.

Authors' contribution TZ participated in conceptualizing the study, designed the study, coordinated and supervised data collection, and supervised data entry. EH and HM participated in initiating the concept, design of the study, interpretation of the findings, and write-up of the manuscript. DD also participated in the write-up and revision of the manuscript. All authors have read and approved the manuscript.

Funding This research was funded by Jimma University Institute of Health Sciences.

Availability of data and materials Data will be available upon request from the corresponding author.

Compliance with ethical standards

Ethics approval and consent to participate Ethical clearance was obtained from the Institutional Review Board (IRB) of the College of Health Science and then from an ethical review committee of JUSH and was taken to the Jimma Town Health Bureau, and letter of permission was written to each kebele administration. Purpose and significance of the study were explained, and informed consent was taken from each study participant. Respondent's confidentiality was ensured during the study period. The interview scripts were numbered and coded and without including personal identifying data. Participants with abnormal blood sugar were advised and informed to go to health institutions to have their blood sugar repeated and have follow-up.

Consent for publication Not applicable.

Competing interests The authors declare that they have no competing interests.

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Abbreviations *AOR*, Adjusted odds ratio; *BMI*, Body mass index; *BP*, Blood pressure; *COR*, Crude odds ratio; *DBP*, Diastolic blood pressure; *DM*, Diabetes mellitus; *FBS*, Fasting blood sugar; *GDM*, Gestational diabetes mellitus; *IGT*, Impaired glucose tolerance; *JUSH*, Jimma University Specialized Hospital; *OGTT*, Oral glucose tolerance test; *WC*, Waist circumference

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):756–763
https://doi.org/10.1007/s13410-019-00738-x

CASE REPORT

Alstrom syndrome: insulin resistance in young with congestive heart failure

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Received: 21 April 2018 / Accepted: 18 March 2019 / Published online: 5 April 2019

Abstract
Alstrom Hallgren syndrome is a rare ciliopathy first described in 1959. It is characterised by progressive cone-rod dystrophy leading to blindness, sensorineural hearing loss, childhood obesity and congestive heart failure. Its pathogenesis is related to development of insulin resistance, and type 2 diabetes mellitus. We report a case of a 20-year-old presenting with decompensated heart failure and had been blind since childhood who was eventually diagnosed as Alstrom syndrome based on clinical criteria.

Keywords Ciliopathy · Congestive heart failure · Insulin resistance · Diabetes mellitus

Background

Alstrom Hallgren syndrome is a rare ciliopathy with only 1053 individuals being reported worldwide since its first description in 1959 [1]. It is caused by mutations in ALMS1 gene (OMIM #203800) [2]. Thus, the importance of the syndrome lies in its clinical variability and phenotypic diversity with a varied range of symptoms and severity and a variable age of onset. Most characteristic symptom is cone-rod dystrophy in infancy, clinically presenting with extreme photophobia and nystagmus often progressing to complete blindness by second decade [3]. Sensorineural hearing loss of moderate to severe intensity occurs in about 89% of the patients with most children requiring hearing aids. There is presence of childhood obesity with insulin resistance which increases with age resulting in type 2 diabetes mellitus occurring at a mean age of 16 years [4]. Hypertriglyceridemia and hypercholesterolemia occur which can be serious enough to cause pancreatitis. Dilated cardiomyopathy is a common finding, occurring in 60% of patients with congestive cardiac failure being precipitated at any age [5]. Hyper- or hypogonadotropic hypogonadism is seen in both males and females but is more common in males. There is accelerated skeletal maturity which leads to kyphosis, scoliosis and short stature. Most patients demonstrate normal intelligence although autistic spectrum behaviors and seizure activity have been reported.

Case presentation

A 20-year-old illiterate male born out of consanguineous Muslim marriage presented to the emergency department with progressive shortness of breath for the last 15 days. It was gradual in onset, associated with palpitations during time of exertion, progressive and finally orthopnoea had set in. It was associated with dry cough which increased in lying down position. The dyspnoea was not associated with any chest pain or fever. He had frequent complaints of decreased appetite and bloating and intermittent abdominal pain occurring diffusely all over the abdomen for the last 2 months. The patient had no history of similar complaints in the past although he had few episodes of recurrent minor pulmonary infections. The patient's mother elaborated on his vision and weight problems since childhood. He had started having difficulty in vision when he was 9 months of age. He was unable to fixate his vision with progressive decreasing visual acuity which first began as day blindness. He was completely blind by the age of four and in the last few months, he started having hearing difficulties. He did not attend school because of impaired vision. The mother also noted unusual darkening of skin on the nape of the neck since early childhood. There is a significant family history of blindness on paternal side. His father's elder brother and sister both had sons with blindness with type 2 diabetes mellitus (one each), but the rest of their children were normal. His younger brother was also blind, but died in childhood.

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On examination, the patient's height was 150 cm and weighed 85.2 kg (BMI, 37.7). His waist circumference was 115 cm and hip circumference was 124 cm. He was obese with bilateral gynecomastia and flat feet. Extensive acanthosis nigricans was present in all flexures of the body and the nape of the neck. (Fig. 1). Eye examination revealed bilateral blindness with no visual acuity, cataract in the left eye and horizontal nystagmus at rest, which was equal in all directions. Pupils were sluggishly reactive. Fundus examination showed multiple refractive granules in the vitreous humour. Optic disc pallor was present with pigmentation seen in clumps, suggestive of cone dystrophy. He had significant pitting pedal edema. His blood pressure was 160/100 mmHg and heart rate was 104/min. His jugular venous pressure was raised about 8 cm above the sternal angle. On auscultation, there was decreased air entry with bilateral basal crepitation's and a pan-systolic murmur present in the tricuspid area. Hepatosplenomegaly was present. Muscle tone and all reflexes were normal. There was no abnormality detected in higher mental functions.

Lab investigations

A mild hypothyroidism and deranged lipid profile were observed (Table 1). High levels of insulin, fasting blood glucose and HbA1c confirmed the diagnosis of diabetes mellitus. Low testosterone with normal LH and FSH was reported. The cortisol measured in the morning (8 am) was also in the normal range. Significant proteinuria of about 1 g/24 h, with normal blood urea and creatinine, was observed. Cardiac biomarkers and D-dimer were normal. Chest X-ray revealed cardiomegaly and ECG showed poor progression of R wave. 2D echocardiogram findings were global hypokinesia of the left ventricle, dilated cardiomyopathy with ejection fraction of 20%, and moderate tricuspid regurgitation with moderate pulmonary artery hypertension. USG abdomen revealed hepatomegaly with a portal vein diameter of 10 mm. Contrast-enhanced computed tomography of the abdomen reported enlarged spleen and liver and narrowed celiac trunk and post-stenotic dilatation indicating the presence of median arcuate ligament syndrome (Figs. 2 and 3). Pancreatic lipomatosis was also a concurrent finding. Contrast-enhanced computed tomography of the thorax revealed significant adipose tissue deposition on the chest wall and a mild bilateral pleural effusion with atelectasis of adjacent parenchyma (Fig. 4). Magnetic resonance imaging of the brain showed a normal sella turcica. Audiometry revealed mild bilateral sensorineural hearing loss. Gene analysis and electroretinography (ERG) were not done due to the financial constraints.

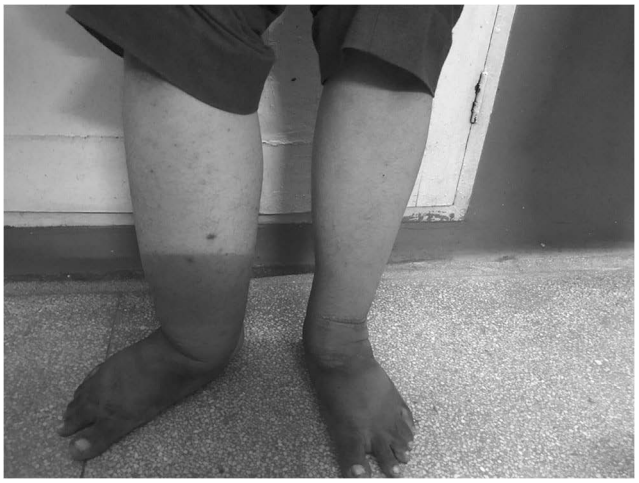

Fig. 1 Patient showing bilateral oedema and flat feet with acanthosis nigricans present in the flexor part of the ankle joints

Differential diagnosis

The diagnosis remains essentially clinical with the available age-specific criteria [2]. Differential diagnosis include Bardet-Biedl syndrome, Wolfram, Cohen, Biemond II and Usher syndromes. Based on the criteria (Table 2) [2] for more than 15 years of age, the diagnosis of Alstrom syndrome was made as the patient was legally blind since childhood and had nystagmus, obesity, dilated cardiomyopathy with hepatic dysfunction, sensorineural hearing loss and hypogonadism.

Table 1 Lab investigations

TSH	6.070 (0.55–4.78 mIU/mL)
Lipid profile	
Cholesterol	218 mg/dL (< 200 mg/dL)
Triglycerides	414 mg/dL (< 150 mg/dL)
LDL	132 mg/dL (< 100 mg/dL)
HDL	32 mg/dL (> 40 mg/dL)
HbA1c	10.9%
Fasting insulin levels	129.92 mU/L (3–25 mU/L)
Fasting blood glucose	369 mg/dL
Hormones	
Testosterone	165.68 ng/dL (241–827 ng/dL)
LH	6.52 mIU/mL (1.5–9.3 mIU/mL)
FSH	10.14 mIU/mL (1.4–18.1 mIU/mL)
8 am cortisol	13.98 μg/dL (4.3–22.4 μg/dL)
Cardiac biomarkers	
Troponin	Negative
CKMB	8 IU/L (3–25 IU/L)
Urinary protein	1 g in 24 h

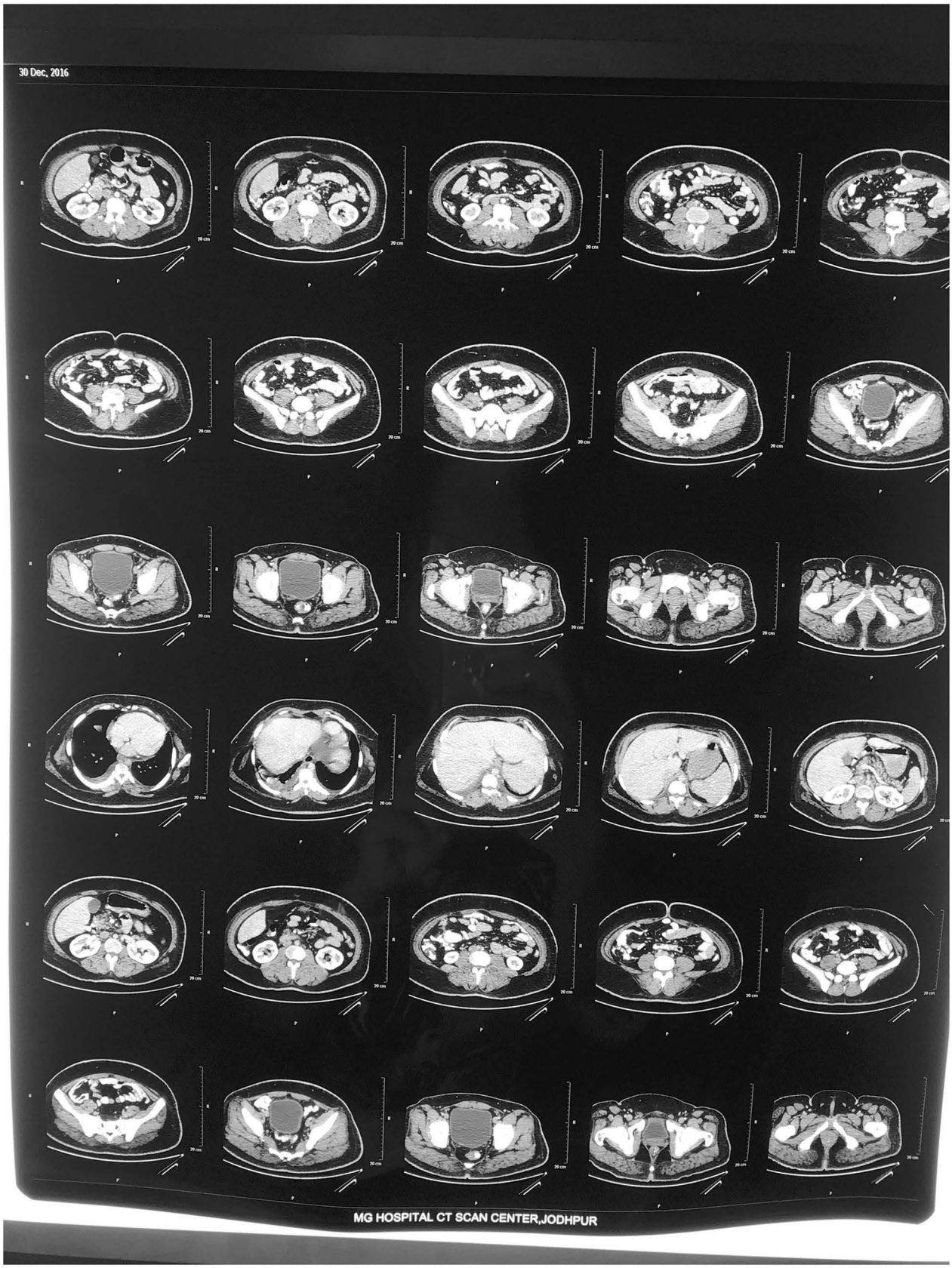

Fig. 2 CECT abdomen showing coeliac trunk compression by median arcuate ligament and post-stenotic dilatation

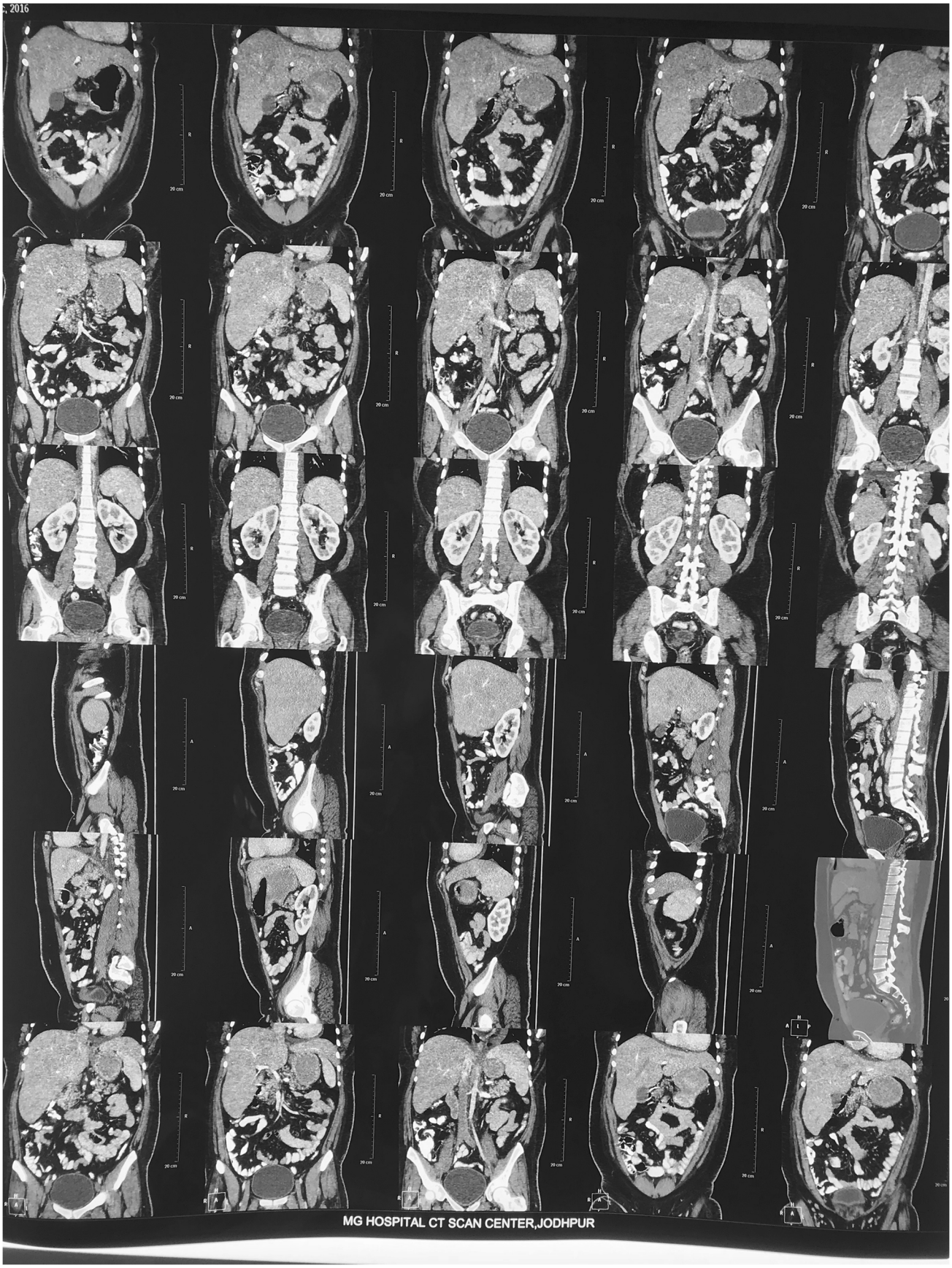

Fig. 3 CECT abdomen showing coeliac trunk compression by median arcuate ligament and post-stenotic dilatation

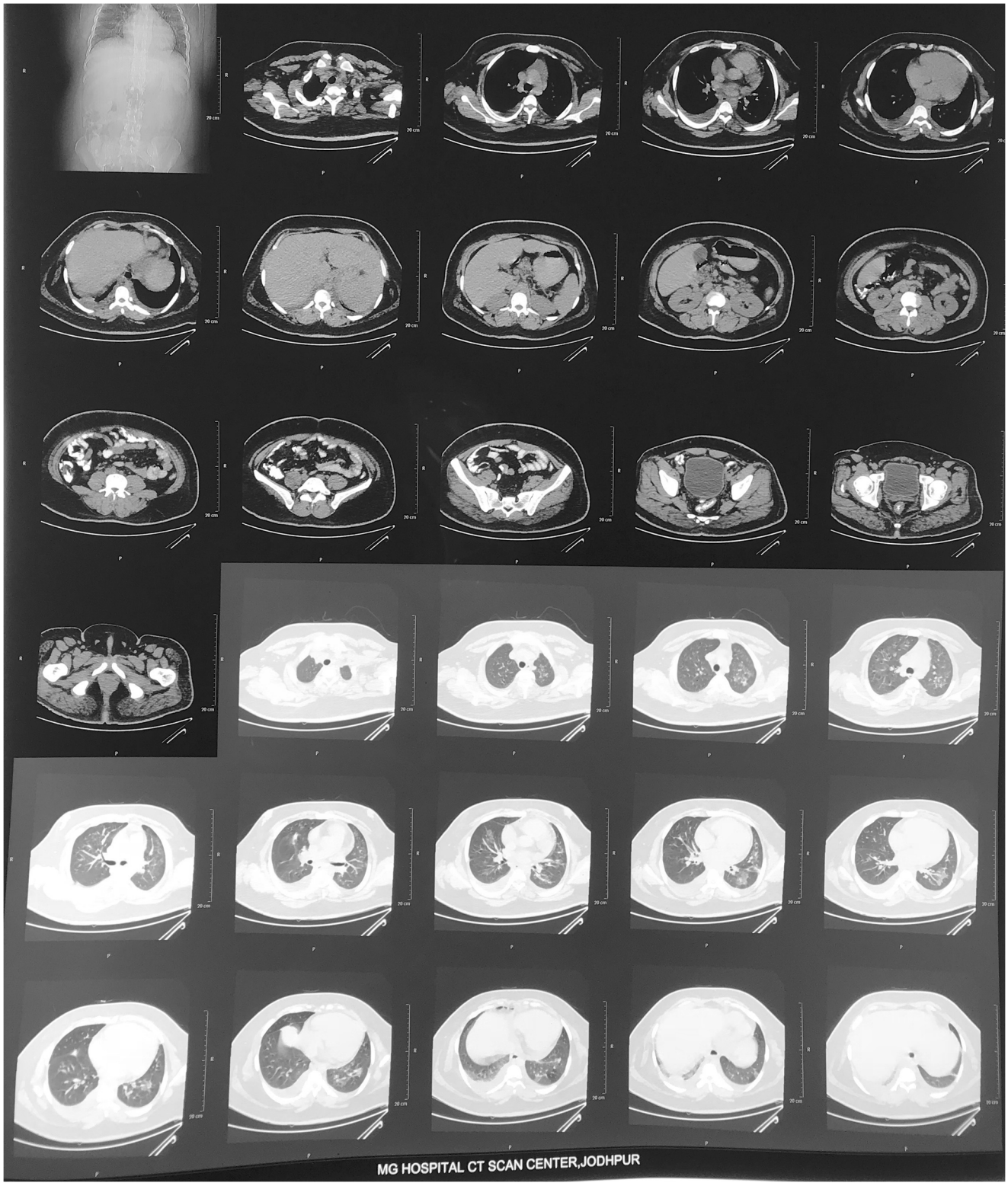

Fig. 4 CT of the thorax showing excess fat deposition in chest wall with mild atelectasis of lower lung

Management

The disease is incurable but its various symptoms can be managed. The patient was given diuretics, low-dose beta blocker and digoxin for the dilated cardiomyopathy. Treatment with statins for deranged lipid profile and diabetes was managed on insulin therapy. Dietary modification and salt restriction were advised. The abdominal pain was managed with dicyclomine

Table 2 Age-specific diagnostic criteria of Alstrom syndrome [2]

Age range	Diagnostic criteria		Minimum required	Other variable supportive evidence
	Major	Minor		
Birth–2 years[1]	• Mutation of *ALMS1* on 1 allele, and/or • Family history of Alström syndrome • Vision (nystagmus, photophobia)	• Obesity • DCM/CHF	2 major criteria or 1 major +2 minor criteria	• Recurrent pulmonary infections • Normal digits • (History of) delayed developmental milestones
3–14 years	• Mutation of *ALMS1* on 1 allele, and/or • Family history of Alström syndrome • Vision (nystagmus, photophobia, diminished acuity, if old enough for testing: cone dystrophy by ERG)	• Obesity and/or insulin resistance and/or T2DM • (History of) DCM/CHF • Hearing loss • Hepatic dysfunction • Renal failure • Advanced bone age	2 major criteria or 1 major +3 minor criteria	• Recurrent pulmonary infections • Normal digits • (History of) delayed developmental milestones • Hyperlipidemia • Scoliosis • Flat wide feet • Hypothyroidism •Hypertension • Growth hormone deficiency • Recurrent UTI
15 years–adult	• Mutation of *ALMS1* on 1 allele, and/or • Family history of Alström syndrome • Vision (history of nystagmus in infancy/childhood, legal blindness, cone and rod dystrophy by ERG)	• Obesity and/or insulin resistance and/or T2DM • (History of) DCM/CHF • Hearing loss • Hepatic dysfunction • Renal failure • Short stature • Males: hypogonadism • Females: irregular menses and/or hyperandrogenism	2 major +2 minor criteria or 1 major +4 minor criteria	• Recurrent pulmonary infections • Normal digits • (History of) delayed developmental milestones • Hyperlipidemia • Scoliosis • Flat wide feet • Hypothyroidism • Hypertension • Growth hormone deficiency •Recurrent UTI/urinary dysfunction • Alopecia

and oral proton pump inhibitors. Surgical reference was sought for medial arcuate ligament syndrome and advised conservative management, since there was no obstruction.

Discussion

Alstrom syndrome is caused by mutations in ALMS1 on chromosome 2 which is a large gene comprised of 23 exons and coding for a protein of 4169 amino acids [6]. ALMS1 protein is found in centrosomes, basal bodies, and cytosol of all tissues affected by the disease. Until now, about 297 mutations have been reported in the whole gene with each mutation having possible phenotypic variation, which are still being discovered [7]. The gene ALMS1 has unclear function but has been shown to be involved in ciliary and endosomal transport of various organs accounting for its myriad of symptoms. It represents a single-gene metabolic syndrome and has shown recent strong positive selection, on par with lactase persistence and resistance to malaria [8]. The gene is related with carbohydrate metabolism, linked to greater insulin resistance. Analysis of the gene has implications in our better understanding of pathogenesis of metabolic syndrome and subsequent pharmacological therapy targeting the same. This is of even greater importance in a country like India which already has genetic and phenotypic predispositions to metabolic syndrome.

Alstrom syndrome is an autosomal recessive disorder. Though autosomal recessive diseases usually do not manifest in the same family, our patient's family has history of consanguineous marriages with his parents being first cousins. The syndrome is a rare cause of dilated cardiomyopathy in young patients, usually associated with viral infection or endocrine dysfunction. The importance of the syndrome lies in its clinical variability and phenotypic diversity, even within the same family. Thus, a high clinical suspicion is necessary, especially if a family history is present. These patients can have varied presentations at the first encounter with the doctors [9]. The diagnosis can be made when the patient first develops cone-rod dystrophy in infancy or much later when they present with dilated or restrictive cardiomyopathy or diabetes mellitus or hepatic, pulmonary or renal dysfunction. Our patient had an episode of acute decompensated heart failure and normal cardiac enzymes, prompting a clinical suspicion of severe thyroid abnormality or a viral infection. But since there was no history of alcohol/drug abuse and no family history of chronic heart disease and TSH was only mildly raised, we pursued to find rare causes of dilated cardiomyopathy with childhood obesity. A diagnosis of Alstrom syndrome was made on the clinical criteria available.

To our best of knowledge, this is the first case of Alstrom syndrome reported to have presented with median arcuate ligament syndrome (MALS). It is estimated that 10–24% of general population may have indentation caused by an abnormally low ligament [10]. However, the pathogenesis of MALS is still uncertain, a few authors support the theory based on a higher origin of the celiac trunk from aorta, while others maintain the exuberant growth of neurofibrous tissue originating from the celiac plexus causing compression [11]. In the case of increased severity of symptoms, Alstrom syndrome with its comorbidities presents a unique challenge for any minor or major surgical intervention required for median arcuate ligament; choosing the right anesthetic agent to comply with reduced ejection fraction, aspiration prophylaxis in view of obesity, blood glucose monitoring and autonomic dysfunction, alleviating anxiety associated with visual and hearing impairments and higher surgical risk in view of multiple organ impairment. The above case also highlights the importance of clinical diagnosis of Alstrom syndrome, especially in our country where genetic workup and mutation analysis are not accessible to all. Greater awareness about the disease can lead to early diagnosis and with proper supportive management and dietary modification, the patients can have an improved quality of life.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any use of animals or drugs by any of the authors.

Informed consent The authors certify that they have obtained all the appropriate consent forms. In the form, the patient has given the consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):764–767
https://doi.org/10.1007/s13410-019-00739-w

CASE REPORT

Diabetic muscle infarction in type 1 and type 2 diabetes mellitus: lessons from two cases

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Received: 12 July 2018 / Accepted: 19 March 2019 / Published online: 4 April 2019

Abstract
Diabetic muscle infarction (DMI) is an underreported complication of poorly controlled diabetes mellitus. We present clinical and laboratory data of two patients, a 27-year-old woman with Down syndrome and type 1 diabetes mellitus (T1DM) and a 47-year-old man with type 2 diabetes mellitus (T2DM) who presented with DMI. Poor control of T1DM and delayed diagnosis of T2DM were the major underlying factors in these cases. Although the condition responds well to conservative treatment, overall prognosis of patients is poor with respect to diabetes complications and mortality.

Keywords Diabetes mellitus · Myonecrosis · Muscle infarction · Type 1 · Type 2

Introduction

Diabetic muscle infarction (DMI) or diabetic myonecrosis is often defined as a spontaneous ischemic necrosis of the skeletal muscle that is unrelated to atheroembolism or occlusion of major arteries [1].

It was first reported by Angervall and Stener in 1965 [2]. It is a less commonly reported complication with the global literature reporting just about 200 cases [3]. Considering the high prevalence of diabetes, it is probably underdiagnosed and underreported [4].

We report two cases of diabetes, a 27-year-old woman with Down syndrome and type 1 diabetes mellitus (T1DM) and a 47-year-old man with poorly controlled type 2 diabetes mellitus (T2DM), who were diagnosed to have DMI. Importance of DMI with respect to presence of significant diabetes complications and mortality is highlighted.

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Case 1

A 27-year-old female, with Down syndrome, T1DM (9-year duration), hypothyroidism, and secondary amenorrhea, presented with pain and progressive swelling of the left leg for 8 days. There was no history of fever, trauma, or any joint pain or swelling. She was being treated twice daily with premixed insulin (Human Mixtard 30/70) and had poor compliance to treatment. Financial constraints and difficult family circumstances contributed to her poor control. An elderly mother with compromised vision was her sole caretaker. Physical examination revealed short stature (132 cm), weight of 30 kg, pallor, and clubbing. A diffuse swelling of the left calf (circumference of 27 cm compared with 22 cm on right side) with tenderness, raised local temperature, and limitation of movements was present. Peripheral pulses were normally palpable. A venous Doppler ruled out deep vein thrombosis (DVT) but a small left calf intramuscular hematoma was noted. Investigations revealed normal white cell counts and very high ESR (Table 1) and a positive celiac screen. Screening for diabetic complications revealed proteinuria (Table 1). Retinopathy could not be assessed due to cataract. There was no clinical evidence of neuropathy. She was managed conservatively with analgesics, limb elevation, and glycerin magnesium sulfate dressing. Thyroxine dose was adjusted, a gluten-free diet was advised, and basal-bolus treatment with glargine and lispro was started. Improvement in swelling was seen in the next 10 days.

Table 1 Results of investigations in case 1 and case 2

Tests (units)	Case 1 (1st admission)	Case 1 (2nd admission)	Case 2
Hb (g/dL)	7.3	9.2	10.3
TLC ($\times 10^3$/cmm)	8.04	11.43	7.9
ESR (mm at 1 h)	92	99	96
CRP (mg/dL) (N 0–10)	25	25.1	14.5
Creatinine (mg/dL)	0.6	0.4	0.9
HbA1c (%, mmol/mol)	12, 108	11.6, 103	10.2, 88
Urine protein/creatinine ratio (N 0–0.2)	3.01	–	2.73
Other reports	TTG IGA 117 IU/L		Procalcitonin < 0.05 ng/mL (N 0–0.05)
			CPK 117 U/L (55–170)
USG Doppler	Small hematoma in the calf muscles, no e/o DVT	No DVT	No DVT, atherosclerotic mural thickening

TLC total leucocyte count, *CRP* C-reactive protein, *TTG* tissue transglutaminase, *CPK* creatine phosphokinase

She presented 6 months later with diffuse swelling of the right thigh and leg extending up to the ankle, which developed over 4 weeks. DVT was ruled out. MRI of the right lower extremity revealed extensive edema and swelling within the adductor compartment muscles of the thigh and posterior compartment muscles (mainly soleus) within the leg, with intrinsic areas of hemorrhage and extensive subcutaneous soft tissue edema, suggestive of diabetic myonecrosis (Fig. 1a, b).

She was managed with rest, ibuprofen, limb elevation, adjustment of insulin, and thyroxine dose. The swelling gradually subsided over next 1 month.

In the follow-up, she continued to have poor glycemic control, poor compliance, and difficult family circumstances. After 6 months of the second admission, she presented with urosepsis and acute kidney injury superimposed on chronic kidney disease. Another 6 months later, she presented with emphysematous pyelonephritis and succumbed to its complications.

Case 2

A 47-year-old male, from Northeast India presented with pain and swelling of the left calf which progressed to the thigh and was associated with difficulty in walking. There was no history of fever or trauma. A venous Doppler ruled out presence of deep venous thrombosis. The patient was diagnosed with type 2 diabetes mellitus and hypertension 2 months prior to visit and had poor glycemic control (glycated Hb of 10.2%) on basal-bolus insulin therapy. Clinical examination (Fig. 2) revealed tender, woody swelling of the thigh and calf muscles with flexion deformity of the left knee and shiny and hyperpigmented skin of both legs. There was limitation of leg movements needing support for routine activities. MRI of the affected extremity showed T2-weighted (T2W) short tau inversion recovery (STIR) hyperintensity of the gastrocnemius and soleus muscles with thickening of the intermuscular fascia with a focal non-enhancing area within it. Aspiration from this area was negative for any infection on Gram stain, KOH mount, ZN stain, and culture. Investigations revealed normal white cell counts but high ESR and C-reactive protein (CRP) (Table 1). Evaluation of diabetes complications revealed presence of distal symmetric polyneuropathy with foot ulcer, severe non-proliferative retinopathy, and proteinuria. The patient was managed with ibuprofen for pain control, low-dose aspirin, intensification of insulin treatment, and local measures and reported significant reduction of swelling with improvement in walking after 3 months. However, some swelling was still persistent.

Discussion

DMI is a less commonly reported complication of poorly controlled diabetes [1]. The occurrence of painful swelling of muscles, particularly of lower limbs, should raise suspicion of DMI. Presence of long duration of poorly controlled diabetes further makes the diagnosis more likely. History of fever and significant trauma is usually absent. Raised ESR and CRP can be seen in 80–90% cases [3]. White cell counts and creatine phosphokinase (CPK) levels can be normal in 60–70% cases [3].

Common differential diagnosis of DMI is pyomyositis and DVT [5]. However, the conditions that should be considered include infective cellulitis, necrotizing fasciitis, hematoma, inflammatory polymyositis, and soft tissue neoplasms [6].

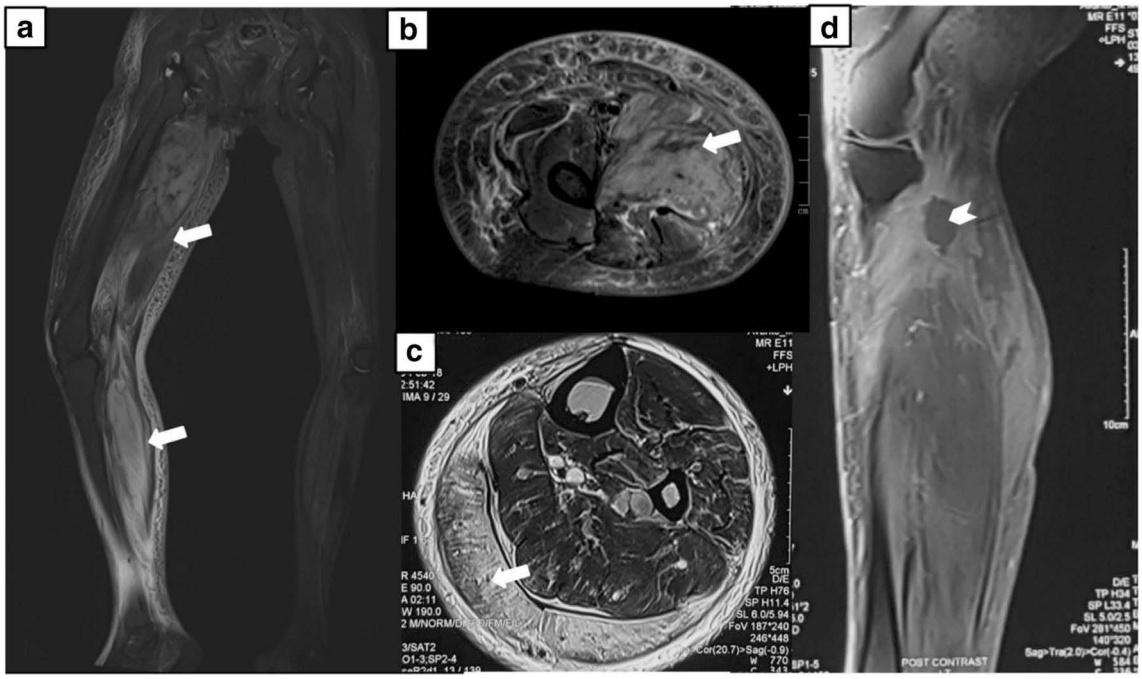

Fig. 1 MRI findings in diabetic muscle infarction. T2W STIR coronal (**a**) and axial (**b**) images (case 1) showing extensive edema and hyperintensity (white arrow) in the adductor compartment muscles of the thigh and posterior compartment muscles (mainly gastrocnemius-soleus muscles) within the leg, with intrinsic areas of hemorrhage and extensive subcutaneous soft tissue edema. T2W STIR images (case 2) showing hyperintensities (white arrow) in the gastrocnemius-soleus muscles (**c**) with post-contrast enhancement (**d**) except for a non-enhancing area (white chevron arrow) possibly of liquefactive necrosis. STIR, short tau inversion recovery

No clinical or bacteriologic evidence of infection was present in our cases, and DVT was ruled out by venous Doppler. Other differential diagnoses of MRI are the most important diagnostic modality with typical findings [7] including a hyperintense signal on T2-weighted images and an isointense to a hypointense signal on T1-weighted images from the affected muscle, with associated perifascial, perimuscular, and/or subcutaneous edema. Muscle biopsy is currently not recommended routinely and should be reserved for atypical cases which do not respond to appropriate treatment. Improvement in swelling with conservative treatment further supports the diagnosis in our cases. There are literature reports [8] linking DMI in T1DM with antiphospholipid antibodies (APLA) and with an associated hypercoagulable state; however, this was not documented in our case. Considering the long-term implications, antiphospholipid syndrome should be ruled out in DMI, particularly in patients with T1DM.

Both our cases highlight the fact that although DMI may be a self-limiting condition by itself, its presence portends poor outcomes with respect to diabetes complications and mortality. One of our patients succumbed within 2 years of presentation, and the other patient had significant diabetes complications in the form of severe neuropathy, foot ulcer, retinopathy, and nephropathy. Financial and social constraints, added to the background of Down syndrome (thus limiting self-management), led to poor diabetes control in the first case whereas the main factors in the second case were residence in a remote and resource-limited area and delay in the diagnosis of diabetes.

In a report of six cases [9], the estimated 1-year survival following DMI was 55% (three deaths in 10 months following DMI) which was comparable to myocardial infarction. In another series of six patients, five succumbed by 4 years of follow-up [10]. Presence of DMI has been associated with presence of diabetes complications in many reported case series [11, 12]. In a systematic review [1], presence of DMI was associated with microvascular complications including retinopathy (71%), nephropathy (57%), and/or neuropathy (55%). This suggests that occurrence of DMI potentially heralds poor outcomes as noted in both our cases.

In general, conservative management (rest, analgesia, and glycemic control) is the preferred treatment over surgery [13]. Some studies have shown prolonged recovery with surgery and physiotherapy in the acute phase [3]. However, physiotherapy after the acute phase may aid rehabilitation [14] and may be important to prevent recurrence [3]. In the present report, low-dose aspirin was used in addition to conservative treatment in case 2. Limited available evidence suggests short recovery time with low-dose aspirin. The basis of aspirin is the prothrombotic state seen in DM and the possible role of thrombotic microangiopathy in DMI [3].

The prognosis of individual episodes is usually good but recurrence is seen in almost half of the patients, as was likely

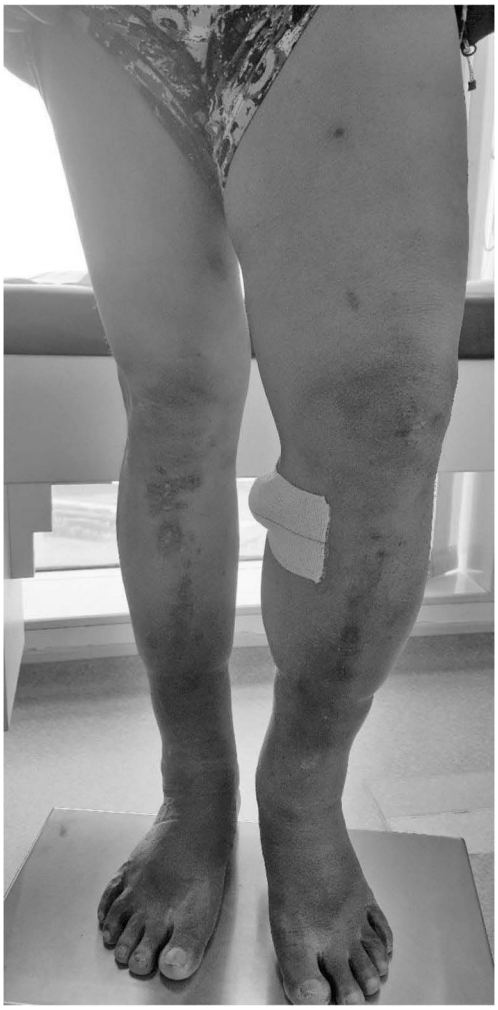

Fig. 2 Clinical photograph (case 2) showing swelling of the thigh and calf muscles in DMI

the case in our patients, who presented twice within a period of 6 months.

Conclusion

DMI is an important but underrecognized complication of diabetes. Timely diagnosis of diabetes and glycemic control can prevent this complication as it is most commonly seen in poorly controlled DM. The presence of DMI is often associated with the presence of microvascular complications of DM. In general, DMI responds well to conservative management; however, recurrences can be seen.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):768–773
https://doi.org/10.1007/s13410-019-00741-2

CASE REPORT

Management of new onset diabetes after transplantation (NODAT) with use of novel algorithm

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Received: 26 September 2018 / Accepted: 2 April 2019 / Published online: 1 May 2019

Abstract
Corticosteroids, calcineurin inhibitors, and mTOR inhibitors are often used as an immunosuppressant in patients after solid-organ transplant. These agents can lead to significant hyperglycemia which is called "New onset of diabetes after transplantation (NODAT)". Tight-glycemic control in patients with NODAT not only reduces the risk of post-transplant infection and graft failure but also reduces the long-term morbidity and mortality. Management of patients with NODAT is complicated because changes in doses of immunosuppressant can lead to change in glycemic status. Here, we present a series of cases involving successful management of hyperglycemia among outpatient department (OPD) patients with NODAT using a novel algorithm which negates the glycemic effects of corticosteroids and calcineurin inhibitors. We have also described the basic components of the algorithm which can be useful for physicians who deal with NODAT.

Keywords NODAT · PTDM · New onset of diabetes after transplantation · Post-transplant diabetes mellitus · Tacrolimus · Glucocorticoid-induced hyperglycemia

Introduction

New onset of diabetes after transplantation (NODAT) is defined by the international consensus guidelines published in 2003, elaborated in Table 1 [1]. Immunosuppressive agents like corticosteroids, calcineurin inhibitors (like tacrolimus and cyclosporine), and mTOR inhibitors (like sirolimus and everolimus) are thought to be the etiological agents for NODAT [2].

Few randomized controlled trials are published for the ideal management hyperglycemia in NODAT patients. We have previously demonstrated good glycemic control in hospitalized patients with NODAT with use of a novel algorithm that negates the effects of prednisolone and tacrolimus on glycemic control [3]. Here, we present a series of cases involving successful management of hyperglycemia among outpatient department (OPD) patients with NODAT. We have also proposed an algorithm for the management of NODAT among OPD patients.

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Case 1

A 41-year-old non-diabetic male underwent renal transplant for end-stage renal disease (ESRD) in July 2016. The patient was prescribed tacrolimus and prednisolone as immunosuppressants after the transplant. The patient developed hyperglycemia following the use of the immunosuppressants. The patient did not achieve good glycemic control; hence, the patient was referred to the endocrinology department for management of hyperglycemia.

At the time of initial assessment by the endocrinologist, the patient was on a stable dose of prednisolone 7.5 mg and tacrolimus 3 mg. The patient had a glycated hemoglobin (HbA1c) of 11.3% with no evidence of target organ damage secondary to hyperglycemia. The patient had normal renal function test. The patient was started on insulin glargine in the dose of 30 units at bedtime and insulin NPH in a dose of 8 units along with the prednisolone. Initially, the dose of insulin glargine was titrated based on the pre-breakfast capillary blood glucose (CBG) levels. The CBG was measured and reported by the patient using text-messaging to the endocrinologist on every alternate day, and the dose was subsequently titrated.

Once the pre-breakfast CBG was stabilized to a range of 100–140 mg/dl, a flash glucose monitoring device (FGM, Abbott Libre pro™) was applied. The patient

Table 1 Definition of new-onset diabetes after transplantation: modified from the 2003 international consensus guidelines for NODAT

To define post-transplant diabetes mellitus, both the following criteria must be fulfilled
1. Raised plasma glucose (Any one of the below)
a. Symptoms of diabetes plus casual PG concentrations of ≥200 mg/dL. Casual is defined as any time of day without regard to time since the last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss OR
b. FPG ≥126 mg/dL. Fasting is defined as no caloric intake for at least 8 h or
c. 2-h PG ≥200 mg/dL during an oral glucose tolerance test. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
2. The patient has undergone solid organ transplantation, other than pancreas or islet cell transplantation

PG plasma glucose, *FPG* fasting plasma glucose, *WHO* World Health Organization

was asked to maintain a diary to record the meal timing and exercise and continue self-monitoring of blood glucose (SMBG) with special reference to measuring 2-h post-lunch CBG readings. The dose of insulin NPH was subsequently titrated based on the post-lunch CBG values. At the end of the 14 days, CGMS period the patient had a mean blood glucose level of 148 mg/dl with an estimated HbA1c of 6.8% (Fig. 1). The standard deviation of blood glucose value calculated from the raw data acquired from the FGM device was 47.9 mg/dl.

The patient reported few episodes of hypoglycemia, especially in the morning after exercise. Management of diabetes mellitus in relation to exercise and appropriate use of carbohydrate during exercise was explained to the patient. The patient is subsequently maintaining good glycemic control on follow-up and is currently on insulin glargine 30 units and insulin NPH of 10 units. The episodes of hypoglycemia post-exercise have ceased.

Case 2

A 19-year-old girl underwent a liver transplant at a high volume center elsewhere, and subsequently, the care was transferred to us for post-operative follow-up. The patient developed NODAT. The patient was referred to the endocrinology department for the management of NODAT. At the time of the initial assessment, the patient was on 1.5 mg of tacrolimus and 2.5 mg prednisolone.

Considering the low doses of prednisolone, the patient was initially placed on basal insulin alone (without insulin NPH) and then subsequently basal-bolus insulin. The basal insulin dose was titrated to maintain pre-breakfast CBG in the range of 100–140 mg/dl. Once the dose of bolus insulin was adjusted based on carb-counting. A flash glucose monitoring was performed once a stable dose was reached to look for any period of hypoglycemia or hyperglycemia. The FGM data showed 14-day average blood glucose of 121 mg/dl with stable-estimated HbA1c of 5.8% without any significant hypoglycemia (Fig. 2).

Subsequently, the dose of Tacrolimus was reduced to 1 mg per day, and hence, the patient was placed again on basal insulin alone. On last follow-up, she was on insulin glargine of 9 units and has maintained good glycemic control.

Case 3

A 68-year-old obese female underwent liver transplant in 2016. She developed NODAT after 6 months. Following this, the patient was on premixed insulin twice a day in a total dose

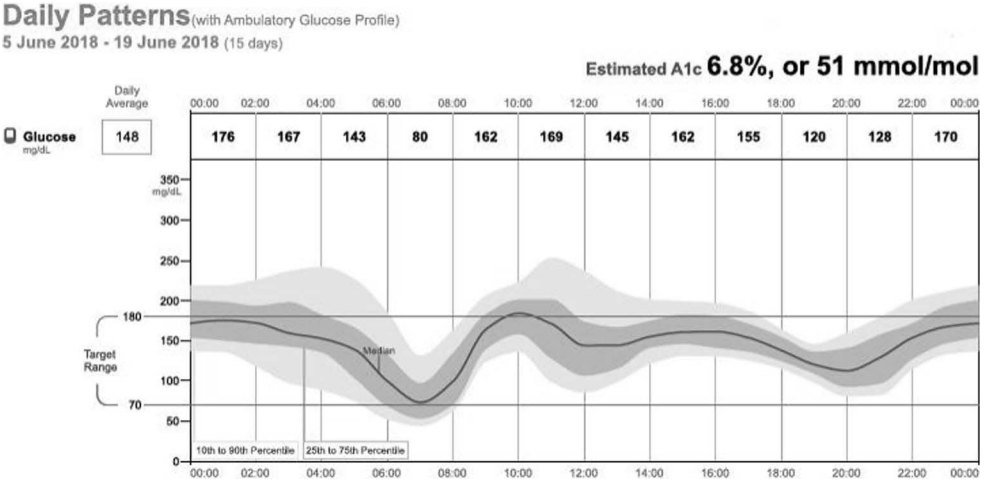

Fig. 1 Ambulatory glucose profile of patient 1

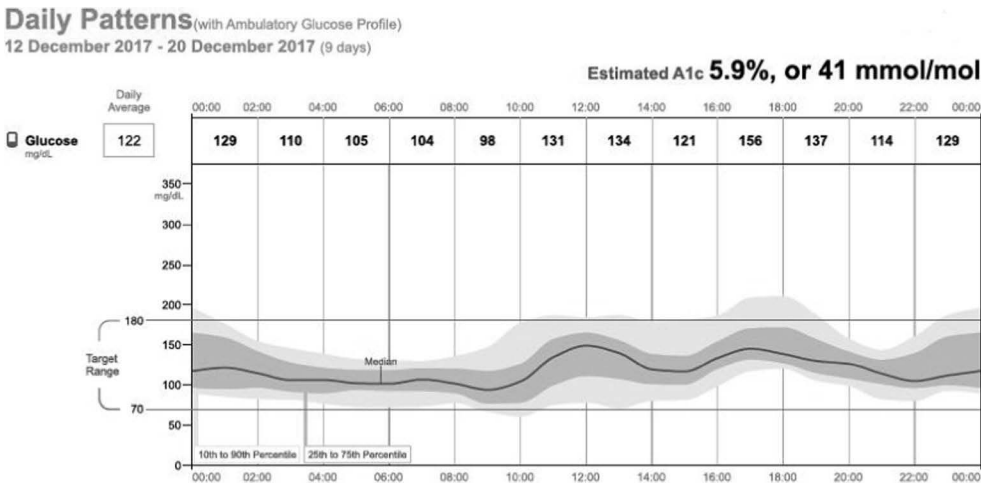

Fig. 2 Ambulatory glucose profile of patient 2

of 50 units. Though her HbA1c was 7.1%, she developed frequent episodes of hypoglycemia. The glycemic control was especially a problem when the dose of tacrolimus was changed. The patient presented to the hospital with gastroenteritis and an endocrinology consultation was sought to help with the management of diabetes mellitus. The patient was on a stable dose of tacrolimus (1 mg/day) and mycophenolate mofetil (1 g/day) at the time of the first consultation. She was not on glucocorticoids.

There was no evidence of any target organ damage due to diabetes mellitus. The patient was shifted to basal insulin with oral antidiabetics. The basal insulin dose was titrated to maintain fasting CBG in the range of 100–130 mg/dl. Subsequently, FGM was placed to look for any periods of hyperglycemia or hypoglycemia. The FGM data showed a 14 day average of 119 mg/dl with an estimated HbA1c of 5.8%. There were no reported episodes of hypoglycemia. The standard deviation of blood glucose value calculated from the raw data acquired from the FGM device was 25.8 mg/dl which suggests low glycemic variability in this patient (Fig. 3).

Discussion

NODAT is associated with increased mortality, cardiovascular complications, infection, and increased chances of graft failure. Hence, tight glycemic control in NODAT patients is essential for good clinical outcomes after a solid organ transplant [4]. The management of NODAT is complicated by the fact that patients are often on immunosuppressant which impacts the glycemic control and change in the dose of these immunosuppressants may mandate changes in doses of oral antidiabetics or insulin.

Tacrolimus and prednisolone are two commonly used immunosuppressive agents in NODAT patients. Tacrolimus is known to have a profound effect on insulin secretion. It is known to induce beta-cell apoptosis, reduce insulin exocytosis, and reduces insulin gene transcription all of which lead to reduced insulin secretion [5]. Transplant physicians and surgeons often change the tacrolimus depending on the clinical situation and serum tacrolimus levels. The effect of tacrolimus on insulin secretion is often reversible, and because of this,

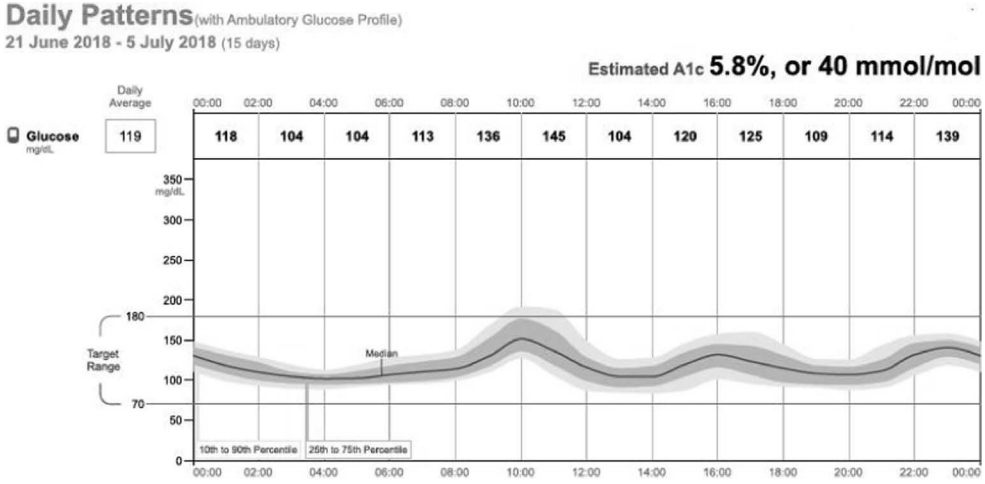

Fig. 3 Ambulatory glucose profile of patient 3

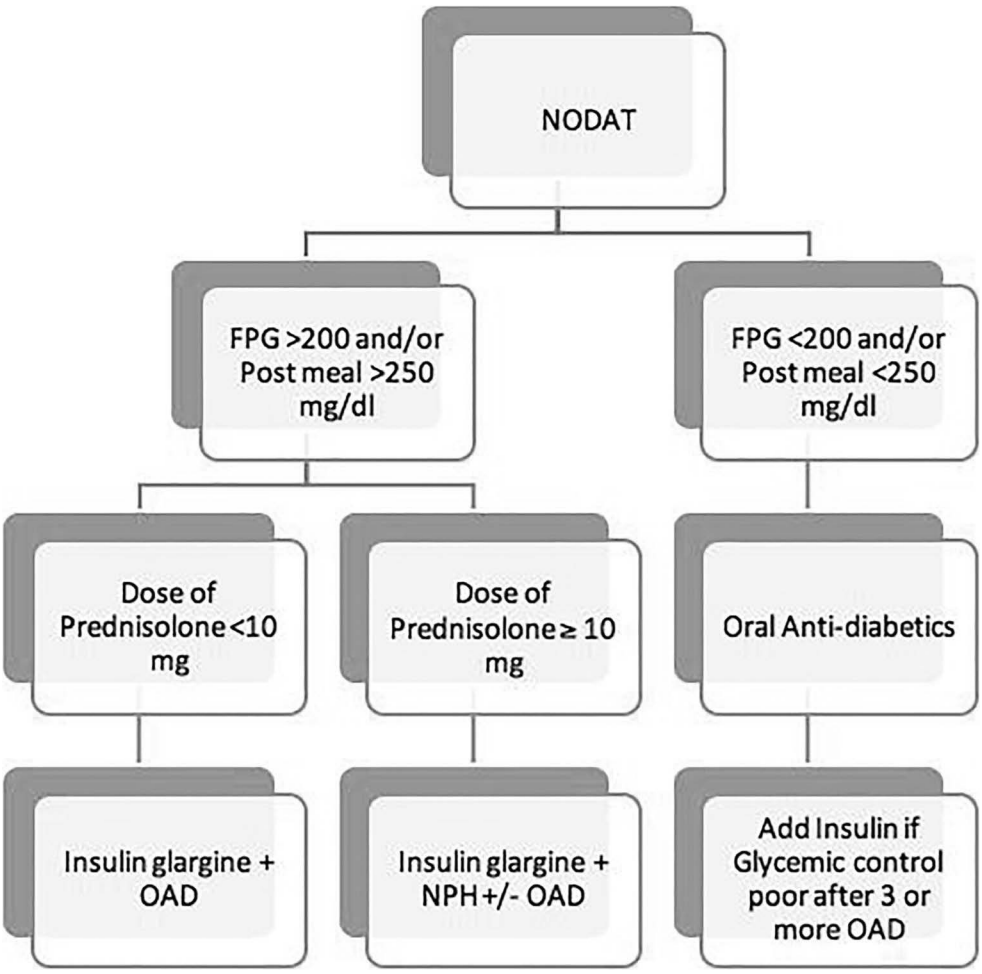

Fig. 4 Suggested algorithm for management of new-onset diabetes after transplantation on outpatient basis. NODAT, new onset of diabetes after transplantation; NPH, neutral protamine Hagedorn; OAD, oral anti-diabetic; FPG, fasting plasma glucose

Table 2 Starting dose and titration of oral anti-diabetics and insulin for patients on tacrolimus and prednisolone

Step 1: Strategic use of oral anti-diabetics	We typically use metformin and DPP-4 inhibitors in patients with NODAT if there are no contraindications to their use. We start with the sustained release or extended release metformin in maximum tolerated dose and then add DPP-4 inhibitors if required. In case the fasting plasma glucose level is > 200 mg/dl and/or post-meal plasma glucose levels are > 250 mg/dl, we usually add insulin. Insulin is also recommended if the glycemic control is not achieved with three or more OAD.
Step 2: Negate the effect of prednisolone	• A patient receiving prednisolone (≥ 10 mg) would be given starting dose of insulin NPH of 0.05 units/kg of insulin NPH (along with the prednisolone) for every 5 mg of prednisolone to a maximum of 0.4 units/kg of insulin NPH. • If the dose of prednisolone is fixed, then the dose of insulin NPH is titrated based on the 2 h post-lunch sugar • If the dose of prednisolone is changed then the dose of insulin NPH is changed proportionately
Step 3: Negate the effect of tacrolimus	Patients on tacrolimus, who have fasting plasma glucose > 200 mg/dl, would receive insulin glargine in a dose of 0.15 units/kg at bedtime.
Step 4: Fix the fasting (if pre-breakfast blood glucose not in target range)	• Once the dose of tacrolimus is fixed, the dose of Insulin glargine is titrated based on the pre-breakfast blood glucose with a target range of 100–140 mg/dl. If pre-breakfast blood glucose is > 140 mg/dl, the dose of glargine is increased by 20% the next day and if the pre-breakfast blood glucose is < 100 mg/dl, the dose of insulin glargine is reduced by 20% the next day. If the pre-breakfast blood glucose is already in the target range, then no adjustment of glargine dose is required. • Once the insulin glargine dose is fixed, If the dose of tacrolimus is changed subsequently, then the dose of insulin glargine is changed proportionately. The pre-breakfast CBG is again monitored closely for titration of the insulin glargine doses.

DPP-4 dipeptidyl peptidase 4, *NPH* neutral protamine Hagedorn

both escalation and reduction of tacrolimus dose can impact the glycemic control. Prednisolone, when used as a single dose in the morning time, produces hyperglycemia peak in the mid-afternoon. We have previously demonstrated that the use of insulin NPH along with prednisolone leads to effective glycemic control without increasing the risk of hypoglycemia [6, 7].

All patients who have undergone solid-organ transplant and are currently on immunosuppressive regimens which include corticosteroids, calcineurin inhibitors (like tacrolimus and cyclosporine), and/or mTOR inhibitors (like sirolimus and everolimus) should undergo regular screening for diagnosis of NODAT. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommended that these patients be screened for NODAT using a combination of fasting plasma glucose (FPG), HbA1c, and/or oral glucose tolerance test weekly for the first 4 weeks post-transplant and then every 3 months for the next 1 year. After this, the screening may be done annually. It is also recommended that regular screening for hyperglycemia may be done in those patients in whom the dose of the immunosuppressant is changed [8].

We have previously shown that the use of a standardized insulin algorithm leads to good glycemic control in hospitalized patients with NODAT [3]. While we exclusively use insulin in hospitalized patients, the strategic use of oral anti-diabetics with or without insulin may be useful in OPD patients with NODAT. Many patients with NODAT may have potential contraindications for use of various OAD. Hence, it is important to rule out any contraindication before starting OAD in patients with NODAT.

Here, we have described an algorithm for management of OPD patients with NODAT which may be useful for practicing clinicians (Fig. 4 and Table 2). The same algorithm was used for the management of NODAT in abovementioned patients. The algorithm is developed to negate the effects of tacrolimus and prednisolone and to make necessary adjustment when the dose of tacrolimus or prednisolone is changed.

The target for glycemic control is the same as that defined for other diabetics as per the American diabetes association guidelines (ADA) [9]. We typically keep the HbA1c < 7% in patients with NODAT as recommended by ADA guidelines. KDIGO guidelines recommend a HbA1c goal of 7–7.5% for those who have undergone a renal transplant to avoid potential hypoglycemia [8]. Regular assessment for microvascular and macrovascular complications of diabetes mellitus must be performed in patients with NODAT [10].

It is important to note that assessment with HbA1c may not be reliable in patients with NODAT, especially those who have undergone renal-transplant because of changes in RBC turnover and blood loss [10], Hence, in such scenarios, use of flash glucose monitoring and regular SMBG is useful.

Conclusion

Despite the use of immunosuppressants like tacrolimus and prednisolone which can alter the glycemic status in post-transplant patients, use of a standardized algorithm which involves the use of oral anti-diabetics with insulin can help in achieving good glycemic control in patients with NODAT.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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International Journal of Diabetes in Developing Countries (October–December 2019) 39(4):774–776
https://doi.org/10.1007/s13410-019-00747-w

LETTER TO THE EDITOR

Analysis of variation in pre-meal exercise effect on fasting interstitial glucose level

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Received: 28 January 2019 / Accepted: 29 April 2019 / Published online: 22 May 2019

To the Editor,

The FreeStyle Libre Flash glucose monitoring system (Abbott Diabetes Care, Alameda, CA, USA) has been used globally for improving plasma glucose control in patients with diabetes mellitus. This system facilitates the assessment of interstitial glucose levels anytime and anywhere without requiring blood samples [1, 2]. The system highlights changes in blood glucose levels that cannot be assessed during exercise by evaluating interstitial glucose levels. Pre-meal exercise has been reported to increase postprandial glucose levels, although postprandial exercise reduces postprandial glucose levels in patients with type 2 diabetes mellitus [3]. Moreover, this effect of pre-meal exercise on blood glucose levels was reported to be inconsistent compared with that of postprandial exercise [4]. This study aimed to analyze the mechanism underlying the effect of pre-meal exercise on fasting interstitial glucose levels. The corresponding author, who was diagnosed with an impaired fasting glucose level based on a 75-g oral glucose tolerance test, wore a FreeStyle Libre system while walking a distance of 10 km every morning at 4:30 am and for 90 min without rest for 24 different days. The walking speed was approximately 6.5 km/h on a set route. He experienced no hypoglycemic episodes during these walks. When the interstitial glucose levels exactly before pre-meal walking were < 120 mg/dL, no effect on the fasting interstitial glucose levels was observed. However, when the interstitial glucose levels exactly before pre-meal walking were > 120 mg/dL, a reduction in fasting interstitial glucose levels was evidenced during the pre-meal walk (Fig. 1). We determined the reduction grade by subtracting the lowest interstitial glucose level during the pre-meal walk, which was recorded every 15 min by the FreeStyle Libre sensors, from the interstitial glucose level measured exactly before initiating the walk (as shown in Fig. 1b). Further, we assessed the correlation between the interstitial glucose level exactly before pre-meal walking and the reduction in the level after the walk. The interstitial glucose levels measured exactly before pre-meal walking were positively correlated with the reduction grade (Fig. 1c, $R^2 = 0.7425$). Therefore, the improvement in the interstitial glucose level by pre-meal walking is expected to be greater when the interstitial glucose level exactly before pre-meal walking is higher, particularly > 120 mg/dL.

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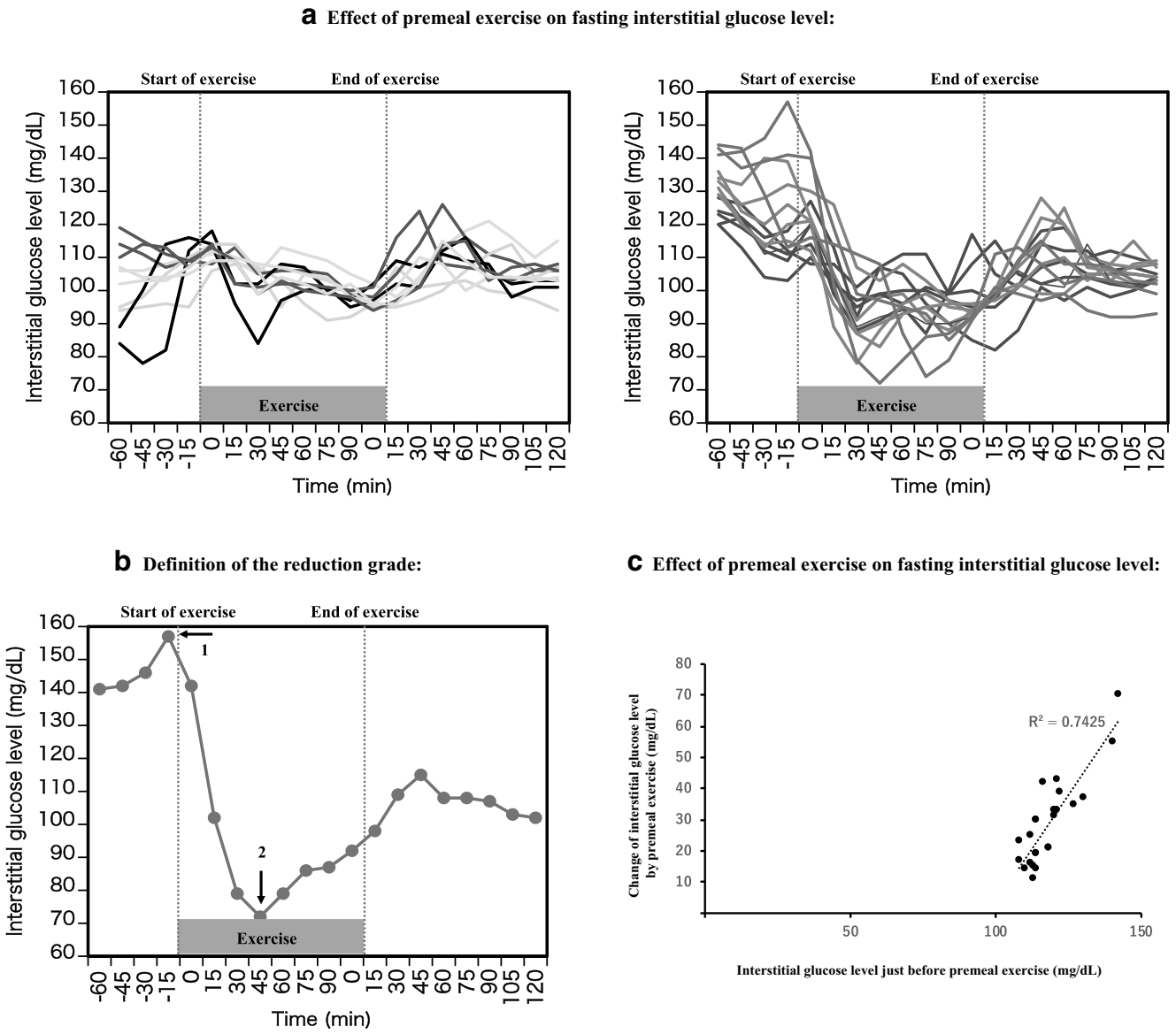

Fig. 1 **a** The graph shows recorded interstitial glucose levels before, during, and after exercise. In the left panel, the interstitial glucose levels exactly before initiating the pre-meal walk were < 120 mg/dL (10 repeated walks on different days). The black line shows interstitial glucose levels of < 90 mg/dL ($n = 2$) exactly before initiating the pre-meal walk. The yellow line shows interstitial glucose levels between 91 and 100 mg/dL ($n = 2$) exactly before initiating the pre-meal walk. The green lines show interstitial glucose levels between 101 and 100 mg/dL ($n = 3$) exactly before initiating the pre-meal walk. The purple lines show interstitial glucose levels between 101 and 120 mg/dL ($n = 3$) exactly before initiating the pre-meal walk. In the right panel, the interstitial glucose levels exactly before initiating the pre-meal walk were > 120 mg/dL (14 repeated walks on different days). The blue lines show interstitial glucose levels between 121 and 130 mg/dL ($n = 5$) exactly before initiating the pre-meal walk. The red lines show that interstitial glucose levels between 131 and 140 mg/dL ($n = 6$) exactly before initiating the pre-meal walk. The dark green lines show the interstitial glucose levels of > 141 mg/dL ($n = 3$) exactly before initiating the pre-meal walk. The vertical blue dotted lines represent initiation and completion of the walk. The light blue bar represents exercise period. **b** Determination of the reduction grade. We subtracted the lowest interstitial glucose level during the pre-meal walk (as indicated by number 2) from the interstitial glucose level measured exactly before initiating the walk (as indicated by number 1). **c** The graph shows the correlation between the reduction grade of the interstitial glucose levels after pre-meal walking (*y*-axis, mg/dL) and the interstitial glucose level measured exactly before pre-meal walking (*x*-axis, mg/dL); the correlation was positive ($R^2 = 0.7425$). The exercise was repeated 24 times on different days

Acknowledgements Text was edited by MARUZEN Editing service.

Authors' contributions All authors had active participation in the preparation of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and consent The Ethics Committee of Gunma University Hospital approved this study. The subject in our experiments signed an informed consent to publish this manuscript and any accompanying images. A copy of this consent is available for review by the Editor-in-Chief of this journal. All procedures followed in this study complied with the ethical standards of the responsible committee for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Declarations We obtained ethical approval and consent to publish. Written informed consent was obtained from the participants to publish this manuscript and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal. All procedures were in accordance with the ethical standards of the responsible committee for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Consent to publish All participants understand that the information will be published anonymously, but that full anonymity cannot be guaranteed. We understand that the text and any pictures or videos published in the article will be freely available on the internet and may be seen by the general public. Pictures, videos, and text may also appear on other websites or in print, may be translated into other languages, or used for commercial purposes.

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VISION STATEMENT

To be recognized as a global leader for clinical care, education, training, research, advocacy and capacity building in the field of diabetes.

MISSION STATEMENT

1. Promotion of excellence in diabetes care to make India the Diabetes Care Capital
2. Empowerment of persons living with diabetes
3. Support for diabetes research
4. Dissemination of information and knowledge in diabetes care
5. Advocacy for the cause of diabetology

RSSDI Research Grants

- For providing research grants, RSSDI invites proposals from Indian scientists, interested in conducting original research in the field of diabetes mellitus. Furthermore, limited grants are also available for the students of medical colleges for smaller projects.
- There is no deadline for submission of the proposals, which can be sent throughout the year. These proposals may fall into one of the following three categories:

1. Projects involving funding up to Rs 40,000 per project (preference will be given to young scientists <40 years).
2. Projects involving funding up to 10 lakhs.
3. We also invite proposals for more than 10 Lakhs as major projects but these have to be preferably multicentric.

- The detailed proposals should include the following:
  - ◊ Title, names of principal and co-investigators, summary, introduction/background, review of literature, aims, methodology, study design, and detailed plan of work and bibliography. Brief biodata of principal investigator and other co-investigators
  - ◊ Importance of work in the context of national priorities. Detailed budget sought along with full justification/ proposed utilization, of funding sought from RSSDI
  - ◊ Whether the project is being partly funded from any other source? If yes, please mention the source and the amount received.
  - ◊ Ethical committee clearance of the institution or other bonafide body.

Travel grants for young diabetes researchers to attend International Conferences

Criteria's for the travel grant are as follows:

- Applicant should apply 2 months in advance.
- Travel Grant is open only to the RSSDI members.
- Applicant should submit Oral paper / Poster acceptance document to RSSDI Secretariat.
- Applicant should submit Declaration that he/she has not receiving grant from any other agency / Organization – In case of receiving grant from any other Organization, RSSDI shall pay only the exceeding amount not covered by that agency.

ADVANCED CERTIFICATE COURSE IN DIABETOLOGY

(IN ASSOCIATION WITH JAIPUR NATIONAL UNIVERSITY)

Research Society for the Study of Diabetes in India (RSSDI) was founded by Prof. M.M.S. Ahuja in 1972. RSSDI is the largest body of professional doctors and researchers in Asia, working in the area of Diabetes & is the National Body recognized by IDF (International Diabetes Federation). One of the key areas of focus is to train doctors at all levels to better manage Diabetes and its complications. RSSDI recognizes this problem and runs a well-structured, full time, residential "Advanced Certificate Course in Diabetology". This two-year course is like any other post graduate course and has immensely helped doctors to practice better diabetes care. RSSDI has carefully looked into all aspects of this course & has accredited & recognized 18 centres across India at present and more centers are being inspected for accreditation. National Faculties and experts of RSSDI chosen from Academia visit these centers from time to time to ensure high standards. Now this Advanced Certificate Course has Dual Accreditation from RSSDI and Jaipur National University.

List of RSSDI Accredited Centres

S.N.	Institute Name	Institute Location
1.	Diacon Hospital	Bengaluru, Karnataka
2.	North Delhi Diabetes Centre	New Delhi, Delhi
3.	Prithvi Hospital	Tumkur, Karnataka
4.	Totall Diabetes Hormone Institute	Indore, Madhya Pradesh
5.	Dia Care A Complete Diabetes Care Centre	Ahemdabad, Gujarat
6.	Sonal Diabetes Hospital	Surat, Gujarat
7.	Jothydev's Diabetes and Research Center	Trivandrum, Kerala
8.	Advanced Endocrine & Diabetes Hospital	Hyderabad, Telangana
9.	G D Hospitals and Diabetes Institute	Kolkata, West Bengal
10.	Aditya Diagnostics & Hospital	Dibrugarh, Assam
11.	Sunil's Diabetes Care N' Research Centre Pvt Ltd.	Nagpur, Maharashtra
12.	Marwari Hospital and Research Centre	Guwahati, Assam
13.	Down Town Hospital	Guwahati, Assam
14.	St.Theresa's Hospital	Hyderabad, Telangana
15.	Aegle Clinic	Pune, Maharashtra
16.	Tulip Hospital	Sonipat, Haryana
17.	Lilavati Hospital & Research Centre	Bandra West, Mumbai
18.	Srajan Hospital	Udaipur, Rajasthan

COURSE DETAILS

Name of the Course: Advanced Certificate Course in Diabetology

Duration: 2 Years – Post MBBS & 1 Year - Post MD / DNB (Gen - Medicine)* (Full Time) Educational.

Qualification: A candidate must possess MBBS degree from ANY of the recognized university approved by Medical Council of India (*The duration of the course is 1 Year for those with MD/ DNB in Internal Medicine. Candidates having MD degree in other specialties will have to do the course over 2 Years).

Number of seats: 2 seats per year for every eligible teacher as per rules of Medical Council of India (MCI).

Selection of Candidates: Selection for the Certificate course is through a performance evaluation by Theory test for 90 marks (90 minutes duration) which is conducted at all accredited centres. The result is displayed WITHIN 3 days on the Web site of JNU and RSSDI. Post MD (Internal Medicine) will be given preference.

COURSE FEES:

- Rs 30000/- (for post MD/DNB (internal medicine), 1 year program)
- Rs. 50000/- (for post MBBS, MD in other branches, 2 years program)

Session: Two sessions are run annually, in January and in July. Prospectus details are available on the RSSDI website. All applications must be sent to Jaipur National University.

Announcements

Dear Member,

Please update your Membership details like Complete Postal Address, Email Id, Pan No. & Mobile no. after log in your membership area on our website www.rssdi.in under sub heading Membership corner, so that we can send you RSSDI Newsletter & Journals.

47th Annual Conference of RSSDI –RSSDI 2019

November 7-10, 2019 at JECC, Jaipur, Rajasthan

Themes:

MMS Ahuja Symposium : "Validation of RSSDI therapeutic Wheel in Indian clinical practice"

BB Tripathy Nutritional Symposium : "Diet and Inflammation"

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International Journal of Diabetes in Developing Countries

Volume 39 | Issue 4 | October–December 2019

Springer