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EDITORIAL

Post-liver transplantation diabetes mellitus — a clinical challenge for diabetologists?

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Liver transplantation has become an effective therapy for patients with acute or chronic end-stage liver disease. With improvement in operative techniques and immunosuppressive regimens, long-term survival after liver transplantation has markedly increased. However, with increased longevity, the attention has shifted towards long-term complications, which are primarily related to the immunosuppressive treatment. One such complication is new-onset diabetes after transplantation (NODAT), often referred to as posttransplantation diabetes mellitus (PTDM).

New-onset diabetes after transplantation refers to individuals who develop new-onset diabetes following solid organ, bone marrow, and hematopoietic stem cell transplant. *It characteristically excludes patients with pretransplant diabetes that remained undiagnosed and posttransplant hyperglycemia that resolves by the time of discharge* [1]. On the other hand, PTDM theoretically describes the presence of diabetes in the posttransplant setting irrespective of the time of onset of diabetes [1, 2]. Nevertheless, in routine clinical practice, the two terms are often used interchangeably.

Hyperglycemia is not uncommon during the early posttransplant period; nearly 90% of liver transplant recipients exhibit hyperglycemia in the immediate posttransplant period [3]. In the majority of the cases, such stress- or steroid-induced hyperglycemia resolves by the time of discharge. Whereas posttransplantation hyperglycemia is an important risk factor for subsequent PTDM, *a formal diagnosis of PTDM should ideally be made once the patient is stable on maintenance immunosuppression and in the absence of acute infection* [4].

The diagnosis of PTDM, which in the context of liver transplantation is referred to as post-liver transplantation diabetes mellitus (PLTDM), has long been a matter of debate [5]. Earlier, the most commonly used clinical definition was the requirement of insulin for a minimum period (usually 30 days) posttransplantation. This definition had resulted in underestimating the prevalence of diabetes after transplantation because it excludes patients treated with oral antidiabetic drugs and those with untreated hyperglycemia, impaired fasting glucose (IFG), or impaired glucose tolerance (IGT). Furthermore, it does not distinguish between patients with new-onset disease from those with preexisting disease [6].

The *International Consensus Guidelines on new-onset diabetes after transplantation 2003* recommended that the diagnosis should be based on the American Diabetes Association (ADA) criteria for type 2 diabetes mellitus [6], which are as follows:

- Fasting plasma glucose (FPG) ≥ 7.0 mmol/l (126 mg/dl) with no calorie intake for at least 8 h, or
- Two-hour plasma glucose during an OGTT (2-h PG post-OGTT) ≥ 11.1 mmol/l (200 mg/dl), or
- Casual plasma glucose ≥ 11.1 mmol/l (200 mg/dl) with classic symptoms of diabetes, all being documented on 2 different occasions.

Thus, the diagnostic criteria for PLTDM are the same as those for diabetes in the general population [5]. Since postprandial hyperglycemia is much more prevalent than fasting hyperglycemia among liver transplant patients [7], the ideal screening test for PLTDM is the oral glucose tolerance test (OGTT) [8]. However, performing an OGTT under supervision might not always be feasible, thereby clinicians might have to rely solely on FPG.

Even in the posttransplant setting, a fasting plasma glucose level of < 5.5 mmol/l (100 mg/dl) is considered to be normal, and 5.5–6.9 mmol/l (100–125 mg/dl) is considered to be IFG. A 2-h post-OGTT plasma glucose level of < 7.7 mmol/l (140 mg/dl) is considered to be normal, and 7.7–11.1 mmol/l (140–199 mg/dl) is considered to be IGT. The importance of diagnosing the pre-diabetic states (IFG and IGT) in the post-liver

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transplant context lies in their relevance as predictors of future risk of PLTDM [5]. Apart from the aforementioned diagnostic criteria, post-liver transplant patients whose blood glucose levels are normal but are using insulin or oral antidiabetic drugs are also diagnosed as having PLTDM [9].

Glycated hemoglobin (HbA_{1c}) has a limited role in the diagnosis of PTDM (or PLTDM). Due to blood loss associated with the transplant procedure, preexisting anemia (and subsequent shortened red blood cell survival), and especially lack of robust evidence regarding its use in the early posttransplant period, HbA_{1c} is not recommended as a first-line diagnostic test for PLTDM, especially in the first 3 months posttransplant [10]. Beyond 3 months, the new hemoglobin would be synthesized and glycated for an appropriate period of time; in such setting, $HbA_{1c} \geq 6.5\%$ can be utilized to diagnose PTDM. On the contrary, many studies do not recommend the use of HbA_{1c} alone as a screening tool for diagnosing PTDM in the first year after transplant [11].

Although the diagnostic criteria for defining PLTDM have been standardized, the timing of the tests remains controversial and unresolved. Most believe that the first month after liver transplantation still falls within the period of surgical stress; hence, plasma glucose levels *beyond 1 month after liver transplantation* should be used as the determining criterion [9, 12]. On the contrary, others opine that if rejection or surgical complications do not occur in the postoperative period, stress-related hyperglycemia would be resolved in most patients until the end of the first month [13].

In this issue of the *International Journal of Diabetes in Developing Countries*, Topaloğlu et al. report on the prevalence of NODAT after liver transplantation in patients with acute liver failure. The diagnosis of NODAT was based solely on fasting blood glucose (FBG) measured at frequent time intervals. Accordingly, the prevalence of NODAT was 26.98%, 14.54%, and 8.3% based on FBG measured at 1 month, 3 months, and 12 months post-liver transplant, respectively [14]. Although a significant fraction of patients who were alive at 1st month had subsequently succumbed at the 3rd month and 12th month, it remains unclear whether NODAT diagnosed in the 1st month could have been one of the predisposing factors contributing to the later demise of the patients. Similarly, it remains unanswered whether the marked decline in the prevalence of NODAT at the 3rd and 12th month could have resulted from the selective demise of patients diagnosed with NODAT in the 1st month, or a spontaneous reversal of stress-related hyperglycemia with time.

Thus, it does not seem to be prudent to label a liver transplant recipient as having NODAT on the basis of blood glucose values measured as early as 1 month posttransplant. The diagnosis of NODAT (or PLTDM) should ideally be based on 2-h PG post-OGTT (or FPG) or need for insulin/antidiabetic drugs beyond 1 month after liver transplant. Nevertheless, putting aside semantics, appropriate management of any degree of hyperglycemia in the posttransplant period is imperative as those with early perioperative hyperglycemia and PTDM have higher rates of graft rejection, infection, and rehospitalization [4, 15, 16].

Data derived from randomized controlled trials on the short- and long-term use of anti-hyperglycemic agents in the setting of PTDM is limited. Insulin remains the agent of choice for the management of hyperglycemia, PTDM, preexisting diabetes and diabetes in the hospital setting. After discharge, PTDM patients with poor glucose control should continue insulin with frequent home self-monitoring of blood glucose to help titrate insulin doses accordingly [4].

Hitherto, there is insubstantial data on the use of noninsulin agents in the context of PTDM. The choice of an appropriate agent is usually made after taking into consideration the side effect profile of the drug and possible interactions with the patient's ongoing immunosuppression regimen. Frequent drug dose adjustments may be needed because of a decline in the glomerular filtration rate, a common complication in transplant patients. A short-term pilot study reported the use of metformin in renal transplant recipients, but the same has not been replicated in other types of organ transplant [17]. Thiazolidinediones have been successfully used in patients with liver and renal transplants; however, frequent side effects that include fluid retention, heart failure, and osteopenia limit its use in the posttransplant setting [18, 19]. Dipeptidyl peptidase-4 inhibitors (DPP4i) have demonstrated safety in some recent clinical trials [20, 21]. Besides, DPP4i do not interact with most immunosuppressant drugs and hence can be safely used in most PTDM patients. Nevertheless, in view of limited clinical data, it would not be prudent to advise one antidiabetic drug (noninsulin) over the other. Well-designed randomized controlled trials examining the efficacy and safety of these and other antidiabetic agents in patients with PTDM are needed.

Declarations

Ethical approval Not required

Informed consent Not applicable

Conflict of interest The authors declare no competing interests.

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REVIEW ARTICLE

Genetic association of vascular endothelial growth factor (*VEGF*) gene variants with the risk for diabetic retinopathy: a meta-analysis

Sanober Kafeel[1] · Khan Muhammad Nangrejo[2] · Roberto Gonzalez-Salinas[3]

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Abstract

Introduction The vascular endothelial growth factor (VEGF) significantly contributes to the manifestation of neovascularization in the retina which progressively develops retinopathy in diabetic patients. The aim of this study was to assess the role of *VEGF* polymorphisms in the pathogenesis of diabetic retinopathy (DR).

Methods This meta-analysis comprised a total of six case-control and cohort studies published in the last 6 years. The selection of studies was done by sorting in reliable database searches: NCBI, Ensemble, GenBank, Embase, UCSC Genome Browser. After the extraction of data, the *Q* test of heterogeneity was performed. The Stata Software version 13.1 was used as the statistical package. Fixed and random effect models were applied for forest plot depiction while funnel plot and Egger's test were carried out for the evaluation of publication bias.

Results A significant relationship was found between the risk allele of *VEGF* polymorphism rs3025039 with predisposition of DR (OR = 1.45, 95%CI = 1.04–1.86) in the absence of heterogeneity by three studies. Furthermore, significant association was also observed for four polymorphisms of *VEGF* (rs833061, s13207351, rs1570360, and rs2010963) with higher susceptibility of DR among the population of Pakistan (OR = 1.46, 95%CI = 1.21–1.71).

Conclusion The meta-analysis suggested the substantial role of *VEGF* polymorphism rs3025039 as a possible biomarker for the assessment of DR risk. However, genome-wide association study (GWAS) is required in future to elucidate the multi-SNP effect of these polymorphisms in *VEGF* gene.

Keywords Diabetic retinopathy · Meta-analysis · *VEGF* polymorphism · Heterogeneity

Introduction

Diabetic retinopathy (DR) is a condition that develops in response of disturbances in the regulation of glycemia, which in turn causes an essential loss of vision among the diabetic population. According to the Atlas of the International Diabetes Federation (IDF), the current prevalence of DR in diabetes mellitus (DM) patients is 27% [1]. However, approximately 150 million cases are reported worldwide, which is estimated to increase up to a double-figure by end of the year 2025 [2]. The formation of DR is predominantly characterized by increased vascular permeability, angiogenesis, and ischemia followed by neovascularization of the retina, iris, optic disc, and angle which could eventually lead to forming neovascular glaucoma (NVG), defined as severe glaucoma associated with the presence of new iris or angle vascularization [3–5].

The VEGF considerably contributes in the exertion of stimulus for neovascularization, increased vascular permeability in

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the retina, and the deterioration of the blood-retinal barrier (BRB) [6]. Furthermore, the antagonists of the VEGF receptor are known to be implicated in causing a decline in vascular permeability and neovascularization of retina, hence developing resistance in the progression of DR [7]. VEGF is primarily released from the pericytes, epithelial cells of retina, Muller cells, astrocytes, glial and endothelial cells. The ischemic cues, generated on the retina, lead to massive production of VEGF, a multifunctional cytokine that promotes angiogenesis and a potent mediator of microvascular permeability [8]. It performs the role of signaling proteins that modulate either the development of new vessels from older branches or de novo vessel growth from the circulatory system of embryonic origin [9]. This cytokine is estimated to be induced by hypoxia, which is a landmark for DR patients [10]. During hypoxia, *VEGF* gene expression increases via several different mechanisms. These mechanisms include increased transcription, mRNA stability, and protein translation using an internal ribosomal entry site, as well as increased expression of oxygen regulated protein 150, a chaperone required for intracellular transport of proteins from the endoplasmic reticulum to the Golgi apparatus prior to secretion [11]. Moreover, the overproduction infers detrimental impacts on BRB and causes the endocytosis of tight junction proteins and enhancement in permeability [12, 13].

The gene encoded for *VEGF* is situated on chromosome no. 6 at position p21.3 contains eight exons and seven introns. It is suggested to be highly polymorphic, as many genetic variants were reported in the promoter region, 5′ untranslated region (UTR), and 3′ UTR region which depicts a certain relationship with the expression of VEGF protein [14]. Since the outcomes of prior genetic studies indicated heterogeneity due to the assessment of a wide range of ethnicities and geographical populations, therefore, the available data is discrete and displays diversification [15–17]. Hence, this meta-analysis is conducted with an aim to quantitatively evaluate the outcomes of the recent 6 years of literature regarding the associations of *VEGF* genetic variants with the pathogenicity of DR. The hypothesis of this meta-analysis is the *VEGF* genetic variants play a robust role in developing the implications on the induction and progression of DR.

Methods

Retrieval of eligible studies

An extensive literature survey in search bars of NCBI, PubMed, Ensemble, GenBank, Embase, UCSC Genome Browser, GWAS Catalog, and Google Scholar was conducted to identify those studies which explored the associations of *VEGF* genetic variants in the patients of DR. All the studies were restricted to English language. The following keywords were typed: VEGF and Diabetic Retinopathy, *VEGF* genetic variants or polymorphisms or SNPs, in integration with NPDR or PDR to carry out searching and sorting relevant publications among discrepancy of ethnicities. The deadline for data retrieval was limited to April 1, 2020. The protocol for this meta-analysis conforms to the preferred reporting items for meta-analysis followed by PRISMA guidelines [18].

Assessment criteria

The studies categorized as case reports, editorial letters, short communications, and reviews were exempted. The selection of potentially eligible studies was made based on the following criteria: (1) contains a related association of VEGF genetic variant with DR group; (2) sufficient statistical analysis for the estimation of odds ratio; (3) reports of proper genotypic and allelic distribution of polymorphisms in comparison to control group; (4) the population of control shows consistency with Hardy-Weinberg equilibrium (HWE); (5) case-control study design; (6) standard diagnostic measures were taken for the confirmation of DR patients according to the guidelines of the American Diabetes Association; (6) adequate sample size with a confidence interval (CI) of 95%; (7) recent publications of the last 6 years which were published from 2014 were included in this meta-analysis.

Data extraction and quality assurance

Independent extraction of data was undertaken by two researchers: Kafeel and Nangrejo. The extraction of essential data from each article was done using the following variables: year of publication, name of the first author, country of origin, sample size, genotype frequency, odds ratio, level of significance, and method of genotyping.

Statistical analysis

The meta-analysis was carried out using an expert statistical software STATA version 13.0 *RRID*:SCR_012763 (64-bit; Stata Corporation, College Station, TX, USA) after importing the data from a Microsoft Excel sheet. A p value of < 0.05 depicted a statistical significance. The strength of genetic association of *VEGF* in the pathogenicity of DR was assessed by calculating the odds ratio (ORs) and 95% confidence interval. The heterogeneity was estimated by inconsistency index I^2 which was based on Q statistics. In the absence of heterogeneity ($I^2 < 50\%$), the fixed effect of the pooling model (peto) was applied, whereas the presence of heterogeneity ($I^2 < 50\%$) employed the random effect model (D-L) instead. The risk for publication bias was evaluated by funnel plot and Egger's statistics.

Results

Characteristics of included studies

Approximately $n = 200$ relevant studies were searched initially. Out of them, $n = 89$ studies contained duplicated data. After the screening, $n = 47$ studies were excluded as they did not investigate the genetic associations of *VEGF* and rather based on its physiological aspects in the developmental mechanism of DR. The eligibility of $n = 64$ studies was tested by reading their full text. The $n = 58$ studies were excluded in the process of final selection due to the subsequent reasons: the research design was not based on case-control pattern, a small sample size of DR patients, older studies dated before 2014, statistical gaps due to the absence of essential statistics, involve type 1 diabetes, and review articles. Finally, $n = 06$ studies were qualified for the qualitative and quantitative assessment in this meta-analysis. The PRISMA flowchart explaining the selection criteria is presented in Fig. 1.

The graphical representation of the sample size recruited in six publications included in this meta-analysis is described in Fig. 2. In four studies, the number of controls is greater than DR cases. However, $n = 128$ is the minimum DR sample size considered in a Egypt study, and $n = 573$ is the maximum number of DR cases analyzed in a Pakistan study.

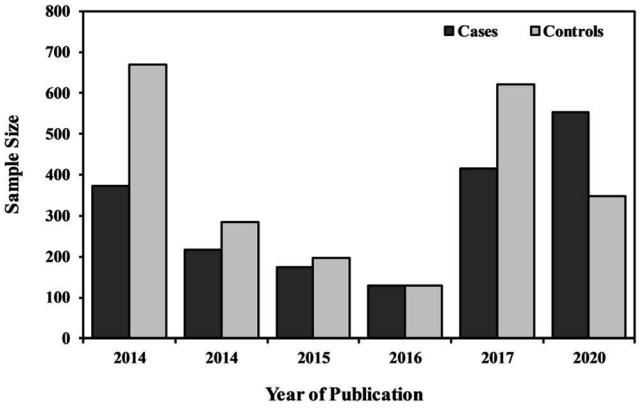

Fig. 2 Graphical representation of DR and control sample size in six publications

The basic data regarding the characteristics of the selected DR and *VEGF* studies is mentioned in Table 1. A total of $n = 06$ studies were analyzed in this meta-analysis. Two of which were published in China, using genotyping technology of Sequenom MassARRAY in 2014. While the Indian and Slovenian studies utilized Taqman SNP Genotyping Assay

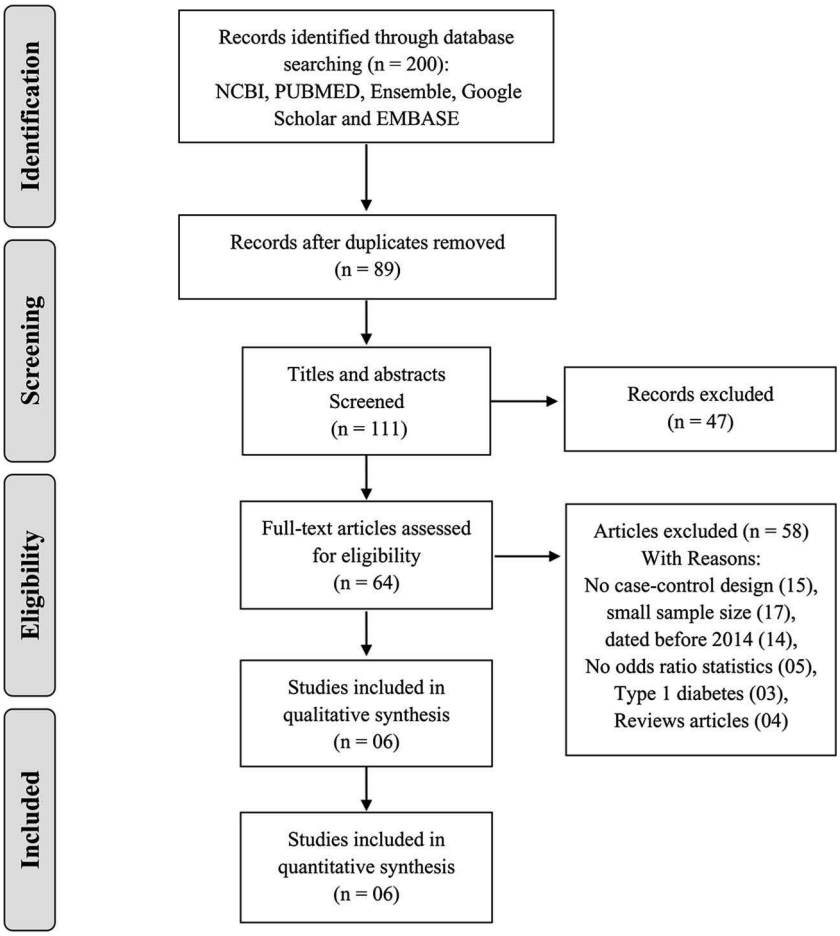

Fig. 1 Flowchart represents the assessment criteria of inclusion and exclusion

Table 1 Basic data of selected studies with *VEGF* genotyping in DR subjects

SN	Authors	Year	Country	Sample size	Genotyping method
1.	Fan [19]	2014	China	$N = 1040$	Sequenom MassARRAY Technology
2.	Yang [20]	2014	China	$N = 500$	Sequenom MassARRAY Technology
3.	Choudhuri [21]	2015	India	$N = 372$	Taqman SNP Genotyping Assay
4.	Fattah [22]	2016	Egypt	$N = 128$	Reverse Transcriptase PCR
5.	Terzic [23]	2017	Slovenia	$N = 1037$	Taqman SNP Genotyping Assay
6.	Khan [24]	2020	Pakistan	$N = 1126$	Sanger Sequencing

published in 2015 and 2017 respectively, an Egyptian study employed Reverse Transcriptase PCR method in 2016 and Pakistani study used Sanger Sequencing method in 2020 for the genotyping of *VEGF* polymorphisms.

The genotypic data of studied polymorphisms of *VEGF* gene analyzed in each of the six studies are summarized in Table 2 (Supplementary material). The frequency of genotypic distributions and the significance of risk allele were demonstrated for each of the polymorphism. It was observed that *VEGF* rs2010963-C and rs3025039-T were considered the most studied polymorphisms among the studies published in the last 6 years.

Pooled effect for the *VEGF* polymorphism and DR risk among various populations

The allelic model of *VEGF* polymorphisms was analyzed in association with DR by their pooled effect in the forest plot mentioned in Fig. 3. Collectively, the two studies of China reported the risk for associations with eight *VEGF* polymorphisms published by Fan et al. and Yang et al. in the year of 2014 [19, 20]. The forest plot suggested that the fixed effect model estimated the overall odds ratio (OR = 1.01) with 95% confidence interval (CI = 0.82–1.21) reflected no significant heterogeneity ($I^2 = 5.4\%$, $p = 0.38$). A 39.3% weightage was estimated from these two studies. Consequently, an Indian study conducted by Choudhuri et al. [21] demonstrated a 17% weightage explaining the risk of four polymorphisms, while a Slovenian study conducted by Terzic et al., [23] targeting two polymorphisms, persisted with a 16.27% weightage. Both studies revealed a significant level of heterogeneity, thus analyzed by the random effect model. In an Indian study, *VEGF* polymorphisms were shown to confer a significant risk role for DR (OR = 1.10, 95%CI = 0.80–1.39). In contrast, the Slovenian study revealed a significant protective role of two polymorphisms against the formation of DR risk (OR = 0.80, 95%CI = 0.54–1.15). However, no evidence of significant heterogeneity was observed in Pakistani and Egyptian population-based studies conducted by Khan et al. [24] and Fattah et al., respectively ($I^2 = 0.0\%$, $p > 0.05$). The comprehensive odds ratio of four *VEGF* polymorphisms with 24.11% weightage suggested their significant relationship with higher susceptibility of DR observed in the Pakistani population (OR = 1.46, 95%CI = 1.21–1.71). Besides that, the two polymorphisms of Egyptian study have a 2.62% weightage and showed an implication in preventing the development of DR (OR = 0.49, 95%CI = 0.27–1.25). Furthermore, the overall odds ratio suggested a significant role of these polymorphisms (rs3025039-T $p < 0.05$, rs2146323-A $p < 0.01$, rs2010963-C $p < 0.001$, rs1570360-A $p < 0.05$, rs2071559-G $p < 0.05$, rs833061-T $p < 0.05$, s13207351-G $p < 0.001$) in the pathogenicity of DR with some level of heterogeneity between the groups of different populations (OR = 1.09, 95%CI = 0.97–1.22).

Pooled effect for the *VEGF* polymorphism (rs2010963-C) and DR risk

The forest plot for *VEGF* rs2010963 polymorphism was assessed to estimate its pooled effect with DR represented in Fig. 4. Gene promoter region polymorphism rs2010963 at the + 405 position, mediating the displacement of base G to C, is considered of great importance and has been investigated among various population-based studies. In our set of consideration, we identified four independent studies exploring the association between this *VEGF* polymorphism and DR. Due to a relative degree of heterogeneity, the random effect model was employed to measure the odds ratio and revealed no association between this polymorphism and its impact on the development of altered *VEGF* expression with DR (OR = 1.08, 95%CI = 086–1.31).

Pooled effect for the *VEGF* polymorphism (rs3025039-T) and DR risk

The association of the *VEGF* rs3025039 polymorphism with DR using the pooled effect evaluation is characterized in Fig. 5. This polymorphism at + 936 position of *VEGF* promoter region has been repeatedly assessed among three different populations. The significant level of heterogeneity was absent between the studies ($p = 0.227$). The statistical analysis using the fixed effect model showed that the risk allele (T) of this polymorphism *rs3025039* demonstrated to develop a

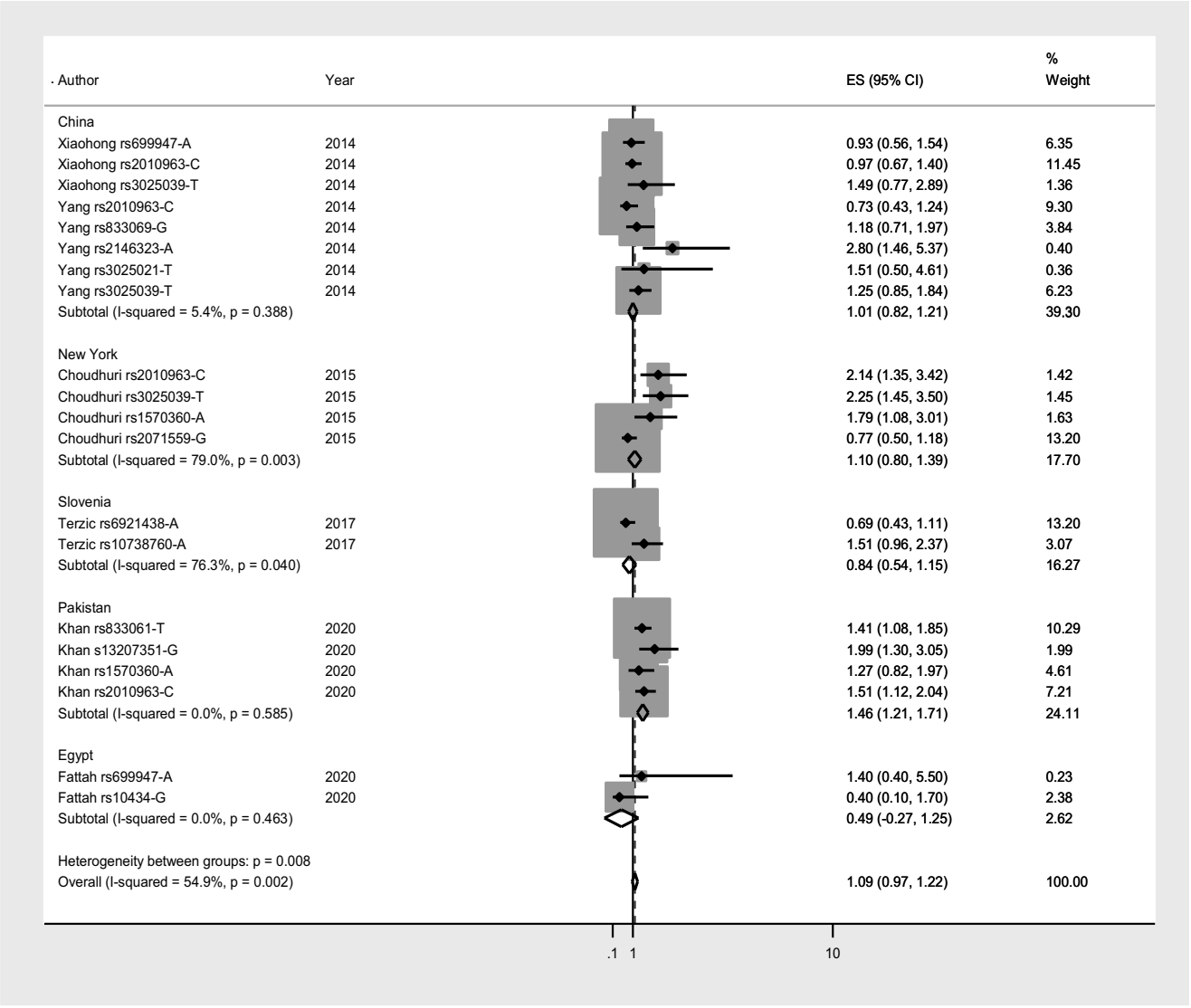

Fig. 3 Forest plot explaining the effect size of various *VEGF* polymorphisms with respect to DR in six studies on five populations

significant role in the progression of pathogenicity for DR (OR = 1.45, 95%CI = 1.04–1.86).

Publication bias

The publication bias was evaluated by qualitative and quantitative examination. The funnel plot was made for the qualitative expression of the six included studies in this meta-analysis, measuring the degree of bias represented in Fig. 6. The plot illustrates the symmetrical distribution which shows that the observed effect sizes have analogous precision and exhibit no substantial amount of publication bias among the studies [25]. Furthermore, Egger's test was also carried out for the quantitative estimation of significant bias. However, the outcomes did not demonstrate any evidence of significant publication bias among the *VEGF* genetic polymorphisms in a considerable set of population studies ($p = 0.32$). This determines the stability of the results without any influential impact of publication bias in this meta-analysis.

Discussion

The pathogenesis of DR is demonstrated to be multifactorial in nature, and display interactions between both environmental and genetic risk factors [26]. Considerable evidence has shown that the tendency of DR can be affected not only by the duration of diabetes and the blood glucose but also by genetic predisposition [27]. All of these phenomena suggest that genetic factors display a significant impact on the development and progression of DR.

This meta-analysis comprised of twelve *VEGF* polymorphisms reported in the DR population investigated in six

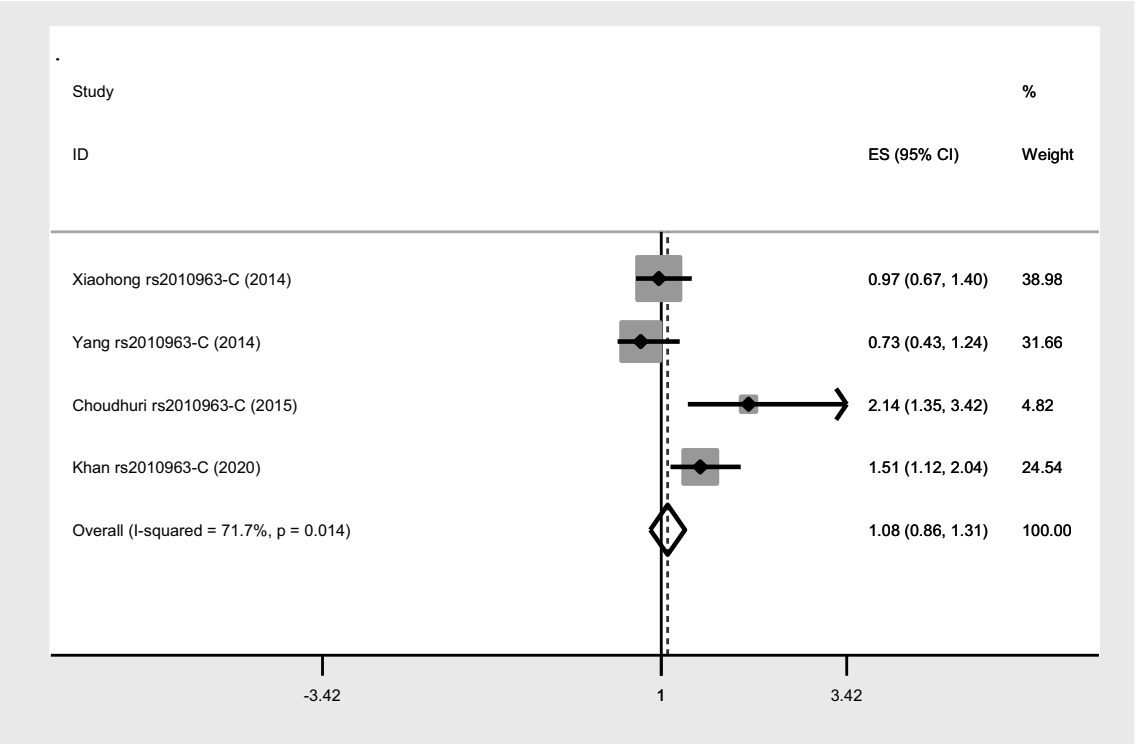

Fig. 4 Forest plot depicting the association between the *VEGF* rs2010963 polymorphism with diabetic retinopathy among four studies

studies. Our analysis confirmed the significant association of C/T *VEGF* polymorphism at the + 936 position (rs3025039) with an increased DR risk among the Asian population as revealed by Fan et al., Yang et al., and Choudhuri et al. [19–21]. These findings are in concordance with previously reported data by Han et al. [28]. Moreover, another study conducted by Kim et al. demonstrated similar outcomes in the Korean population [29]. Conversely, a Japanese study

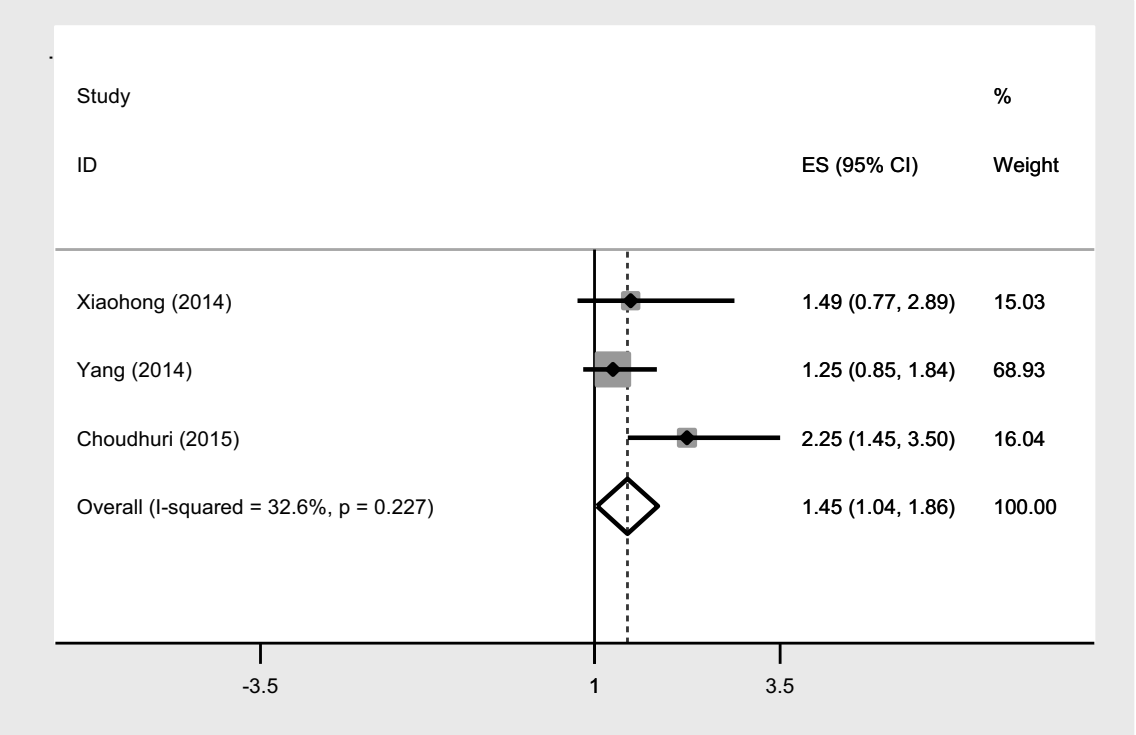

Fig. 5 Forest plot depicting the association between the *VEGF* polymorphism rs3025039 with diabetic retinopathy among three studies

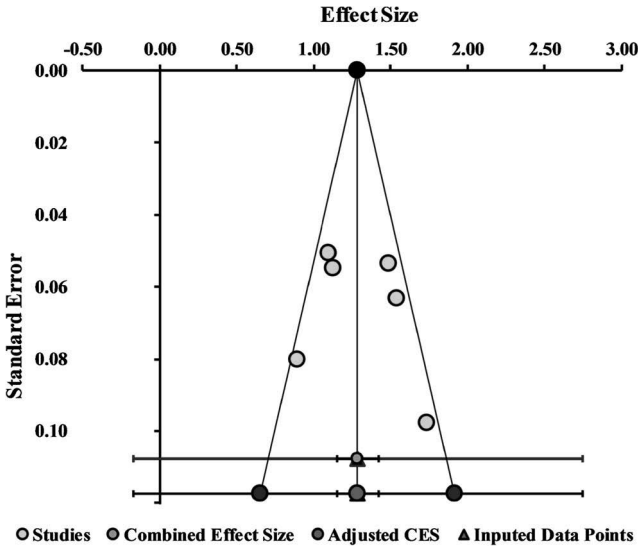

Fig. 6 Funnel plot for the qualitative evaluation of publication bias

conducted by Awata et al. reported a negative association of this polymorphism rs3025039 with an increased risk of DR [30]. These discrepancies might be partially attributed to several factors, including alterations in races, population structure, variations in inclusion criteria, sample recruitment bias, and others.

Another G>C *VEGF* polymorphism (rs2010963), localized at the − 634 position, studied dynamically its association with DR [19, 21, 24]. This meta-analysis showed consistency with earlier findings that state a non-significant association of rs2010963 with a DR group and subgroup analysis [31]. Nevertheless, a meta-analysis considering the rs2010963 polymorphism was carried out on 1525 DR subjects and 1422 with no DR subjects, from nine distinct studies, which revealed significant observations in a recessive model (OR = 1.26), whereas the distribution of genotypes showed inconsistency with Hardy-Weinberg equilibrium (HWE) in one of its included studies which might be due to the small population size [32].

The expression of the gene and its related transcriptional activity are controlled by the genetic variations in the promoter sequence [33]. A diverse range of potential variants has been reported among various populations. This meta-analysis also revealed the associations of such *VEGF* polymorphisms, showing that variants (rs833061, s13207351, rs1570360, and rs2010963) of the Pakistani population exhibit a strong relationship with a higher susceptibility of developing diabetic retinopathy [24]. Previously, two polymorphisms rs833061 (promotor) and rs2010963 (5′UTR) were also explored for *VEGF* expression. The study conducted by Szeto et al. showed no influence of the rs833061 TC and CC genotypes on the secretion and production of VEGF, whereas CC genotype of rs2010963 polymorphism demonstrates a decline in VEGF production [34]. The molecular grounds suggest the adherence of a transcriptional factor: the myeloid zinc finger protein (MZF1), which becomes defected due to the occurrence of this polymorphism (rs2010963), which possibly plays a significant role in the reduction of VEGF protein production [35]. Conversely, an increase of VEGF production was observed in rs833061 carriers, which contain the risk allele C [36]. Though the variations related to VEGF expression showed a significant association with the pathogenesis of DR, they are also found to be involved in several ocular pathologies which are linked to angiogenesis [24].

Furthermore, the direct mechanism of VEGF involvement in the developmental pathway of DR is not transparent. It is anticipated that VEGF holds an essential role in elevating the vascular permeability and the neovascularization mechanism [37]. Before this meta-analysis, various polymorphisms of *VEGF* have demonstrated significant associations with the susceptibility for DR [29, 38, 39]. The significantly associated *VEGF* polymorphisms have a direct effect on expression of gene and protein [21] predominantly in the vitreous of diabetic individuals [36]. However, this analysis revealed the inference of statistics from studies published in the last 6 years, which predict the role of different *VEGF* polymorphisms in order to weigh their impact on the developmental pattern of DR.

The following limitations are considered in this meta-analysis. Firstly, although we pooled the data of all the available studies to get the results through the most reliable way, the final sample size was still relatively small and only six studies were selected for consideration, which means more research of high quality should be carried out. Secondly, type 1 and type 2 diabetes respond differently to these polymorphisms. Mechanism of DR pathogenicity in association with *VEGF* polymorphism might show variation in different types of diabetes. However; separate data was clearly indicated in the literature, and a vast majority of subjects belonged to the group of type 2 diabetes. Thirdly, the confounding effect of variables (such as duration of diabetes, blood pressure, blood glucose, gender, age, drug history, and comorbidities) used for the stratification of cases and controls was not considered due to unavailability of data in recruited studies. These factors might contribute to the development of amplified heterogeneity among populations. However, it was not found to develop any impact on the strategy of distribution revealed by publication bias.

Conclusions

This meta-analysis demonstrates and validates the significant association of the *VEGF* rs3025039 polymorphism with the higher susceptibility of DR. Other variants showed inconsistencies and need to be further elucidated in cohort studies among different populations. Moreover, there are probabilities of linkage disequilibrium among the *VEGF* polymorphisms.

Therefore, it should also be analyzed in association with nearby polymorphisms to reveal its potential implications. Correspondingly, a genome-wide association study (GWAS) should be established in future for the assessment of *VEGF* role in the pathogenesis of DR in coordination with clinical profile to develop significant biomarkers.

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Data and/or code availability Not applicable.

Compliance with ethical standards

Human and animal rights This article does not contain any studies with human or animal subjects performed by any of the authors.

Informed consent Not applicable

Ethical approval Not applicable

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

Consent to publish Not applicable

Consent to participate Not applicable

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REVIEW ARTICLE

Association between maternal alcohol use during pregnancy and gestational diabetes mellitus: a meta-analysis

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Abstract

Purpose Maternal alcohol use and gestational diabetes mellitus (GDM) have been serious public health issues worldwide. This study aimed to investigate the association between maternal alcohol use during pregnancy and risk of GDM via a meta-analysis.

Material and methods PubMed, ScienceDirect, and Cochrane Library databases were systematically searched up to March 25, 2020. Observational studies on associations between maternal alcohol use during pregnancy and risk of GDM were retrieved. The pooled odds ratios (ORs) and their 95% confidence intervals (CIs) for with versus without alcohol use during pregnancy were calculated using a random-effect model. The publication bias was assessed by Begg's rank correlation test.

Results A total of 7 observational studies (185,235 participants, including 8368 GDM cases) were included in this meta-analysis. Compared with women without any use of alcohol during pregnancy, the pooled OR for women with alcohol use was 0.74 (95% CI 0.50–1.10). In subgroup analysis, the pooled OR was 0.79 (95% CI 0.60–1.05) and 0.71 (95% CI 0.28–1.80), respectively, for individual study with and without adjusting for body mass index.

Conclusions Our findings suggest that there is no discernible association between maternal alcohol use during pregnancy and risk of GDM. However, given other possible pregnancy complications and adverse birth outcomes induced by alcohol use, women who have been pregnant and are planning to become pregnant should quit drinking.

Keywords Alcohol · Gestational diabetes mellitus · Meta-analysis · Pregnancy · Risk factor

Introduction

Maternal alcohol use during pregnancy has been and remains a serious public health problem worldwide. Based on results of a recent systematic review study, 9.8% of women reported alcohol use during pregnancy globally and the highest prevalence was seen in European region (25.2%) [1]. Specific to countries, data from the 2015–2017 Behavioral Risk Factor Surveillance System (BRFSS) showed that 11.5% of the US pregnant women aged 18–44 years were current drinkers [2]. Consisted of 7905 women, a multinational European study suggested that the prevalence of alcohol consumption during pregnancy in UK and Russia was 28.5% and 26.5%, respectively [3]. Besides, in Spain, although alcohol consumption among expectant mothers has declined, up to 2014, 5.4% of women still used alcohol during pregnancy [4]. Alcohol use during pregnancy is reported to be associated with a wide range of pregnancy complications and adverse birth outcomes, including miscarriage, preterm delivery, as well as fetal alcohol spectrum disorder, fetal mortality, and birth defects [5–10]. Gestational diabetes mellitus (GDM), characterized by high blood glucose levels during any time of pregnancy (although most likely after week 24), is one of the most common medical complications in pregnancy. Estimated by the International Diabetes Federation (IDF), 20.4 million or 15.8% of live births to women in 2019 had some form of hyperglycemia in pregnancy, of which 83.6% were due to GDM [11]. Considerable evidence indicated that the GDM was influenced by various factors, such as maternal body mass index (BMI), age, and family history of diabetes [12–14].

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Recently, the association between maternal alcohol use during pregnancy and GDM risk has been investigated in previous studies, while the findings have been inconclusive [15–17]. Therefore, in this study, we conducted a meta-analysis to estimate the overall risk of developing GDM among women with alcohol use during pregnancy.

Materials and methods

Literature and search strategy

The present study followed the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]. Based on databases of PubMed, ScienceDirect, and Cochrane Library up to March 25, 2020, we searched relevant studies on the association between maternal alcohol use during pregnancy and GDM risk. The alcohol exposure searching was conducted using the main terms of "alcohol," "alcohol consumption," "antenatal alcohol exposure," "alcohol intake," "alcohol drinking," as well as "factor," "predictor," and "determinant" with OR. The study outcome was identified by searching keywords of "gestational diabetes mellitus," "gestational diabetes," and "GDM" with OR. Additionally, the above searching keywords of exposure and outcome were linked with AND.

Eligibility criteria

Studies included in this meta-analysis study must meet the following criteria: (1) the studies were observational epidemiological studies of cross-sectional, cohort, or case-control; (2) on the association between maternal alcohol use during pregnancy and GDM risk; and (3) provided the odds ratio (OR) or relative risk (RR) with 95% confidence intervals (CIs) after adjusting for confounders.

Data extraction

Two authors independently extracted the following information from each study: (1) the name of first author and publication time, (2) country of study, (3) data source, (4) the number of GDM cases and total sizes, (5) diagnosis of GDM, (6) effect estimates of maternal alcohol use during pregnancy on GDM, and (7) potential confounders adjusted in each study. The quality of selected studies was evaluated using the 9-star

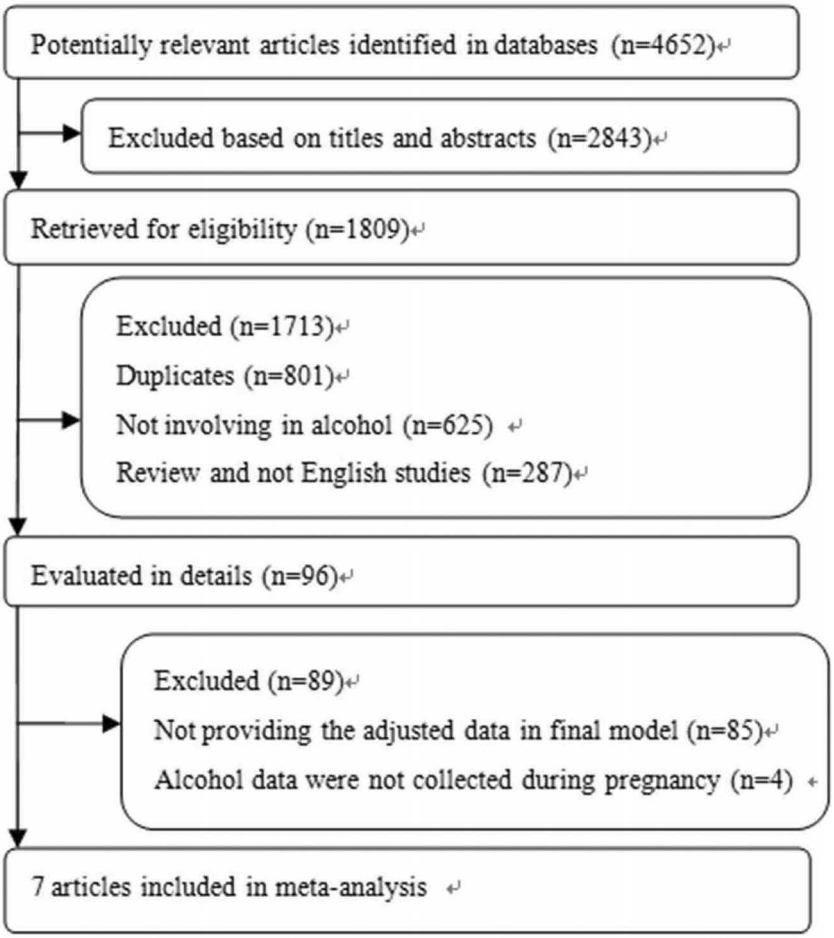

Fig. 1 Process of study selection

Table 1 Characteristics of the studies included in the meta-analysis

Study ID	Location	Data source	Case/total	Diagnosis of gestational diabetes mellitus (GMD)	OR (95% CI) for alcohol use during pregnancy (yes versus no)	Adjustment for potential confounders
Bouthoorn et al. 2015 [15]	Netherlands	A population-based cohort study in Rotterdam. 2002–2006.	71/7511	GDM was diagnosed using the following criteria: either a random glucose level > 11.0 mmol/L, a fasting glucose level ≥ 7.0 mmol/L, or a fasting glucose level between 6.1 and 6.9 mmol/L with a subsequent abnormal glucose tolerance test. In clinical practice and for this study sample, an abnormal glucose tolerance test was defined as a glucose level > 7.8 mmol/L after glucose intake.	0.51 (0.28–0.93)	Age, ethnicity, family history of diabetes, maternal education level.
Carroll et al. 2018 [16]	China	One matched case-control study conducted in Beijing Chaoyang District Hospital of Maternal and Child Health and Beijing Chuiyangliu Hospital. 2012–2014.	276/552	Women with plasma glucose ≥7.8 mmol/L in the 1-h glucose screening test were referred for the standard 75 g oral glucose tolerance test (OGTT). The International Association of Diabetes Study Group criteria were used for diagnosis of GDM as defined by one of the following: fasting plasma glucose ≥ 5.1 mmol/L and/or 1-h PG ≥ 10.0 mmol/L and/or 2-h PG ≥ 8.5 mmol/L.	1.76 (1.03–3.01)	Environmental tobacco smoke, tobacco smoking, physical activity, TV viewing, sleeping, fruit intake, sugar-sweetened soft drink.
Domanski et al. 2018 [21]	Germany	A population-based cohort study titled the Survey of Neonates in Pomerania (SNiP). 2002–2008.	232/4548	Women having suspicious results of urine glucose were referred to the hospital, where a 75 g OGTT was administered. If at least one of the following values was exceeded, a woman was classified as having GDM: fasting state ≥ 5.1 mmol/L (92 mg/dL) After 1 h ≥ 10.0 mmol/L (180 mg/dL) After 2 h ≥ 8.5 mmol/L (153 mg/dL)	0.61 (0.41–0.90)	Maternal age, smoking, prepregnancy body mass index (BMI), parity, education level, and monthly income.
Esteves Lima et al. 2013 [17]	Brazil	A case-control study in the Odete Valadares Maternity Hospital, Belo Horizonte.	90/360	The OGTT test was performed with standardized measures of fasting glucose, 1 and 2 h after ingestion of 75 g anhydrous glucose. For the OGTT curve, the cutoff points were considered to be 95 mg/dL in fasting analysis, 180 mg/dL for the sample taken 1 h after the ingestion of glucose loading, and 155 mg/dL for the sample taken after 2 h. A single abnormal value in OGTT was considered sufficient for the diagnosis of GDM.	0.57 (0.13–2.59)	Age, education level, marital stability, parity, smoking, chronic hypertension, BMI, and periodontitis.
Inneset al. 2002 [22]	USA	Two large, computerized state databases maintained by the New York State Department of Health: the live birth registry and the New York State Hospital discharge records. 1994–1998.	440/23395	Cases were defined as eligible women with a record of GDM on their first born's birth certificates and/or a diagnosis of GDM (International classification of Diabetes, Ninth Revision [ICD-9] code 648.0 or abnormal glucose tolerance (ICD-9 code 648.8) on their hospital discharge records.	0.93 (0.23–3.83)	Age, race, education, employment status, smoking, prepregnancy BMI, height, pregnancy weight gain, and exposure to maternal diabetes.

Table 1 (continued)

Study ID	Location	Data source	Case/total	Diagnosis of gestational diabetes mellitus (GMD)	OR (95% CI) for alcohol use during pregnancy (yes versus no)	Adjustment for potential confounders
Khajehei et al. 2020 [23]	Australia	A single-center, retrospective cohort study in Australian tertiary hospital in Sydney. 2011–2017.	4504/37450	Fasting blood sugar was measured in the morning, and it was considered normal if the blood sugar was ≤ 5.5 mmol/L. The women then had a standard 75 g OGTT. If the 2-h glucose (mmol/L) following 75 g oral glucose load was ≤ 8 mmol/L, it was considered normal, and if it was ≦ 8 mmol/L, gestational diabetes was diagnosed.	0.96 (0.71–1.30)	Age, country of birth, parity, type of conception, model of care, health status, and behaviors including BMI, smoking, endocrine diseases, renal diseases, autoimmune diseases, and hypertension.
Xiong et al. 2001 [24]	Canada	Northern and Central Alberta Perinatal Audit and Education Program. 1991–1997.	2755/111419	GDM is diagnosed when any two of these plasma glucose values (i.e., fasting > 5.8 mmol/L, 1 h > 10.5 mmol/L, 2 h > 9.2 mmol/L, 3 h > 8.0 mmol/L) were equal or greater.	0.40 (0.25–0.76)	Parity, maternal age, maternal weight, maternal smoking, history of neonatal death, history delivery < 37 weeks, history of cesarean section, history of major fetal anomaly.

Newcastle-Ottawa Scale, a validated technique for assessing the quality of observational studies [19].

Statistical analysis

After the test of heterogeneity, the pooled OR with 95% CI for maternal alcohol use during pregnancy was calculated with a fixed- or random-effect model. The heterogeneity in each study was assessed with indicator of I^2 [20]. The I^2 values ranged from 25, 50, and 75% represented the low, moderate, and high degrees of heterogeneity, respectively. If there was a significant heterogeneity ($I^2 > 25\%$), a random-effect model would be used. If there was no heterogeneity ($I^2 \leqq 25\%$), we used a fixed-effect model. In the main analysis of exploring the association between maternal alcohol use during pregnancy and risk of GDM, a sensitivity analysis was conducted to test the robustness of the findings. To explore the possible sources of heterogeneity, we also carried out the subgroup analysis based on whether the effects of maternal alcohol use during pregnancy were adjusted for BMI. The publication bias was assessed by Begg's rank correlation test ($p < 0.1$). The meta-analysis was conducted with STATA Version 11 software.

Results

Process of study selection

After the literature searching, totally, 4652 potential articles were identified in our meta-analysis study. Among them, 2843 articles were excluded based on the title/abstract. In the process of eligibility assessment, 1713 articles were excluded because those were duplicates, not including the exposure of alcohol use, review, and not the English studies. Furthermore, 89 articles were further excluded due to not providing the adjusted estimates and limiting alcohol use during pregnancy. After these exclusions, 7 articles were included in the final analysis. The details of study selection process are shown in Fig. 1. Briefly, we identified 7 studies published between 2001 and 2020 for this meta-analysis, and the main information extracted from the studies is shown in Table 1. The quality score of studies ranged from 3 stars to 6 stars according to the 9-star Newcastle-Ottawa Scale.

Meta-analysis of maternal alcohol use during pregnancy and GDM risk

In this meta-analysis, there were 8368 GDM cases among 185,235 participants. After the formal test for heterogeneity, we found a moderate level ($I^2 = 69.8\%$) of heterogeneity, and thus, a random-effect model was used (Fig. 2). Compared with women without alcohol use during pregnancy, the pooled OR for women with alcohol use during pregnancy was 0.74 (95% CI 0.50–1.10). When subgroup analysis was performed on

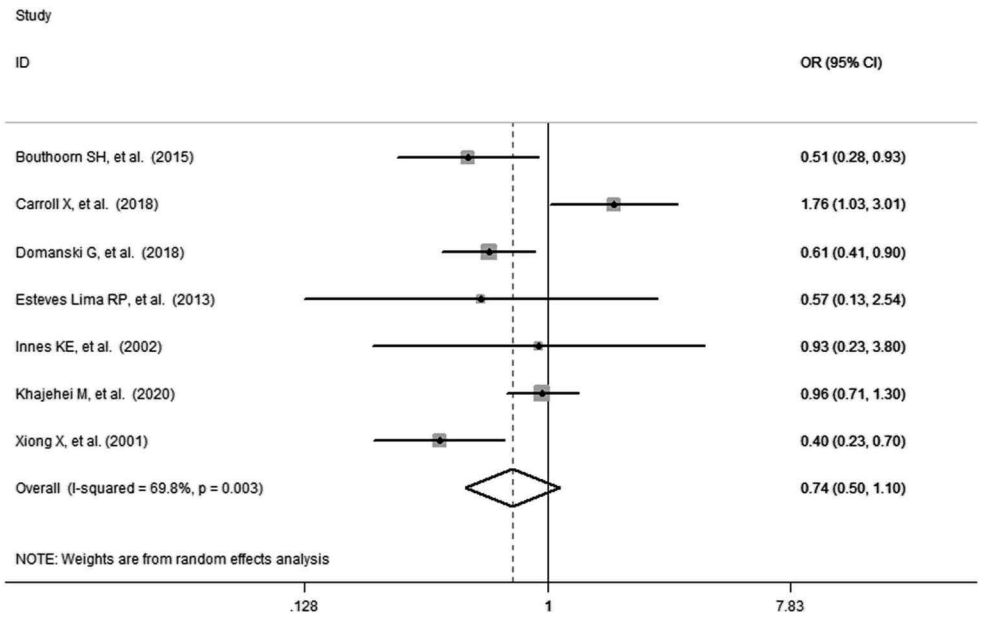

Fig. 2 The pooled effect of maternal alcohol use during pregnancy on GDM risk

whether adjusting for BMI, we found that the pooled ORs were 0.79 (95% CI 0.60–1.05) and 0.71 (95% CI 0.28–1.80) for with and without adjusting for BMI, respectively (Fig. 3).

Sensitivity analysis

The sensitivity analysis results showed that the study by Carrol et al. [16], Khajehei and colleague [23] substantially influenced the pooled estimates for GDM risk. After excluding the two studies, the OR was 0.54 (0.41–0.71) and there was no heterogeneity ($I^2 = 0\%$).

Publication bias

With the p value 0.76 in the Begg's rank correlation test, we reported that there was no potential publication bias.

Discussion

Previous findings have indicated that moderate alcohol consumption may be protective for type 2 diabetes in women [25]. Given that the GDM is a special type of

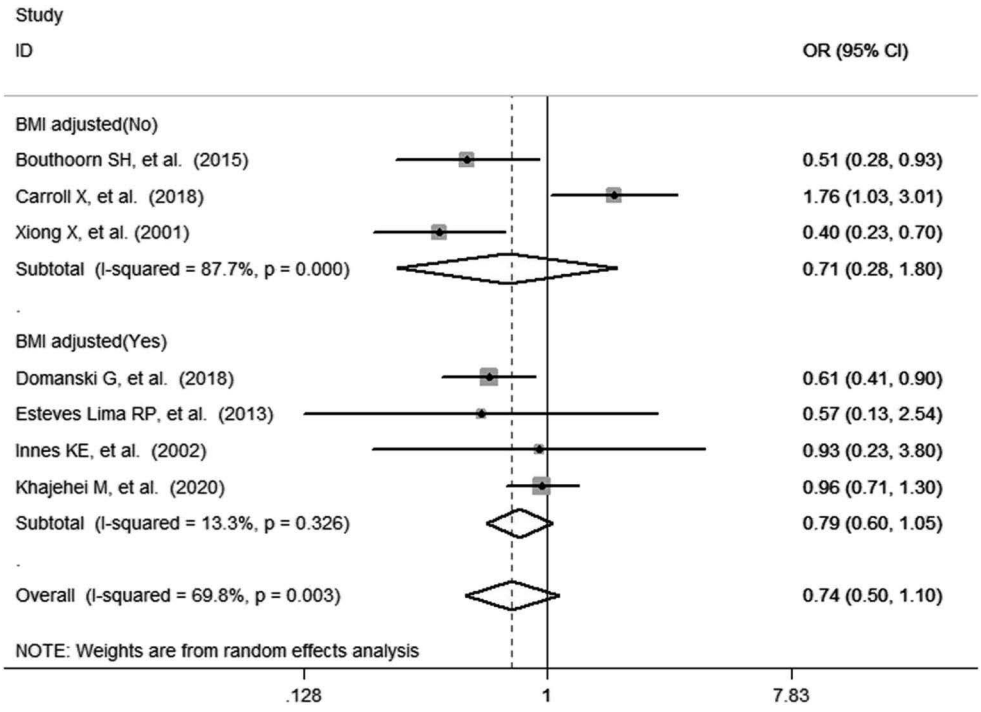

Fig. 3 The subgroup analysis on the effects of maternal alcohol use during pregnancy on GDM risk with or without adjusting for body mass index

diabetes for women during pregnancy, it is essential to extend the knowledge to the association of maternal alcohol use during pregnancy with the GDM risk. With a meta-analysis method, this current study attempted to pool estimates from observational studies to explore the possible effects of maternal alcohol use during pregnancy on the risk of developing GDM. Overall, our result showed that maternal alcohol use during pregnancy was not significantly associated with the risk of GDM (OR 0.74, 95% CI 0.50–1.10), even after adjusting for the potential confounders. This finding was in line with the pooled estimate in a meta-analysis exploring the risk factors of GDM, which showed a decreased but non-significant effect of drinking alcohol on GDM risk (OR 0.79, 95% CI 0.54–1.14) with no heterogeneity among Asian women [26]. However, it is worth noting that the timing of maternal alcohol drinking in this study was not specifically classified into before or during the pregnancy, which would decrease the reliability of findings. Considering the difference in study design, sample, size, and GDM diagnosis, we also conducted a sensitivity analysis. After excluding the two studies included, a lower and significant pooled estimate for GDM was seen in the meta-analysis (OR 0.54, 95% CI 0.41–0.71) without any heterogeneity. However, due to the small number of studies (only five), the updated result in the sensitivity analysis could not support the protective effect of maternal alcohol use during pregnancy on GDM risk. BMI has been reported to be the strongest risk factor for GDM in previous study [12]. To explore the possible mediating effects of BMI on the association between maternal alcohol use during pregnancy and GDM risk, we performed the subgroup analysis. Based on the results, we found a much higher effect estimate in subgroup of adjusting for BMI with low heterogeneity, which indicated that the study association of maternal alcohol use during pregnancy with GDM might be mediated by BMI and the mediating effects of other GDM-related factors should be considered in future studies.

Our meta-analysis study had some limitations. First, there was moderate-to-high heterogeneity between studies in the main analysis and subgroup analysis by adjusting for BMI, suggesting that other confounding factors for variation still existed. Second, as the included studies only provided estimated effects on GDM with yes versus no alcohol use, the condition of former drinkers with possible sick-quitter effect [27] was not considered in this meta-analysis. Third, with limited number of studies included in our analysis, the observed association between maternal alcohol use during pregnancy and GDM risk in the present study should be interpreted with cautions.

In conclusion, findings from this study indicated that maternal alcohol use during pregnancy was not significantly associated with GDM risk. However, given other possible pregnancy complications and adverse birth outcomes induced by alcohol use, we call for those women who have been pregnant and are planning to become pregnant should quit drinking.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Sai-Ling Hu, Bi-Tong He, and Ren-Jie Zhang. The first draft of the manuscript was written by Sai-Ling Hu, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The data used for the analysis are available upon the request for corresponding author.

Compliance with ethical standards

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

Ethics approval Not available.

Consent to participate Not available.

Consent for publication Not available.

Code availability Analysis was conducted using STATA Version 11 software, and the code is available upon the request for corresponding author.

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REVIEW ARTICLE

The association between gallstone disease and metabolic syndrome related abnormalities: a systematic review and meta-analysis

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Abstract

Background Bile excretion is one of the important metabolite excretion pathways of the human body. In recent years, it has been reported that metabolic diseases are associated with the occurrence of gallstone disease. The main purpose of this systematic review is to examine the relationship between metabolic syndrome and cholelithiasis, including components of the metabolic syndrome such as abnormal blood glucose regulation, hyperlipidemia, and obesity.

Methods PubMed, Cochrane Library, and Embase were searched for all English language articles for the following relevant keywords: Metabolic Syndrome, Reaven Syndrome X, Biliary Calculi, Cholelithiasis Gallstones. Case-control study, cross-sectional study, and cohort study were included. Pooled relative risks (RRs) or odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated. The pooled mean differences of the outcome measures were compared between patients with and without metabolic syndrome.

Results After screening, a total of 5 cross-sectional studies and 1 cohort study were included in the meta-analysis. The 6 studies evaluated a total of 49,101 people, of whom 9055 had metabolic syndrome and 2308 had gallstone disease. There is a significant correlation between metabolic syndrome and gallstone disease ($z = 6.65$, $p = 0.000$), and it's more significant in female. All studies displayed increasing odds of gallstone disease with increasing number of metabolic syndrome traits, where patients with three or more metabolic syndrome traits tended to have a higher prevalence of nephrolithiasis.

Conclusions Our review shows a definite association of metabolic syndrome with gallstone disease, and the more the components of metabolic syndrome, the higher the prevalence of gallstone disease. Although not as obvious as women, men also support this conclusion.

Keywords Gallstone disease · Insulin resistance · Meta-analysis · Metabolic syndrome

Background

Gallstones disease (GSD) is the most common digestive disease needing admission to hospital in the West. With a prevalence of 10–15% in adults in Europe and the USA, 5–20% in Asian populations, gallstone disease is one of the most common and most expensive to treat among the digestive disorders that need admission to hospital [1–4]. It constitutes a major health burden that has increased more than 20% over the last 3 decades in the USA [5].

Gallstones are a disease that is more common in female than in male [6]. Risk factors include gender, obesity, and chronic liver diseases such as fatty liver, cirrhosis, and gastrectomy. Patients with disease such as diabetes are also susceptible to gallstone disease [5].

Metabolic syndrome (MetS/MS) is a state in which multiple metabolic risk factors for cardiovascular disease build up within an individual [7]. The main components of MetS are obesity, especially visceral obesity, diabetes, or impaired glucose regulation, hypertension, and lipid disorders which are characterized by hypertriglyceridemia (TG) and low-density lipoprotein cholesterol (HDL-C). In addition, MS also includes tissue insulin resistance, hyperuricemia, and microalbuminuria that reflects vascular endothelial cell dysfunction [8, 9]. The prevalence of

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metabolic syndrome has increased dramatically worldwide [7, 10, 11]. Studies about the association between gallstone disease and MetS suggested that MetS is a risk factor for gallstone disease [12]. Most of the key components for the diagnosis of MetS are also key risk factors of GSD [8]. As a whole, metabolic syndrome is also associated with cholelithiasis; the purpose of this meta-analysis was to examine the association of MS and gallstones integrated and independent by component.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was performed in accordance with MOOSE guidelines [13]. The major medical databases in the English language, among which were Cochrane, Embase, and PubMed, were searched independently by two authors (ZN and XL) up to September 15, 2019, using the following keywords in combination with both medical subject heading terms and text words: "Metabolic Syndrome X," "Metabolic syndrome," "Insulin Resistance Syndrome X," "Reaven Syndrome X," "Cholecystolithiasis," "Cholelithiasis," "Choledocholithiasis," "Biliary Calculi," and "Gallstones".

Gray trials were excluded in this study. But this may increase the publication bias, because the included studies were not complete and comprehensive and published trials had an overall greater intervention effect than gray trials. On the other hand, unpublished studies may be of lower methodological quality than published studies [14].

Study selection and data extraction

Two reviewers (ZN and XL) independently screened all the titles and abstracts in an effort to minimize selection bias, and a third reviewer was consulted for resolution of disagreement. The following information was extracted from all the literatures: research design type, region, number of patients included, diagnostic methods of cholelithiasis, diagnostic criteria of metabolic syndrome, BMI (Body Mass Index), age, and prevalence of metabolic syndrome and its components such as waist circumference, blood pressure (systolic pressure, diastolic pressure), fasting blood glucose, LDL-C, TG (triglyceride), and other blood biochemical indicators in cholelithiasis group and control group. For continuous data (such as age, blood pressure, fasting blood glucose), mean ± SD and the number of people in the group were extracted respectively. For count data (such as hypertension and diabetes mellitus), the corresponding number of people in the two groups and the total number of people in the group were extracted respectively.

Studies were included if the following criteria were met: (1) retrospective or prospective cohort study, cross-sectional study, case-control study. (2) The experimental group met the diagnostic criteria for MetS. (3) The diagnosis of cholelithiasis was confirmed by imaging evidence or surgical evidence. (4) The control group was included in the study and odds ratios (ORs) in case-control studies or relative risks (RR) in cohort studies were reported with the 95% confidence intervals (CIs) (or, if 95% CIs were not reported, the reported data were sufficient to calculate them). Studies were excluded if (1) literature was not the above research type, or the unpublished. (2) The study did not set up a control, or the number of cases less than 10; patients with long-term use of drugs proved to be conducive to stone formation or stone discharge. (3) The patients in the study had organic lesions, liver dysfunction or viral hepatitis in the hepatobiliary system. (4) Only the latest research involving more cases included in the similar study of the same authors.

Quality assessment

The Newcastle-Ottawa scale was used to assess the quality of the included studies [15]. Briefly, the instrument contains 8 items categorized into 3 dimensions: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. An 8-point scoring system is used for a semiquantitative assessment of study quality; score of 5–8 were classified as qualified studies [16]. Cross-sectional studies use the quality evaluation criteria recommended by AHRQ (Agency for Healthcare Research and Quality) which includes eleven items. Article quality was assessed as follows: low quality = 0–3; moderate quality = 4–7; high quality = 8–11 [17].

Outcome measures and data analysis

The primary outcome was the interrelation between the period/point prevalence of cholelithiasis with metabolic syndrome patients and that in non-metabolic syndrome patients, and the prevalence of cholelithiasis in different sexes, the relationship between the components of metabolic syndrome and the prevalence of cholelithiasis, and the relationship of number of components of metabolic syndrome and cholelithiasis. The effect measures of interest were odds ratios for case-control studies and cross-sectional studies, relative risks for cohort studies, and the corresponding 95% confidence intervals are given.

The heterogeneity of the study was evaluated by I^2 statistics. The $I^2 > 50\%$ was taken to indicate high levels of heterogeneity and the random effect analysis model is used. Otherwise, the fixed effect model will be used. Subgroup analysis was performed to explore potential heterogeneity. A p value < 0.05 was considered statistically significant, and 95% confidence intervals (CIs) are given. Publication bias

was evaluated by using the Egger test [18]. A p value < 0.05 indicates statistically publication bias. The meta-analyses were performed using Stata software (version 14; Stata Corp, College Station, TX). The Z test was used to examine differences in experiment group and control group. A Z value more than 1.96 and $p < 0.05$ was considered statistically significant, and the 95% confidence intervals (CIs) are given. Cochran-Armitage test for trend was used in the SAS system (version 9.2); $p < 0.05$ was considered statistically significant.

Results

A flow diagram of study selection is shown in Fig. 1. After the initial literature searching and eliminating duplicate articles, 94 were excluded from 432 identified articles (Fig. 1). Three hundred nineteen unrelated articles and reviews were excluded after examination. Read the full text carefully to rule out inconsistencies in the type or purpose of the study. Finally, 6 articles were included in the study which including 5 cross-sectional studies and 1 cohort study [6, 12, 19–22]. We found no related or relevant meta-analyses in the Cochrane Library. A summary of the 6 included studies is given in Table 1. The 6 studies included in the meta-analysis contained a total of 48,858 people, wherein 5451 had MetS and 43407 did not have MetS.

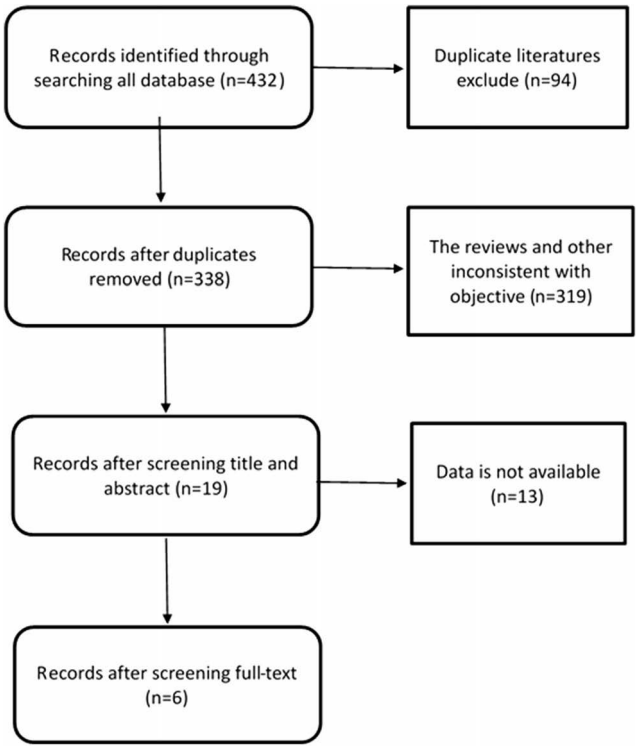

Fig. 1 Flow diagram of the literature search in this meta-analysis

Primary outcome

The main findings of the study were the prevalence of cholelithiasis in MetS and non-MetS populations (Fig. 2). In the six studies included, significant heterogeneity was observed. Heterogeneity chi-squared = 18.69 (d.f. = 5), $p = 0.002$, I-squared (variation in RR attributable to heterogeneity) = 73.2%, and thus a random-effects model of analysis was performed. The result indicates that patients with MetS had a significantly higher GSD prevalence than patients without MS ($z = 6.65$, p = 0.000). Egger's test suggested no statistically significant publication bias for the study, $p = 0.959$ (Supplementary Fig. 1). Funnel plots can't be used for the reviews as insufficient numbers of included studies (10 or more studies) [23].

A subgroup analysis conducted to investigate people from different regions that led to strong heterogeneity. Four and two studies were included in the analysis of the associations between Asian and European and American countries in the prevalence of GSD (Fig. 3). The pooled estimates indicated that neither Asian populations ($p = 0.007$, I-squared = 75.4%) nor European and American ($p = 0.026$, I-squared = 79.9%) populations contribute to the heterogeneity of prevalence of cholelithiasis in MetS and non-MetS populations.

An analysis was also conducted to investigate the effect of gender on the prevalence of GSD between MetS populations and non-MetS. Three studies reported the gender data were included (Fig. 4a.). Significant heterogeneity was observed in male patient ($p = 0.030$, $I^2 = 71.5\%$) and overall patient ($p = 0.000$, $I^2 = 78.5\%$), and thus a random-effects model of analysis was performed. Male patients ($z = 10.22$, $p = 0.000$) and female patients ($z = 8.45$, $p = 0.000$) and overall patients ($z = 12.45$, $p = 0.000$) with MS have more rate for gallstone disease than without MS.

Four studies reported age data (Fig. 4b). No significant heterogeneity was observed (heterogeneity chi-squared = 5.82, $p = 0.121$, I-squared = 48.5%), and thus a fix-effects model of analysis was performed. We found old patients ($z = 21.16$, $p = 0.000$) have higher prevalence for gallstone disease than the youngers.

Four studies reported BMI data (Fig. 5a). Significant heterogeneity was observed (heterogeneity chi-squared = 12.19, $p = 0.007$, I-squared = 75.4%) and thus a random-effects model of analysis was performed. Patients with high BMI are more likely to suffer from GSD ($z = 5.74$, $p = 0.000$).

Four studies reported WC (waist circumference) data (Fig. 5b). Significant heterogeneity was observed (heterogeneity chi-squared = 11.23, $p = 0.011$, I-squared = 73.3%) and thus a random-effects model of analysis was performed. Patients with high WC are more likely to get GSD ($z = 6.57$, $p = 0.000$).

Table 1 Characteristics of 6 studies included into present meta-analysis

Basic characteristics of included studies								
Study (year)	Country/area	Sample size	Definition of MetS	Imaging technique	Blind method	Study design	Quality evaluation method	Score
Tsai (2000–2009)	Taiwan, China	8188	NCEP-ATPIII	Ultrasonography	Double blind	Cross-sectional	AHRQ	8
Lin (2011–2012)	Taiwan, China	11527	NCEP-ATPIII	Ultrasonography	Double blind	Cross-sectional	AHRQ	8
Zhu (2005–2010)	China	18291	CDS	Ultrasonography	Double blind	Cohort	NOS	6
Méndez-Sánchez (2005)	Mexico	245	NCEP-ATPIII	Ultrasonography	Double blind	Cross-sectional	AHRQ	5
Chen (2012)	China	7570	NCEP-ATPIII	Ultrasonography	Double blind	Cross-sectional	AHRQ	9
Shabanzadeha (2017)	Denmark	2650	IDF, AHA/NHLBI, 2009	Ultrasonography	Double blind	Cross-sectional	AHRQ	8

Four studies reported TC (total cholesterol) data (Fig. 5c). Significant heterogeneity was observed (heterogeneity chi-squared = 8.44, $p = 0.015$, I-squared = 76.3%) and thus a random-effects model of analysis was performed. There was no significant difference in two groups of people ($z = 0.66$, $p = 0.508$) indicating that there was no significant increase in the prevalence of cholelithiasis among people with higher TC levels.

Four studies reported FPG (fasting plasma glucose) data (Fig. 5d). Significant heterogeneity was observed (heterogeneity chi-squared = 7.41, $p = 0.060$; I-squared = 59.5%) and thus a random-effects model of analysis was performed. Patients with high FPG develop GSD more often than normal ($z = 5.23$, $p = 0.000$).

With regard to the number of components and the prevalence of GSD, we merged data from three articles; participants were divided into 4 levels according to the counts of their metabolic disorders. The Cochran-Armitage test for trend was used in the SAS system (version 9.2). Among the subjects with different numbers of metabolic abnormalities, there was an increased prevalence of gallstones as the number of metabolic abnormalities increased (test for trend, $p < 0.001$, Table 2). Even if the diagnostic criteria for MS are not met, the independent component remains a risk factor for GSD, and as the number increases, the risk of GSD increases.

Discussion

Gallstones can be divided into the following types: cholesterol stones, pigment stones, and mixed stones. Cholesterol stones must be at least 80% cholesterol by weight. Other common constituents are primarily of bilirubin (insoluble bilirubin pigment polymer) and calcium (calcium phosphate) salts that are found in bile. Between 35% and 90% of stones are cholesterol stones [24]. During the formation of cholesterol stones,

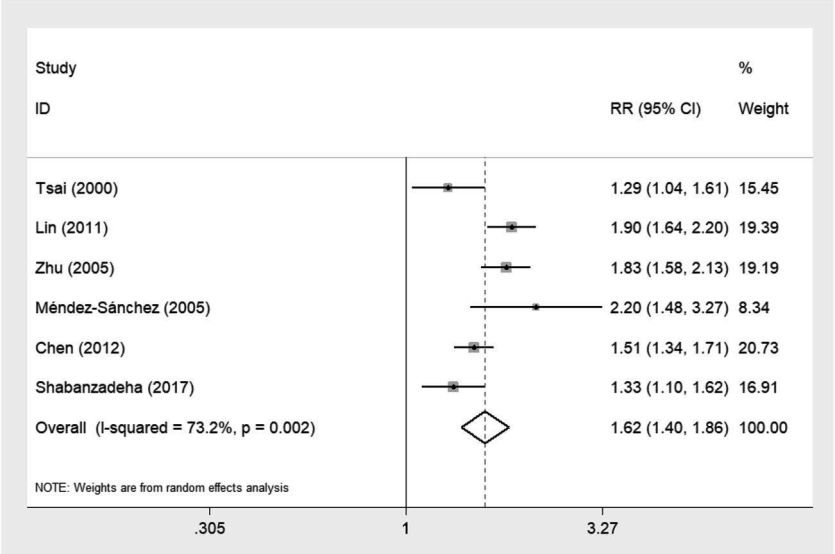

Fig. 2 The prevalence of cholelithiasis between MetS and non-MetS population

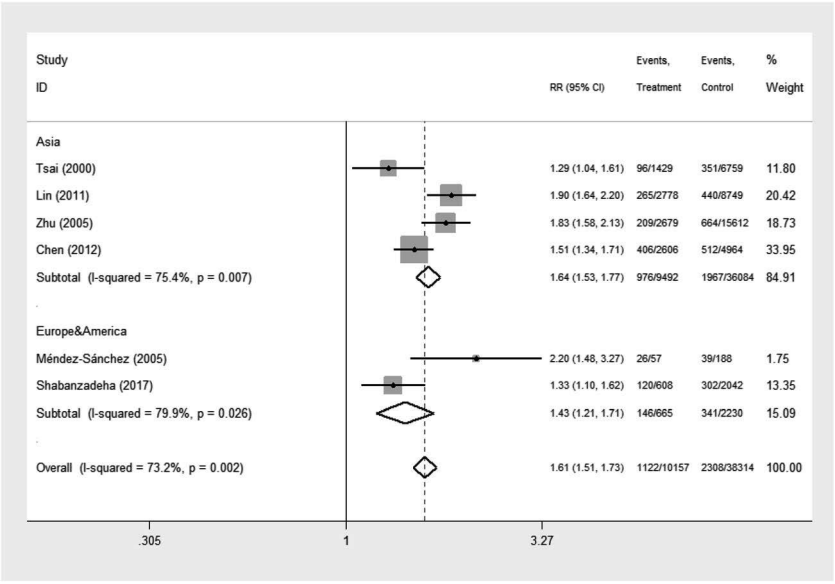

Fig. 3 Subgroup analysis by region

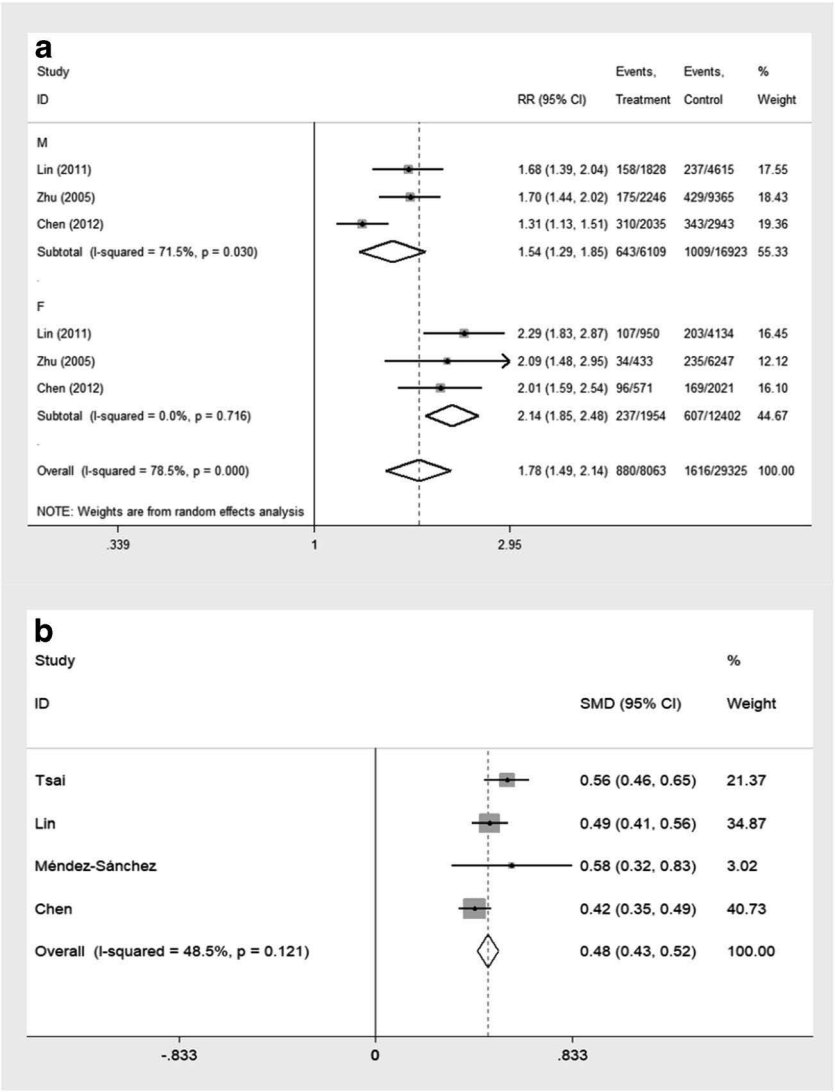

Fig. 4 Influence of age and gender on prevalence of GSD in MS patients. **a** Gender on the prevalence of GSD between MetS populations and non-MetS. **b** Age on the prevalence of GSD between MetS populations and non-MetS

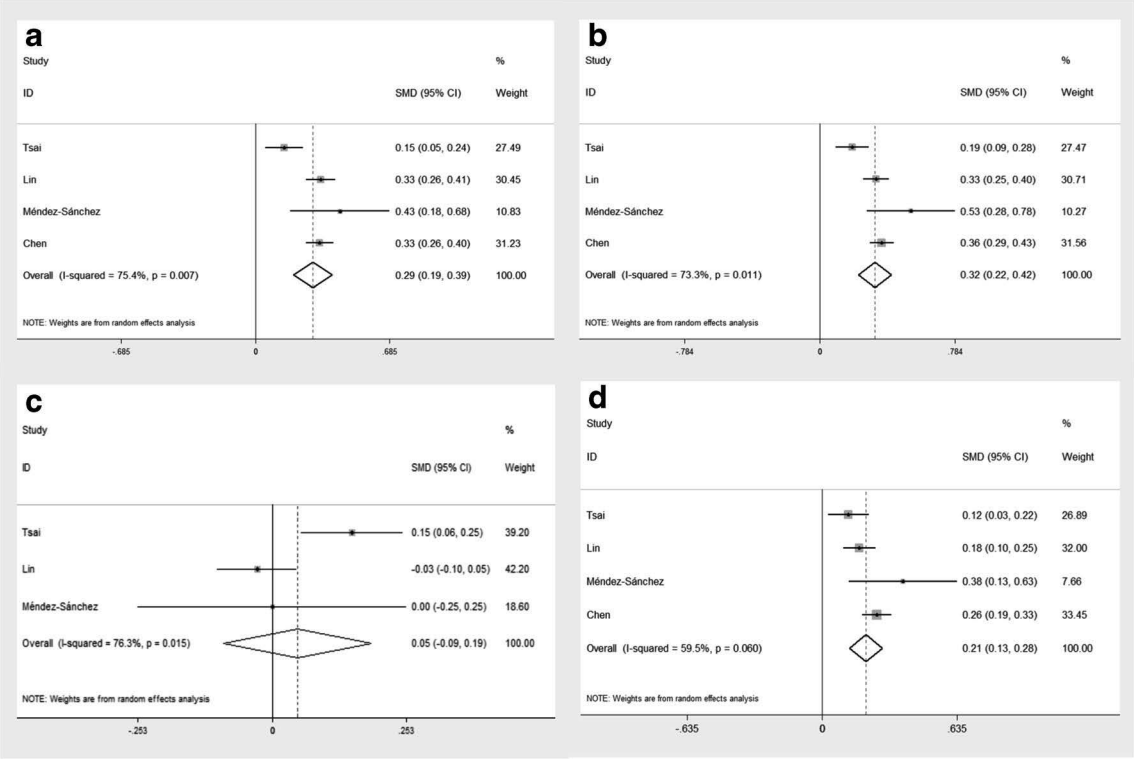

Fig. 5 Factors of MS components on prevalence of GSD. **a** BMI on the prevalence of GSD between MetS populations and non-MetS. **b** WC on the prevalence of GSD between MetS populations and non-MetS. **c** TC on the prevalence of GSD between MetS populations and non-MetS. **d** FPG on the prevalence of GSD between MetS populations and non-MetS

impaired motility of gallbladder smooth muscle (GBSM), increased residual volume of fasting gallbladder, and decreased contractility plays an important role [25–27]. Long bile retention time in gallbladder may lead to high concentration in gallbladder bile and promote cholesterol precipitation in epithelial cells [28]. Occasionally chronic bacterial infections, although asymptomatic, can also be a cause of GSD [29, 30].

Metabolic syndrome was first proposed by Reaven in 1993, which was then called X syndrome [31]. The main clinical manifestations were insulin resistance (IR), hyperinsulinemia, impaired glucose tolerance (IGT), hypertension, and abnormal atherogenic lipid metabolism [32]. Different definitions of MetS have been proposed, reviewed, recommended, and even questioned over the decades. The World Health Organization (WHO) first proposed a working definition centering on IR or hyperglycemia [33]. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) of the USA proposed diagnostic criteria for MS in 2001 [34].

In the past 20 years, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) of the USA and IDF have proposed new definitions successively, but they have these core components including central observatory, dyslipidemia, hypertension, and insulin resistance. In fact, it also proved to be reliable and universally accepted diagnostic tool [35–37]. As a result of different diagnostic criteria, the results of our statistical analysis may have deviation, which may lead to a decrease in the reliability of the conclusions to a certain extent, but this is inevitable.

Table 2 The prevalence of gallstone in subjects with different numbers of metabolic abnormalities

Cochran-Armitage test for trend					
Number of metabolic abnormality	Number yes	Number no	Number total	Prevalence	Test for trend
0	283	8308	8591	3.29	$p < 0.0001$
1	377	7537	7914	4.76	$Z = 12.3032$
2	394	5660	6054	6.51	
≥ 3	331	3834	4165	7.95	

This study aimed to evaluate the association of MS with characteristics of gallstone. There are great differences in body shape or WC among different ethnic groups, men, and women where studied as one group, a fact that it could have introduced a bias in the final analysis, even if appropriate adjustments of data were performed in the final statistics. We included 5 cross-sectional studies in the literature, which means that these studied under normal living conditions in only one point in time; thus, the relationships found in the analysis have limitations. And the exclusion of gray literature from the meta-analysis will exaggerate the positive results of the meta-analysis and lead to decision errors.

In spite of the limitations described above, conclusions can also be drawn from these studies that the prevalence of gallstones in MetS patients is increased compared with patients without MetS. A subgroup analysis by sex analysis showed that both men and women had an increased prevalence. Analysis of various factors including MS components, the prevalence of cholelithiasis increased in older patients. Obesity-related factors like high blood lipids TC, WC, BMI, fasting blood glucose were positively correlated with the prevalence of cholelithiasis. Diabetes and hypertension are also positively correlated with the prevalence of cholelithiasis. In male subjects, metabolic syndrome was associated with presence of gallstones, and the size of gallstones [38].

In recent years, insulin resistance is another hot topic among metabolic abnormalities associated with GSD. Not only in obese people but insulin resistance can also occur in people with normal weight. A study in a Hispanic population found that GS was associated with insulin resistance, fatty liver, and metabolic syndrome. Insulin resistance is a risk factor for GS [39]. Insulin resistance may play an important role in the pathogenesis of GS favoring the production of cholesterol supersaturated bile and altering gallbladder function [39]. Nakeeb et al. [40] demonstrated that insulin resistance alone may be responsible for gallbladder dysmotility, which may result in acalculous cholecystitis or gallstone formation.

Even evidence supports the contention that insulin resistance not only directly induces gallbladder inflammation increase mucus production and alter gallbladder function but could also favor the secretion by the liver of cholesterol supersaturated bile [41]. The latter seems more accepted pathogenic link. GS increases cholesterol saturation in gallbladder bile, a phenomenon related to increases of body cholesterol synthesis and hypersecretion of biliary cholesterol as observed in obesity [30]. Adiponectin acted as a critical element in the development of insulin resistance; the lower the rate of obesity, weight, and BMI, the higher the concentration of adiponectin and that this information would be helpful for the treatment of diabetes [42].

The definition presented by the IDF that emphasizes abdominal obesity as a sine qua non diagnostic factor [43]. In fact, it has been confirmed that some indicators such as larger waist circumference, higher BMI, and hyperlipidemia are obese manifestations. Recent data from animal and human studies have shown that the gallbladder of obese people is enlarged and their response to neurotransmitters is usually reduced. A high-fat diet can lead to abnormal emptying of the gallbladder. In addition, obese and high carbohydrate diet had increased gallbladder tissue levels of tumor necrosis factor-alpha, interleukin-6, and interleukin-1 beta. These changes lead to decreased smooth muscle function and diminished gallbladder absorption [44].

The function of bile components secretory also increased in GS patients. In a study from Chile, increased bile synthesis was found in GS patients [45]. Hepatic bile acid and body cholesterol were significantly increased by 50% in patients with cholelithiasis, hepatic hypersecretion of cholesterol, and supersaturated bile which give life to precipitating cholesterol crystals that accumulate and grow in a sluggish gallbladder.

Although there is no parallel relationship with blood lipids level, increased lipid components excretion through bile directly promote the formation of cholesterol stones. Total cholesterol, direct bilirubin, and especially lean body weight might provide simple stratification tools for obese women, outlining a high-risk profile for developing gallstones [46].

In the next step of the study, the number of included literature should be increased as much as possible, especially the gray literature, to reduce publication bias, and subgroup analysis of each component, thereby reducing heterogeneity, and, more importantly, investigating the priority or order of Mets and GSD in cross-sectional studies.

Conclusions

Despite there may be some heterogeneity due to different diagnostic criteria of metabolic syndrome or some other errors, the result trend shows that metabolic syndrome is closely related to cholelithiasis. Even some researchers propose that GD is another member of the metabolic syndrome [43]. These results also suggest that the metabolic syndrome can even be regarded as another indication for prophylactic surgery in patients with GSD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13410-020-00890-9.

Authors' contributions PJ and HH conceived and designed the study. ZN and XL performed the experiments. PJ and SH wrote the paper. PJ, ZN, XL, YL, and HH reviewed and edited the manuscript. All authors read and approved the manuscript.

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Data availability Not applicable

Compliance with ethical standards

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

Code availability Not applicable

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ORIGINAL ARTICLE

New-onset diabetes mellitus after liver transplantation in the patients with acute liver failure

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Abstract

Background To detect the frequency and possible risk factors of new-onset diabetes after liver transplantation in the patients with acute liver failure. The frequency of new-onset diabetes after transplant (NODAT) is 5–30% in liver transplant recipients. We aimed to analyze the frequency and predictors of NODAT in the patients undergoing liver transplantation due to acute liver failure.

Methods Adult patients undergoing liver transplantation due to acute liver failure were analyzed retrospectively. The patients with chronic liver failure or diabetes were excluded. We measured pretransplant random blood glucose and posttransplant fasting blood glucose. NODAT was diagnosed according to principally 1st month fasting blood glucose (group 1 < 100, group 2 100–125, group 3 > 125 mg/dL). The participants were subgrouped according to age, gender, body mass index, etiology, antiviral medication, thyroid function, pretransplant random blood glucose, donor type, immunosuppressive drug, common infection, and surgical complication.

Results Mean age of total 91 patients was 33.48 (± 13.35), and 52.7% ($n = 48$) of them was female. The ratio of NODAT was 26.98% on the 1st month. NODAT group had a higher pretransplant random blood glucose than the others. Pretransplant hyperglycemia increased the risk of NODAT by 4.065 times ($p = 0.018$).

Conclusion We showed that pretransplant hyperglycemia increased NODAT risk by 4 times, but hypoglycemia did not affect. So, pretransplant hyperglycemia should be controlled also in the patients with acute liver failure as in the patients with chronic liver failure.

Keywords NODAT · Acute liver failure · Liver transplant · Posttransplant diabetes · New onset diabetes · Diabetes mellitus

Introduction

New-onset diabetes after transplant (NODAT) may develop in the patients after transplantation of solid organs such as the liver, kidney, bone marrow, lung or heart [1–4]. It may be diagnosed with the same criteria as the nontransplant population at any time after transplantation [5]. However, oral glucose tolerance test may be sensitive but not a practical method

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for transplant patients, and HbA1c may be used for the diagnosis after 3rd month of transplantation [6]. The prevalence of NODAT was found as 5–30% in liver transplant recipients [7, 8]. Several pretransplant (prediabetes, obesity, hypertension, dyslipidemia, or HCV infection) and posttransplant (immunosuppressive drugs, weight gain, CMV infection, acute rejection) factors had been defined to increase the risk for new-onset diabetes after liver transplantation (LTx) [1, 3].

NODAT was shown to be associated with higher rate of rejection, cardiovascular morbidity, fatal infections, neurological complications, poor graft survival, and mortality in liver transplant recipients [3, 9]. Therefore, it should be detected and managed properly. Diabetes mellitus should be managed with lifestyle changes as well as pharmacological treatment, and they may be considered also for NODAT [5, 7, 10, 11].

LTx may be indicated in the patients with acute liver failure (ALF), cirrhosis, hepatic neoplasm, or metabolic liver disease [7]. Hence, the patients with ALF is one of the potential populations for the development of new-onset diabetes after LTx. Cause and effect relationship between diabetes mellitus and ALF has not been clarified in previous studies [12, 13]. Due to a defect in glycogenolysis and gluconeogenesis, hypoglycemia may be observed in ALF at a rate of about 45% [14]. In ALF, pretransplant glycemic status may be different from that in chronic liver failure. Hence, the frequency of NODAT may be expected to be different in the patients with ALF from those with chronic liver failure.

However, the frequency of NODAT has not been studied yet comparatively in acute or chronic liver failure [7, 8]. No study has focused on new-onset diabetes mellitus after liver transplantation in the patients with acute liver failure. There is no report analyzing the risk factors of NODAT in this patient population. We aimed to analyze the frequency of and the clinical and laboratory features associated with new-onset diabetes mellitus after liver transplantation in the patients with acute liver failure.

Materials and methods

Adult patients who were admitted to our clinics (of Inonu University Medical Faculty) with a diagnosis of ALF and underwent LTx between 2010 and 2018 were included in our study. Our study was designed as retrospective, observational, cross-sectional study, and approved by the Ethics Committee of Inonu University (Malatya Clinical Researches Ethics Committee). We performed our study in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

ALF may be defined as coexistence of severe acute liver injury, hepatic encephalopathy, and dysfunction of hepatic synthesis of proteins and coagulation factors (international normalized ratio ≥ 1.5) in the patients without preexisting liver disease [15, 16]. We diagnosed the patients as ALF based on the clinical and laboratory features, and duration cutoff to discriminate ALF from chronic liver disease was defined as 26 weeks. The causes of ALF were defined as Budd-Chiari syndrome (BCS), acute viral hepatitis, drugs and toxins, and the other/unknown etiological factors in our study. The patients younger than 18-year-old, those with chronic liver failure, known type 1 or 2 diabetes mellitus, who had been taking any antidiabetic regimen, or lacking data were excluded from the study.

Basic demographic (age) and clinical (height, weight, body mass index) features were recorded preoperatively and analyzed. Body weight (kg) and height (m) were measured with patient barefoot and having light clothes. Body mass index (BMI) was calculated as weight/square of height (kg/m^2).

We measured random venous blood glucose (RBG) before LTx on admission and fasting blood glucose (FBG) on the 1st and 7th day, on the 1st, 3rd, and 12th month of LTx after an overnight fasting for at least 8 h. Based on the diagnostic criteria of diabetes mellitus, we evaluated the patients according to FBG levels: < 100 mg/dL as normal FBG, 100–125 mg/dL as prediabetes, ≥126 mg/dL as NODAT [5]. We mainly grouped the patients by FBG level on 1st month (group 1 < 100 mg/dL normal FBG, group 2 100–125 mg/dL prediabetes, group 3 ≥ 126 mg/dL NODAT). We analyzed the patients principally according to the 1st month FBG. We could not measure FBG before LTx due to inappropriate clinical condition of the patients. We could not analyze HbA1c levels. We also analyzed donor FBG. Blood glucose was designated as mg/dL, TSH mIU/L, free T4 (fT4) ng/dL, and free T3 (fT3) pg/mL. Blood glucose was measured from venous blood sample by glucose oxidase method with the Olympus AU-2700 analyzer. TSH, fT4, and fT3 were measured with chemiluminescence method by using the Beckman Coulter marked and DxI 800 model device (Beckman Coulter, Inc. 4300 N. Harbor Blvd., Fullerton, CA 92835, USA). The reference range of our laboratory was used to determine the upper and lower limit of normal for all laboratory parameters.

The participants were grouped according to age (< 40 vs ≥ 40), gender (female vs male), BMI (< 30 vs ≥ 30 kg/m^2), etiology (other vs acute viral hepatitis), antiviral medication (absence vs presence), thyroid function (euthyroid vs subclinical thyrotoxicosis), pretransplant RBG (hypoglycemia < 54/≥ 54 or < 70/≥70 mg/dL, or hyperglycemia < 200/≥ 200 mg/dL), donor type (cadaver vs living donor), immunosuppressive drug (other vs tacrolimus), common infection (absence vs presence), and surgical complication (absence vs presence). Subclinical thyrotoxicosis was defined as TSH lower than normal limits, with fT4 and fT3 levels in the reference range. We defined pretransplant hypoglycemia according to alert value (70 mg/dL) or clinically important hypoglycemia threshold (54 mg/dL) based on the report of International Hypoglycemia Study Group [17]. We defined common

infection as upper respiratory or urinary tract infection and surgical complication as common biliary or vascular complications which might be observed in the postoperative period.

Statistical analysis

SPSS 22.0 (IBM Corporation, Armonk, NY, USA) program was used in the analysis of data. We used Shapiro-Wilk test to assess whether the data showed normal distribution or not. Homogeneity of variance was evaluated by Levene test. We used Mann-Whitney *U* test when comparing independent two groups according to quantitative data, Kruskal-Wallis for comparison of more than 2 groups. In comparison of categorical variables, each other, Pearson Chi-Square test was used. To analyze the correlations of variables with each other, Spearman's correlation (r) analysis was used. To determine the risk groups for parameters affecting the development of NODAT according to posttransplant 1st month FBG, we used univariate logistic regression analysis. Multivariate test was not applicable. Odds ratio (OR) was used with 95% confidence intervals (CI) to show that risk groups had how higher risk than the other subjects. Quantitative variables were defined as mean (X) ± standard deviation (SD) in the tables. Categorical variables were demonstrated as number (n) and percent (%), and p value of < 0.05 was accepted as statistically significant.

Results

Of total 91 patients, 52.7% ($n = 48$) was female and mean age was 33.48 (± 13.35). The etiology of ALF was BCS in 3(3.29%) patients, acute viral hepatitis in 38(41.75%), drug or toxin-related in 21(23.07%), and other/unknown causes in 29(31.86%) patients.

Of total 91 patients, transplantation was performed from living donors in 59 patients. All living donors in our study were related to the recipient (living related donor), and degree of relation was as follows: 18 living related donors (LRD) were 1st degree relative, 22 LRD 2nd degree relative, 4 LRD 3rd degree relative, 3 LRD 4th degree relative (cousin), 3 LRD relative-in-law, and 9 LRD husband-wife.

A total of 11(12.08%) patients died in the 1st week, 28(30.76%) in the 1st month, 36 (39.56%) in 3 months, and 43(47.25%) in 12 months of LTx. The mortality rate was higher in 1st month in the patients with pretransplant hypoglycemia than in the remainder (42.85 vs 29.76%).

The ratio of prediabetes and NODAT in survivors of LTx was 23.07% and 67.03% on the 1st day, 28.75% and 58.75% on the 1st week, 36.5% and 26.98% on the 1st month, 32.72% and 14.54% on 3rd month, and 20.83% and 8.3% on 12th month.

Pretransplant RBG was significantly higher in group 3 than in group 2 ($p = 0.041$) or in group 1 ($p = 0.022$); 3rd month FBG was significantly higher in group 3 than in group 1 ($p = 0.018$); 12th month FBG was significantly higher in group 2 ($p = 0.037$) or group 3 ($p = 0.006$) than in group 1. Age, gender, body weight, BMI, thyroid function tests, and donor FBG were similar in all groups (Table 1).

Among survivors on 12th month of LTx, NODAT persisted in 3, changed to prediabetes in 1, and then turned to normal FBG in 5 patients. Prediabetes persisted in 7, changed to normal FBG in 10, to NODAT in 1 patient. Normal FBG persisted in 19 patients and changed to prediabetes in 2 patients.

There were no significant predictors for NODAT in 1st day (not demonstrated on the table). Pretransplant hyperglycemia was found as a positive predictor for NODAT (OR 4.065, 95% CI, $p = 0.018$) (Table 2).

Pretransplant RBG was positively correlated with 1st month ($p = 0.014$) and 3rd month FBG ($p = 0.043$) (Table 3).

Discussion

We found that the frequency of NODAT was about 70% on 1st day and decreased progressively until the 12th month. Those without diabetes on the 1st month had almost stable normoglycemia on the 12th month. We showed that pretransplant hyperglycemia increased the risk of NODAT by 4 times, but pretransplant hypoglycemia was not a predictor for NODAT.

Several pretransplant (age, family history of diabetes, obesity, hypertension, dyslipidemia) and posttransplant (immunosuppressive drugs, CMV infection, acute rejection) risk factors were shown to be important in the occurrence of NODAT [18, 19]. Studies analyzing NODAT usually included a mixed study sample consisting of patients with acute or chronic liver failure [3, 9, 19, 20]. There is no report that focuses NODAT in the patients with ALF.

In ALF, hypoglycemia may be observed due to depleted glycogen stores, a defect in glycogenolysis and gluconeogenesis, and as high as 45% [14]. Increased level of serum insulin may also contribute to the development of hypoglycemia in ALF [21, 22]. We proposed that catabolic state contributing hypoglycemia in the patients with ALF might continue after LTx, and it might blunt the development of hyperglycemia. However, we showed that preoperative hypoglycemia did not have any negative impact on NODAT. Due to that a higher mortality rate was observed in the patients with pretransplant hypoglycemia than the rest, the effect of pretransplant hypoglycemia on NODAT might be underestimated.

Perioperative hyperglycemia was known as a risk factor for NODAT [23]. In one study, transplant candidates with impaired glucose tolerance which was detected by glucose load

Table 1 Comparison of demographic, clinical and laboratory parameters according to the 1st month FBG

	1st month FBG groups				
	Group 1 (n =23)	Group 2 (n=23)	Group 3 (n =17)	Total (n =63)	p value
	***X* (± SD)**				
Age	29.43 (8.46)	34.39 (16.18)	37.71 (13.73)	33.48 (13.35)	0.223
Body weight	70.96 (8.37)	73.17 (10.27)	74.14 (11.72)	72.63 (9.97)	0.528
BMI	25.58 (2.07)	25.75 (2.69)	26.32 (2.47)	25.84 (2.40)	0.556
TSH	1.25 (0.63)	1.08 (0.87)	1.28 (1.13)	1.19 (0.87)	0.329
fT4	1.07 (0.18)	1.11 (0.18)	1.09 (0.18)	1.09 (0.17)	0.703
fT3	3.18 (0.37)	3.01 (0.61)	3.11 (0.65)	3.10 (0.54)	0.737
Donor FBG	105.43 (15.63)	104.69 (18.49)	116.80 (25.58)	108.96 (20.70)	0.409
Pretransplant RBG	92.52 (36.20)	98.43 (29.60)	128.53 (56.59)	104.40 (42.75)	0.044*+
1st day FBG	182.22 (92.60)	174.70 (54.62)	179.59 (80.94)	178.76 (76.18)	0.888
1st week FBG	137.83 (50.51)	151.91 (47.06)	145.41 (33.88)	145.02 (44.99)	0.547
1st month FBG	83.83 (7.32)	111.39 (8.28)	161.29 (28.89)	114.79 (34.81)	0.00
3rd month FBG	95.36 (23.16)	111.0 (28.13)	115.67 (38.42)	105.76 (29.65)	0.038**
12th month FBG	89.29 (7.95)	98.5 (16.83)	107.22 (20.79)	96.10 (15.80)	0.011++***
	N				*p* value
Gender (female/male)	12/11	10/13	9/8	31/32	0.787

*$p = 0.022$ (groups 1–3), $^{+}p = 0.041$ (groups 2–3), **$p = 0.018$ (groups 1–3), $^{++}p = 0.037$ (groups 1–2), ***$p = 0.006$ (groups 1–3)

were found to have an increased risk for posttransplant diabetes [24]. We showed that pretransplant hyperglycemia increased NODAT by approximately 4–fold. However, in the preoperative setting, we measured only random blood glucose but could not perform oral glucose tolerance test because of unstable clinical condition. Hypoglycemia may frequently be seen in the clinical setting of ALF and may be a confounding factor which affects the association between NODAT and ALF. When a patient is admitted to hospital in the situation of ALF, it is mandatory to manage hypoglycemia and other clinical consequences of ALF. Intravenous fluids including dextrose or isotonic fluids, or parenteral nutrition may be

Table 2 Pretransplant and posttransplant factors affecting the development of NODAT according to the 1st month FBG

Variables	Number	Univariate	
		OR (95% CI)	p value
Pretransplant			
Age (<40/≥40)	47/16	1.964 (0.582–6.629)	0.273
Gender (female/male)	31/32	0.815 (0.267–2.483)	0.718
BMI (<30/≥30)	61/2	2.813 (0.166–47.65)	0.456
Etiology (other/acute viral hepatitis)	34/29	0.764 (0.248–2.354)	0.638
Antiviral medication (absence/presence)	56/7	1.093 (0.191–6.249)	0.920
Subclinical thyrotoxicosis (absence/presence)	52/10	2.000 (0.487–8.211)	0.330
Hypoglycemia (<54/≥54)	4/59	0.712 (0.605–0.837)	0.209
Hypoglycemia (<70/≥70)	7/56	3.368 (0.389–29.18)	0.247
Hyperglycemia (absence/presence)	58/5	0.246 (0.158–0.382)	0.018
Donor type (cadaver/living)	18/45	4.000 (0.811–19.71)	0.073
Posttransplant			
Immunosuppressive (other/tacrolimus)	6/56	2.000 (0.216–18.48)	0.534
Common infection (absence/presence)	33/29	1.955 (0.630–6.068)	0.243
Surgical complication (absence/presence)	48/14	1.077 (0.287–4.043)	0.913

Table 3 Correlation of clinical and laboratory parameters

Variables	Age r (p)	Weight	Height	BMI	TSH	fT4	fT3	Pretransplant RBG	Donor FBG
Age	1.000	0.244 (0.020)	0.138 (0.192)	0.214 (0.041)	0.249 (0.017)	−0.119 (0.263)	−0.187 (0.076)	0.093 (0.379)	0.084 (0.527)
Weight	0.244 (0.020)	1000	0.668 (0.00)	0.713 (0.00)	0.092 (0.385)	−0.112 (0.290)	−0.025 (0.815)	0.075 (0.482)	0.412 (0.001)
Height	0.138 (0.192)	0.668 (0.00)	1000	0.048 (0.654)	0.036 (0.732)	0.036 (0.732)	−0.054 (0.609)	−0.143 (0.177)	0.372 (0.004)
BMI	0.214 (0.041)	0.713 (0.00)	0.048 (0.654)	1.000	0.088 (0.409)	−0.179 (0.090)	0.046 (0.664)	0.201 (0.056)	0.205 (0.120)
TSH	0.249 (0.017)	0.092 (0.385)	0.036 (0.732)	0.088 (0.409)	1000	−0.130 (0.219)	0.163 (0.124)	0.088 (0.407)	0.063 (0.635)
fT4	−0.119 (0.263)	−0.112 (0.290)	0.036 (0.732)	−0.179 (0.090)	−0.130 (0.219)	1000	−0.106 (0.315)	−0.158 (0.134)	−0.104 (0.431)
fT3	−0.187 (0.076)	−0.025 (0.815)	−0.054 (0.609)	0.046 (0.664)	0.163 (0.124)	−0.106 (0.315)	1000	0.109 (0.305)	0.224 (0.087)
Pretransplant RBG	0.093 (0.379)	0.075 (0.482)	−0.143 (0.177)	0.201 (0.056)	0.088 (0.407)	−0.158 (0.134)	0.109 (0.305)	1.000	0.202 (0.125)
Donor FBG	0.084 (0.527)	0.412 (0.001)	0.372 (0.004)	0.205 (0.120)	0.063 (0.635)	−0.104 (0.431)	0.224 (0.087)	0.202 (0.125)	1.000
1st day FBG	−0.056 (0.601)	0.110 (0.298)	−0.057 (0.593)	0.152 (0.149)	0.077 (0.470)	−0.033 (0.756)	0.207 (0.049)	0.140 (0.186)	0.154 (0.243)
1st week FBG	0.295 (0.008)	0.197 (0.080)	0.101 (0.371)	0.193 (0.086)	0.126 (0.267)	−0.131 (0.247)	0.010 (0.930)	0.046 (0.687)	0.174 (0.201)
1st month FBG	0.228 (0.072)	0.080 (0.535)	0.001 (0.994)	0.095 (0.458)	−0.148 (0.246)	0.010 (0.941)	−0.020 (0.876)	0.307 (0.014)	0.166 (0.276)
3rd month FBG	0.083 (0.545)	0.166 (0.225)	0.021 (0.877)	0.173 (0.207)	0.040 (0.773)	−0.195 (0.154)	0.001 (0.994)	0.273 (0.043)	0.164 (0.307)
12th month FBG	0.103 (0.486)	0.248 (0.090)	0.279 (0.055)	0.044 (0.768)	−0.164 (0.264)	0.009 (0.953)	−0.048 (0.746)	0.160 (0.279)	0.017 (0.922)

administered during perioperative period. Hence, It may be impossible to measure fasting blood glucose or perform glucose load after an overnight fasting. We showed that pretransplant glucose was associated with posttransplant FBG. The patients with normal FBG on the 1st month did not develop NODAT until the 12th month. Hence, perioperative glycemic regulation is important to prevent NODAT. However, it may be complicated to maintain a stable pretransplant glycemia in such a patient with ALF.

Timing of the test for diabetes mellitus may affect the diagnosis of NODAT and hence the frequency of it [1]. Perioperative stress may result in acute postoperative hyperglycemia. The effect of immunosuppressive drugs on glycemic status and dosage of them in the postoperative period may alter during the follow-up. Spontaneous remission may be observed in some patients with NODAT, especially after tapering the dose of immunosuppressive drugs [25]. In some studies, including renal transplant patients, NODAT was divided as early-onset, late-onset or temporary [26]. It may be thought that evaluation of post-transplant diabetes mellitus would be done under more stable clinical conditions. If rejection or surgical complications did not occur, NODAT might be recovered in most of the patients until the end of the 1st month [1]. Based on the previous reports, we evaluated NODAT based on the 1st month FBG. Our findings suggested the temporary alteration of NODAT.

We could measure only FBG in the posttransplant period, but we could not perform glucose load or HbA1c. Mortality rate was relatively high in posttransplant period in the patients with ALF. It was especially high in those with pretransplant hypoglycemia. One of the causes of unable to perform oral glucose tolerance test in the posttransplant period is the mortality rate. Immunosuppressive medications given after transplantation may contribute to development of overt diabetes in the posttransplant period. Together with other factors, overt diabetes occurs in the most patients. In case of overt diabetes, glucose load may be unnecessary in the postoperative period. In some patients, due to complications, the acuity of the situation may continue along a few weeks after transplantation. Therefore, oral glucose tolerance test may be inappropriate in these patients.

Pretransplant obesity, higher age, and gender were defined as risk factors for the development of NODAT [1]. We showed that obesity, gender, and older age (> 40) were not as significant predictors for NODAT. In one study, posttransplant 12th month BMI was also shown as an important factor for NODAT after LTx [8]. However, we could not analyze posttransplant BMI. Sick euthyroid syndrome was frequently observed in chronic liver disease, and free T3 level was shown to be corrected after LTx [27]. In one study, free T3 was significantly lower in the patients with HBV related acute-on-chronic liver failure than in chronic HBV infection [28]. Thyroid dysfunction was shown to be increased after

liver transplantation [29]. Systematic analysis of thyroid function tests in ALF is limited in the literature. Anastasiou et al. showed that the patients who recovered from ALF had higher TSH, total T4, and T3 levels than the patients undergoing LTx or died from ALF [30]. We showed that subclinical thyrotoxicosis was found in 15.38% of the patients; it was not a predictor for NODAT.

Strength and limitations

There is no previous report that focuses on the development of NODAT in the patients with ALF. To our knowledge, our study is the first to evaluate NODAT in a specific large group of the patients with ALF. We measured only random blood glucose but could not perform oral glucose load or HbA1c due to unstable clinical condition of the patients in the pretransplant setting. We could not analyze HbA1c or oral glucose load after LTx. Our study was designed as a retrospective manner, because prospective study design might be difficult in such a clinical condition of ALF.

Conclusion

Our findings suggested that NODAT was observed in more than 60% of the patients on 1st day, and the ratio was decreased progressively during follow-up. The patient without NODAT on the 1st month had almost stable normoglycemia on 12th month. Pretransplant hyperglycemia increased the risk of NODAT by 4 times, but pretransplant hypoglycemia did not have any protective role against NODAT. We recommend that perioperative glycemic regulation should be instituted to prevent the development of NODAT or at least to alleviate posttransplant hyperglycemia. It should be kept in mind that constitution of stable pretransplant glucose level in such a patient with ALF might be complicated. Prospective studies including patients with ALF will give a more detailed information about NODAT in this population.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

We had accepted that "the previous form" of our article could be located on a website of "https://www.researchsquare.com/article/rs-14864/v1" as a preprint, before we have submitted the article to your journal. We changed some parts of the article and title, before we have submitted our article to your journal. The authors assure that this paper has not been published before nor has been submitted for publication to another scientific journal.

The abstract of previous form of our article was accepted as an "Audio Electronic Poster" (AEP-306) with a heading of "New-Onset Diabetes Mellitus After Liver Transplantation In The Patients With Acute Liver Failure: Is There Any Effect Of Pretransplant Hypoglycemia?" in 2020 online congress of European Society of Endocrinology (e-ECE 2020).

Compliance with ethical standards

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

Ethics approval and consent to participate Our study was designed as retrospective manner, and we performed our study in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Our study was approved by the Ethics Committee of Inonu University (Malatya Clinical Researches Ethic Committee, approval date:04 January 2017, approval number:2017/11).

Human rights Due to the retrospective design of the study and the use of already available data, written informed consent was unavailable.

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ORIGINAL ARTICLE

Prevalence, risk factors and perinatal outcomes of gestational diabetes in Mexican adolescents when applying diagnostic criteria from three different international guidelines

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Abstract

Objective To compare the prevalence, risk factors and perinatal outcomes of gestational diabetes mellitus (GDM) for Mexican adolescent population when applying different diagnostic criteria based on the 2-h 75-g oral glucose tolerance test, as established by three international guidelines.

Materials and methods Comparative, observational, and retrospective study, which included pregnant women under 19 years, who underwent screening for GDM in our center. Data were obtained from the hospital's electronic records and were analyzed using descriptive statistics. The X^2 test was used to compare group proportions. Statistical significance was set at $p \leq 0.05$.

Results A total of 999 adolescents were screened for GDM. The observed prevalence was 3%, 14.4%, and 29.3% when using the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (FIWC), National Institute for Health and Care Excellence (NICE-2015), and International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, respectively. Of our sample, 42.5% presented at least one risk factor. An association was observed regarding the need for cesarean section in patients with GDM diagnosed through IADPSG criteria (OR = 1.35, $p = 0.04$). On the other hand, the use of the FIWC and NICE standards showed an association between GDM and obstetric hemorrhage (OR = 17.8, $p = 0.000$, and OR = 4.8, $p = 0.01$, respectively) and preeclampsia with severity criteria (OR = 5.1, $p = 0.001$, and OR = 2.4, $P = 0.025$, respectively).

Conclusions The prevalence of GDM in adolescents is high, and we can conclude that the prevalence varies based on which international diagnostic guideline is applied. While there is an association with adverse pregnancy outcomes such as hypertensive disorders of pregnancy, obstetric hemorrhage, and the need for cesarean section, this requires further evaluation.

Keywords Pregnancy · Diabetes gestational · Adolescent pregnancy · Pregnancy outcomes · Glucose tolerance test

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Introduction

Gestational diabetes mellitus (GDM) prevalence varies according to age, ethnic group, or location of the population under study, and the criteria used to define the diagnosis [1].

In 2013, the International Diabetes Federation (IDF) estimated that GDM affects 16.9% of women between 20 and 49 years old worldwide. Prevalence rates of GDM have been reported to be higher in Hispanic, African American, and Asian women [2]. A lower prevalence has been reported for adolescent women, between 0.85 and 1.2% [3, 4].

International diabetes mellitus guidelines do not specify the ideal age to start screening for gestational diabetes or the diagnostic criteria to use in young pregnant women [5].

In Mexico, teenage pregnancy rates have increased in the past decade, representing now one third of the total births in the country [6]. Commonly, these patients are not being screened for GDM because of their young age. Knowing that a high percentage of them might have an increased risk of developing gestational diabetes, it is of utmost importance to understand how the prevalence of this disease behaves when using different diagnostic criteria. It is also essential to determine how or if it relates to adverse perinatal results and which risk factors are present in our adolescent population, to be able to plan effective interventions.

Material and methods

The study included adolescent women whose prenatal care was performed in the same facility from May to December 2017. The data analyzed were obtained from the Fetal-Maternal Medicine Department files, as well as from the hospital's electronic medical records (EMR). The patients were included in our sample as they arrived at screening and obstetric control.

During the first prenatal care appointment, we registered family, medical, obstetric, and socioeconomic history, as well as body weight and height. Gestational age was calculated using the last menstrual period. If unknown or unreliable, gestational age was estimated by crown-rump length measured before the 14 weeks of gestation or cephalic circumference in the second trimester. As per hospital policy, due to a high prevalence of type II diabetes in the general population and the particular ethnic group that we are studying, and as part of the inclusion criteria for this study, a 2-h, 75-g OGTT was applied to every pregnant woman at her first prenatal visit, irrespective of gestational age, patient's age, or preexisting risk factors. The test was performed at the center's laboratory, with 8–12-h fasting and a regular diet for 3 days before the sample retrieval. GDM diagnosis was determined according to the Fifth International Workshop Conference on Gestational Diabetes Mellitus criterion (two or more altered values regarding serum glucose; fasting, ≥ 95 mg/dl, 1 h ≥ 180 mg/dl, and 2 h ≥ 155 mg/dl), and treatment was only administered to these patients groups. Treatment consisted of a low glycemic index diet provided by the clinical nutrition department, with monitoring every 2–4 weeks, alongside obstetric and fetal medical checkups. Two different methods evaluated plasma glucose levels: (1) fasting and 2 h after breakfast glucose levels from venous blood were obtained at their perinatal checkup; (2) glucose self-monitoring with a glucometer 2 to 6 times a day (after overnight fast, 2 h after breakfast, 2 h after lunch, and 2-h after dinner). Patients who reported fasting glucose levels ≥ 95 mg/dl and/or 2-h postprandial ≥ 140 mg/dl or a self-monitoring reporting 30% higher glucose levels than the first reported were prescribed metformin (1000–2550 mg per day). In case of noncompliance or failure to achieve the goal glucose levels, human regular and NPH insulin was prescribed subcutaneously.

The primary objective of this study was to assess and compare gestational diabetes mellitus prevalence in a Mexican teenager population when applying three different international criteria based on their 75-g OGTT results. Women were retrospectively assigned to the following study groups:

1) International Association of Diabetes and Pregnancy Study Groups (IADPSG): One or more altered values, regarding serum glucose; fasting, ≥ 92 mg/dl, 1 h ≥ 180 mg/dl, and 2 h ≥ 153 mg/dl [7]
2) National Institute for Health and Care Excellence (NICE-2015): One altered value regarding serum glucose; fasting, ≥ 100 mg/dl and/or 2 h ≥ 140 mg/dl [8]
3) Fifth International Workshop-Conference on Gestational Diabetes Mellitus (FIWC GDM): Two or more altered values regarding serum glucose; fasting, ≥ 95 mg/dl, 1 h ≥ 180 mg/dl, and 2 h ≥ 155 mg/dl [9]

The presence of risk factors for developing gestational diabetes mellitus, such as the family history of type 2 diabetes mellitus, prior history of gestational diabetes or macrosomic newborn, and body mass index > 25, was also documented.

Our secondary objective was to analyze the relationship between positive screening with each diagnostic criterion and the following adverse perinatal results:

(1) Pregnancy-associated hypertensive disorder (preeclampsia with or without severity criteria or gestational hypertension) according to American College of Obstetrics and Gynecology criteria [10]; (2) obstetric hemorrhage, blood loss ≥ 500 ml during vaginal birth and ≥ 1000 ml during cesarean section, as defined by American College of Obstetrics and Gynecology [11]; (3) large for gestational age newborn, considering birth weight greater than 90th percentile based on the

Table 1 General characteristics of pregnant adolescents at the time of their first prenatal care visit

Characteristics	M ± SD/frequency (%) $n = 999$	Range
Age	17.36 ± 1.32	12–19
Height (cm)	158.19 ± 6.13	138–183
Weight (kg)	64.29 ± 13.28	38–127
BMI	25.65 ± 4.81	14.66–46.37
First pregnancy	794 (79.4)	–
Second pregnancy	180 (18.01)	
Third pregnancy	21 (2.10)	
Fourth pregnancy	4 (0.40)	
Gestational age at the time of OGTT	32.4 ± 7.0	(7.5–40.5)
Number of risk factors		
0 Risk factor	574 (57.46)	
1 Risk factor	358 (35.84)	-
2 Risk factors	65 (6.5)	
3 Risk factors	2 (0.20)	

BMI body mass index; *OGTT* oral glucose tolerance test

Mean ± standard deviation and/or frequency (%)

international newborn size standards from the Project INTERGROWTH-21st [12]; (4) small for gestational age newborn, defined as birth weight ≤ 10th percentile based on the international newborn weight standards from the Project INTERGROWTH-21st [12]; (5) preterm rupture of membranes [13]; (6) birth by cesarean section; (7) preterm birth before 37 weeks of gestation; (8) fetal death, (9) Apgar ≤ 7 at 5 min; (10) congenital defects, defined as abnormalities to bodily structure detected by prenatal sonography or at the moment of birth [14].

The sample size was calculated using the Epi Info® software as 775, for a prevalence rate of gestational diabetes mellitus of 14%, with a 99% confidence interval, a 3% margin of error, and a total population of 5061 pregnant teenagers. Every patient meeting selection criterion was included in the study.

For group analysis, descriptive statistics was used, with mean and standard deviation for quantitative variables and frequency with percentage for qualitative variables. We used a chi-square (X^2) test to compare proportions between different groups and Student's t or Mann Whitney-U test to compare group means. Statistical significance was set at $p \leq 0.05$. The odds ratio was calculated with 95% CI, using 2 × 2 contingency tables, using IBM SPSS 25 (Statistical Package or the Social Sciences) software.

Results

The analysis included a total of 999 adolescents who matched inclusion criteria; from this group, 79.4% were pregnant for the first time. The mean gestational age at the time of OGTT was 32 ± 4 weeks. General characteristics of the patients at the first prenatal visit are summarized in Table 1.

Gestational diabetes mellitus prevalence was 3% (30/999), 14.4% (144/999), and 29.3% (293/999) when using the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (FIWC), National Institute for Health and Care Excellence (NICE 2015), and International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, respectively, with fasting glucose being the most frequently altered (Table 2). The mean gestational age at which OGTT was performed was 32.4 weeks, with 13.1% of the tests having been made before week 24. Out of the total, 315 cases (31.5%) presented with one or more GDM diagnostic criteria, with 28 cases (8.8%) that had all of the different criteria. All of the cases positive through FIWC were also positive by IADPSG and NICE. Only 22 cases (7%) of the total presented diagnostic criteria exclusively for NICE (Fig. 1).

In all, 42.5% of the participants presented at least one risk factor for gestational diabetes, having a first-degree family member with diabetes being the most frequent, present in 32.8% of patients, followed by obesity (BMI ≥ 30) in 18.4% (Table 3). Obesity presence was higher in patients positive for GDM by any one of the three criteria ($p < 0.05$). Maternal weight during the first checkup and BMI were significantly higher in those patients who had the criteria for GDM by IADPSG and NICE, while the family history of diabetes mellitus as a risk factor was only significantly higher in the patients diagnosed by IADPSG. The history of macrosomia as a risk factor was higher in patients diagnosed by FIWC and NICE (Table 3).

The percentage of live births at term was 94.8% (947), of which 261 (26.1%) were delivered by cesarean section. Median birth weight was 3141 g, with 31 (3.1%) large for gestational age newborns (≥ percentile 90) and 82 (8.2%) small for gestational age newborns (≤ percentile 10). In 92

Table 2 Gestational diabetes prevalence in adolescent patients using all three diagnostic criteria methods

Gestational week during which OGTT was applied $n = 999(\%)$	Total	IADPSG	FIWC	NICE
< 24 weeks	GDM (+) 58	GDM (+) 55	GDM (+) 8	GDM (+) 26
$n = 131$ (13.1)	GDM (−) 73	GDM (−) 76	GDM (−) 123	GDM (−) 105
OGTT (+)	58 (44.3)	55 (42)	8 (6.1)	26 (19.8)
FPG	-	48	-	17
1H	-	0	-	0
2H	-	0	-	4
Any 2 values elevated	-	4	5	5
All 3 values elevated	-	3	3	0
OGTT (−)	73 (55.7)	76 (58)	123 (93.9)	105 (80.2)
24–28 weeks	GDM (+) 126	GDM (+) 120	GDM (+) 11	GDM (+) 53
$n = 401$ (40.1)	GDM (−) 275	GDM (−) 281	GDM (−) 390	GDM (−) 348
OGTT (+)	126 (31.4)	120 (30)	11 (2.7)	53 (13.2)
FPG	-	98	-	27
1H	-	4	-	-
2H	-	1	-	16
Any 2 values elevated	-	11	5	10
All 3 values elevated	-	6	6	-
OFTT (−)	275 (68.6)	281 (70)	390 (97.3)	348 (86.8)
> 28 weeks	GDM (+) 131	GDM (+) 118	GDM (+) 11	GDM (+) 65
$n = 467$ (46.7)	GDM (−) 336	GDM (−) 349	GDM (−) 456	GDM (−) 402
OGTT (+)	131 (28)	118 (25.2)	11 (2.4)	65 (14)
FPG	-	103	-	31
1H	-	2	-	--
2H	-	0	-	24
Any 2 values elevated	-	12	11	10
All 3 values elevated	-	1	0	-
OGTT (−)	336 (72)	349 (74.8)	456 (97.6)	402 (86)
Total OGGT (+)	315 (31.5)	GDM (8+) 293 (29.3)	GDM (+) 30 (3)	GDM (+) 144 (14.4)

Patients were divided by gestational week at the time of the test (< 24 weeks, 24–28 weeks, and ≥ 24 weeks) and by plasma glucose values from the 2-h, 75-g OGTT. *GDM* gestational diabetes mellitus, *OGTT* oral glucose tolerance test, *IADPSG* International Association of Diabetes and Pregnancy Study Groups, *FIWC* Fifth International Workshop-Conference on Gestational Diabetes Mellitus, *NICE* National Institute for Health and Care Excellence, *FPG* fasting plasma glucose

(9.2%) cases, pregnancy was complicated with a hypertensive disorder; also, a structural fetal abnormality was present in 10 (1%) of cases, and in 5 (0.5%) cases, there was fetal death (Table 4).

As shown in Table 5, using the IADPSG criteria, an association was established between GDM and the increased risk of undergoing cesarean section (OR 1.35, $p = 0.04$). No other adverse outcomes were found to be related to GDM using these criteria. On the other hand, obstetric hemorrhage and preeclampsia with severity criteria were observed in association with DMG when diagnosed using FIWC ([OR 17.8, $p = 0.000$]) and ([OR 5.1, $p = 0.001$]) and NICE criteria ([OR 4.8, $p = 0.010$]) and ([OR 2.4, $p = 0.025$]).

Hypertensive disorders developed during pregnancy were only associated with diagnosis by FIWC (OR 2.05, $p = 0.038$). There were no other significant differences in maternal and fetal outcomes.

Birth weight percentile and neonatal complications were not significantly higher for any diagnostic criteria.

Discussion

Worldwide, gestational diabetes prevalence diagnosed when using IADPSG criteria varies from 3.5 to 45.3% for the general population depending on the country under study [15].

In Mexico, DMG prevalence varies according to the studied region. Reyes-Muñoz et al. [16] studied gestational diabetes in central Mexico and found a 6.3% prevalence, using the IADPSG criteria, and 0.2% with FIWC criteria, with no association between DMG and adverse outcomes. Our study was conducted in northern Mexico in a close-to-USA city. We observed a 5-fold increase in prevalence (29.3% vs. 6.3%), when compared with central Mexico, according to the IADPSG criteria [16]. Although GDM prevalence increases with age [4], the rates observed in our teenage population are similar to the reported for adults in central Mexico (29.3% vs. 30%), according to IADPSG.

Several lines of research, both prospective and retrospective in design, have analyzed the relationship between gestational

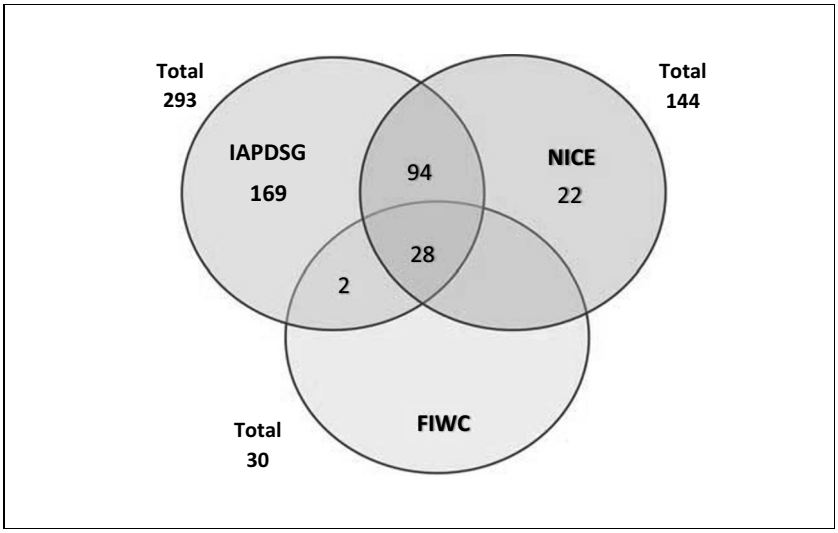

Fig. 1 Gestational diabetes prevalence according to the three diagnostic criteria and their overlapping

diabetes and adverse perinatal outcomes in the general population using IADPSG criteria. These studies have found a heightened risk for polyhydramnios [17], preeclampsia [18], first-time cesarean section [18], large for gestational age newborns [18], and preterm birth [19]. In our research, screening using IADPSG was only associated with an increase in cesarean section form of delivery. Also, when applying other criteria such as FIWC and NICE, GDM increase in obstetric hemorrhage and preeclampsia with severity risk were observed.

Table 3 Risk factors for gestational diabetes identified at the first prenatal care checkup grouped according to the GDM classification

	Total $n = 999$	IADPSG		p value	FIWC		p value	NICE		p value
		GDM (−) 706 (70.6)	GDM (+) 293 (29.3)		GDM (−) 969(97)	GDM (+) 30(3)		GDM (−) 855 (85.5)	GDM (+) 144 (14.4)	
Weight (Kg)	64.29 ± 13.26 (38–127)	63.10 ± 12.65 (38.3–127)	66.7 ± 14.38 (38–114.9)	*0.001*	64.17 ± 13.08 (38–127)	68.3 ± 17.94 (42–100.5)	0.389	63.85 ± 12.97 (38–127)	66.95 ± 14.63 (42–114.9)	*0.022*
Height (cm)	158.19 ± 6.13 (138–183)	158.06 ± 6.1 (138–183)	158 ± 6.1 (144–179)	0.448	158 ± 6.1 (138–183)	157.67 ± 5.9 (147–167)	0.743	158.11 ± 6.1 (138–183)	158.66 ± 5.9 (144–172)	0.273
BMI	25.65 ± 4.81 (15.1–46.4)	25.29 ± 4.56 (15.10–46.37)	26.52 ± 5.29 (15.22–46.03)	*0.002*	25.60 ± 4.74 (15.10–46.37)	27.41 ± 6.67 (16.41–39.93)	0.192	25.49 ± 4.71 (15.1–46.4)	26.58 ± 5.30 (16.4–46)	*0.025*
Obesity BMI										
< 30	815(81.5)	606 (85Y .8)	213 (72.7)	*0.000*	797 (82.2)	19 (63.3)	*0.008*	709(82.9)	107(74.3)	*0.013*
≥ 30	184(18.4)	103 (14.6)	80 (27.3)		172 (17.8)	11 (36.7)		146(17.1)	37(25.7)	
Family history for DM										
Negative	671(67.1)	488 (69.1)	183 (62.5)	*0.041*	655 (67.6)	16 (53.3)	0.101	580(67.8)	91(63.2)	0.272
Positive	328(32.8)	218 (30.9)	110 (37.5)		314 (32.4)	14 (46.7)		275(32.2)	53(36.8)	
Macrosomia in previous pregnancies										
Negative	992(99.3)	703 (99.6)	289 (98.6)	0.105	964 (99.5)	28 (93.3)	*0.000*	852(99.6)	140(97.2)	*0.001*
Positive	7(0.70)	3 (0.4)	4 (1.4)		5 (0.5)	2 (6.7)		3(0.4)	4(2.8)	
No. Pregnancy										
<3	974(97.5)	691 (97.9)	283(96.6)	0.235	945 (97.5)	29 (96.7)	0.767	834(97.5)	140(97.2)	0.819
≥3	25(2.5)	15 (2.5)	10 (3.4)		24 (2.5)	1 (3.3)		21(2.5)	4(2.8)	

BMI body mass index, *OGTT* oral glucose tolerance test, *IADPSG* International Association of Diabetes and Pregnancy Study Groups, *FIWC* Fifth International Workshop-Conference on Gestational Diabetes Mellitus, *NICE* National Institute for Health and Care Excellence

Mean ± standard deviation and/or frequency (%)

Values in italics in Tables 3 and 5 indicate statistically significant difference ($P \leq 0.05$)

Table 4 Perinatal outcomes in adolescent woman

	M ± SD/frequency (%) $n = 999$	Range
Delivery mode		
Cesarean section	261 (26.1)	
Vaginal birth	738 (73.9)	
Gestational age at birth	39.2 ± 1.7	24–42
Preterm birth	52 (5.2)	
Newborn weight (g)	3141 ± 484	300–4660
Fetal malformations	10 (1)	
Skeletal dysplasia	1	
Fetal cardiopathy	1	
Severe ventriculomegaly	1	
Omphalocele	1	
Gastroschisis	2	
Abdominal tumor	1	
Body stalk	1	
Limb body wall complex	1	
Fetal hydrops	1	
Hypertensive disorder of pregnancy	92 (9.2)	
Gestational hypertension	8	
Preeclampsia with severity criteria	29	
Eclampsia	3	
Preeclampsia without severity criteria	52	
Apgar 5 min ≤ 7	56 (5.6)	
Large for gestational age (≥ percentile 90)	31 (3.1)	
Small for gestational age (≤ percentile 10)	82 (8.2)	
Fetal death	5 (0.5)	

Mean ± standard deviation and/or frequency (%)

Although only patients who met the FIWC criteria received treatment for gestational diabetes, it was this group that presented the highest risk of preeclampsia with severity criteria (OR = 5.1). This higher risk might be related to the delayed treatment initiation after 28 weeks in 11 patients (36%). However, more studies are needed to confirm this association.

Our study shows how GDM risk factors by FIWC, obesity (BMI ≥ 30), and history of macrosomia, as well as obstetric complications, are also associated with the NICE criteria; this could be due to an overlapping of both diagnostic criteria, since 93.3% of the cases diagnosed by FIWC also present criteria for diagnosis by NICE.

Our study is the first one to analyze the differences in the prevalence of DMG among IADPSG, FIWC, and NICE diagnostic criteria using the 2-h, 75-g OGTT. Also, we consider our work to be the first one to investigate the association of GDM with alterations in birth weight using the international newborn weight standards from the INTERGROWTH-21 in teenage pregnancy [12].

Our study has two main limitations, including its retrospective nature and the wide time range in which the OGTT was performed. Since gestational diabetes diagnosis was made retrospectively according to both, the IADPSG and NICE criteria, the groups did not receive treatment. Despite this, patients in the IADPSG group did not show adverse perinatal outcomes compared with patients without the diagnosis. It only showed a higher rate in cesarean sections. We analyzed OGTT made between 7 and 40 weeks of gestation, with 21 positive cases (6.6%) meeting the IADPSG criteria before the 14th week, using elevated fasting glucose as the diagnostic criteria. This could slightly decrease the prevalence in this group, even though the IAPSG establishes that FPG > 92 mg/dl at any pregnancy week can diagnose gestational diabetes, Zhu et al. [20] reported in a study carried out in China that a cut-off point above 92 mg/dl during the first trimester may not be adequate for diagnosing GDM, since fasting glucose decreases as pregnancy progresses, with a plateau around 10–20 weeks. Therefore, fasting glucose level

Table 5 Comparison between complications during pregnancy and delivery in women screened positive and negative for gestational diabetes

Adverse perinatal result	Total $n = 999$	IADPSG				FIWC				NICE			
		DMG $n = 293$ (%)	Negative for DMG $n = 706$ (%)	OR	p value	DMG $n = 30$ (%)	Negative for DMG $n = 969$ (%)	OR	p value	DMG $n = 144$ (%)	Negative for DMG $n = 855$ (%)	OR	p value
Obstetric hemorrhage	9 (0.9)	5 (1.7)	4 (0.6)	3.04 (0.8–11.4)	0.08	3 (10)	6 (0.6)	*17.8 (4.2–75)*	*0.000*	4 (2.8)	5 (0.6)	*4.8 (1.2–18.3)*	*0.010*
Hypertensive disease in pregnancy	92 (9.2)	28 (9.6)	64 (9.2)	1.060 (0.6–1.6)	0.87	6 (20)	86 (8.9)	*2.05 (1.02–6.4)*	*0.038*	18 (12.5)	74 (8.7)	1.5 (0.87–2.6)	0.14
Preeclampsia with severity criteria	32 (3.2)	11 (3.8)	21 (3.0)	1.27 (0.6–2.6)	0.52	4 (13.3)	28 (2.9)	*5.1 (1.6–15.8)*	*0.001*	9 (6.3)	23 (2.7)	*2.4 (1.09–5.3)*	*0.025*
Large for gestational age newborn ($p \geq 90$)	31 (3.1)	11 (3.8)	20 (2.8)	1.3 (0.6–2.8)	0.44	2 (6.7)	29 (3)	2.3 (0.5–10)	0.25	6 (4.2)	25 (2.9)	1.4 (0.9–5.7)	0.42
Small for gestational age newborn ($p \leq 10$)	82 (8.2)	23 (7.8)	59 (8.4)	0.93 (0.5–1.5)	0.79	1 (3.3)	81 (8.4)	0.37 (0.05–2.85)	0.32	10 (6.9)	72 (8.4)	0.81 (0.4–1.6)	0.55
Premature rupture of membranes	36 (3.6)	12 (4.1)	24 (3.4)	1.2 (0.59–2.4)	0.59	2 (6.7)	34 (3.5)	1.9 (0.44–8.5)	0.36	5 (3.5)	31 (3.6)	0.95 (0.36–2.5)	0.927
Preterm birth < 37 weeks	52 (5.2)	19 (6.5)	33 (4.7)	1.4 (0.7–2.5)	0.24	3 (10)	49 (5.1)	2 (0.6–7.1)	0.23	7 (4.9)	45 (5.3)	0.92 (0.4–2.0)	0.84
Birth by Cesarean section	261 (26.1)	89 (30.4)	172 (24.4)	1.35 (1.0–1.8)	*0.049*	11 (36.7)	250 (25.8)	1.6 (0.7–3.5)	0.18	43 (29.9)	218 (25.5)	1.2 (0.8–1.8)	0.27
Stillbirths	5 (0.5)	2 (0.7)	3 (0.4)	1.6 (0.2–9.6)	0.59	0 (0)	5 (0.5)	–	–	0 (0)	5 (0.5)	–	–
Apgar 5 min ≤ 7	56 (5.6)	20 (6.8)	36 (5.1)	1.3 (0.7–2.3)	0.28	1 (3.3)	55 (5.7)	0.57 (0.07–4.2)	0.58	11 (7.6)	45 (5.3)	1.4 (0.7–2.9)	0.25
Fetal malformation	10 (1)	1 (0.3)	9 (1.3)	0.2 (0.03–2.1)	0.17	0	10 (1)	–	–	0	10 (1.1)	–	–

X^2 test. Statistical significance set at p value < 0.05

Values in italics in Tables 3 and 5 indicate statistically significant difference ($P \leq 0.05$)

during the first trimester is not consistent with fasting glucose between 24 and 28 weeks.

Our study shows a high percentage of Mexican pregnant teenagers present with several risk factors for developing gestational diabetes. This is concerning because teenagers who do develop the disease will have a heightened risk of developing chronic conditions, such as type 2 diabetes mellitus [21], cardiovascular disease, or chronic arterial hypertension [22, 23] later in life. Even when of reproductive age, in the future, these patients will have accumulated not only their preexistent risk factors, such as obesity, family history, and ethnicity but also the risk implied by having a previous history of gestational diabetes mellitus. Likewise, these long-term adverse health outcomes can also affect their children's future, as they may develop childhood obesity, glucose intolerance, and vascular disorders after birth [24]. The stakes for the public health system to change these probabilities are high, which calls for the instauration of efficient and integral strategies, starting at the first level of care and focusing on prevention, timely intervention, and identification of patients at risk.

Although the number of macrosomic newborns during the study was small, this is a risk factor for gestational diabetes. Therefore, it could be used as an indicator for early screening in future pregnancies.

Pregnant Mexican adolescents in northern Mexico were found, according to our data, to be at a heightened risk of developing gestational diabetes mellitus. They present with a high percentage of risk factors and a high prevalence of the disease, which is why we emphasize the need to perform OGTT in the adolescent Mexican population. When comparing different diagnostic criteria, gestational diabetes was associated with various adverse perinatal outcomes. We, therefore, recommend that every different region in Mexico should analyze their communities to screen for and analyze using 2-h, 75-g OGTT according to their resources.

Compliance with ethical standards

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

Ethical approval Approval was obtained from the ethics committee of the Hospital Regional Materno Infantil, Secretaria de Salud de Nuevo León, México. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Informed consent This research study employs retrospective and observational research techniques and methodology and does not carry out any intervention or intentional modification to physiological, psychological, or social variables to the participants. For this study, only an electronic file review was used for data collection, creating a database in which the names of the patients were not included. Informed consent is not required as long as the information is anonymized, and the submission does not include images that may identify the person.

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ORIGINAL ARTICLE

Prevalence of diabetes mellitus and hypertension during pregnancy in eastern China after the implementation of universal two-child policy

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Abstract

Aims Few studies have assessed the prevalence of diabetes and hypertension among pregnant women in China after the implementation of universal two-child policy. Therefore, the aim of the study was to determine the prevalence of diabetes and hypertension from 2016 to 2018 among pregnant women in Jiangsu, China, after the policy implementation.

Methods We analysed data from pregnant women who delivered their neonates between 2016 and 2018 in the Northern Jiangsu People's Hospital. All pregnant women irrespective of their gestation weeks underwent oral glucose intolerance tests in a fasting state.

Results A total of 3262 pregnant women were included. The overall prevalence of diabetes and hypertension in pregnant women was 21.8% and 2.4%, respectively. In addition, the prevalence of low birth weight (LBW) and macrosomia for participants with diabetes was significantly higher than those without diabetes (LBW: 4.4. vs. 2.6%, $p = 0.017$; macrosomia: 10.1 vs. 5.8%, $p < 0.001$). There was a significant increasing trend in the prevalence of diabetes, which was from 18.9% in 2016 to 25.4% in 2018 ($p < 0.001$). Similarly, there was also a significant increasing trend in the prevalence of diabetes across the increasing age group (from 16.4% in 18–24 years to 47.6% in 40–45 years) ($p < 0.001$).

Conclusion Our study reported a high prevalence of diabetes among this sample of Chinese pregnant women. In addition, advanced maternal age was found to be a risk factor of diabetes in pregnant women. Therefore, in view of high prevalence of diabetes, screening for diabetes in pregnant women is strongly recommended, regardless of their age, BMI, and gestation weeks.

Keywords Diabetes · Hypertension · Pregnancy · Advanced maternal age · China

Introduction

The prevalence of diabetes mellitus and hypertension is increasing globally and these numbers include pregnant women [1]. Pregnant women with pre-existing diabetes or gestational diabetes are at increased risk of pre-term delivery, congenital defects, and macrosomia [2, 3]. In addition, diabetes during pregnancy is also associated with a higher risk of developing diabetes and obesity in children later in life [2]. Similarly, pregnant women with pre-existing hypertension or gestational hypertension have a higher risk of developing cardiovascular disease (CVD), chronic renal disease, and heart failure [4]. Therefore, diabetes and hypertension during pregnancy are the commonly seen pregnancy complications that can adversely influence the maternal and fetal outcomes [2].

In 2015, China introduced the universal two-child policy in order to address the aging issue in the Chinese population [5]. Following this, there is an increase in the number of births and

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most of the women giving birth are more likely to be aged ≥ 35 years [5]. Advanced maternal age (≥ 35 years) has been identified as a risk factor of diabetes in pregnant women [6]. In addition, due to the vast territory, there are considerable differences in ethnicities, dietary habits, and regions, which can lead to a significant difference in the prevalence of diabetes and hypertension in different regions of China [5].

Therefore, the aim of the study was to assess the prevalence of diabetes and hypertension during pregnancy among the Chinese pregnant women in Jiangsu Province, China, after the implementation of the universal two-child policy.

Materials and methods

Selection of study subjects

The retrospective cross-sectional study included the medical records of pregnant women who delivered their neonates between January 2016 and May 2018 in the Northern Jiangsu People's Hospital, Yangzhou, Jiangsu Province, China. Inclusion criteria included pregnant women aged ≥ 18 years with normal pregnancy (irrespective of gravidity) and must reside in the region for more than 6 months. Pregnant women with incomplete information on the medical records were excluded from the study.

Socio-demographic data collection and anthropometric measurement

Socio-demographic information such as age and weeks of gestation was obtained from pregnant women by the doctors during their hospital visits. The body weight and height of the pregnant women were measured using a stadiometer. Their body mass index (BMI) was classified according to the recommended categorisation for Chinese populations by the Working Group on Obesity in China: underweight, < 18.5 kg/m^2; normal weight, 18.5–23.9 kg/m^2; overweight, 24.0–27.9 kg/m^2; and obese, ≥ 28.0 kg/m^2 [7].

Biochemical measurements

After an overnight fasting, the blood samples of pregnant women were withdrawn for the determination of serum glucose concentration using red-top collection tubes. Gestational diabetes mellitus was diagnosed if one or more of the following criteria were met: (1) fasting blood glucose ≥ 5.1 mmol/L; (2) 1-h blood glucose ≥ 10.0 mmol/L or 2-h blood glucose ≥ 8.5 mmol/L following a 75 g oral glucose load [8]. Blood glucose concentration was analysed using a Roche Cobas 8000 Modular Analyser Series. Blood pressure was measured using a vital signs monitoring system (Model Mindray VS-600, Mindray, Shenzhen, China). Hypertension was defined as systolic blood pressure (SP) ≥ 140 mmHg and/or diastolic blood pressure (DP) ≥ 90 mmHg [9].

Our study also measured the birth weight, appearance, pulse, grimace, activity, and respiration (APGAR) score at 10 minutes (min) of newborns. Newborns with a birth weight of < 2500 g and ≥ 4000 g were categorised as low birth weight (LBW) [10] and macrosomia [11], respectively.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics for Windows ver. 25 (IBM SPSS Statistics for Windows, IBM Corporation, Armonk, NY). All study results for quantitative variables were presented as mean ± standard deviation (SD). An unpaired *t* test was employed to analyse the continuous variables. In addition, a chi-square test was conducted to determine the strength of the relationship between the categorical variables. General linear model (GLM) multivariate analysis was used to analyse the difference between study variables. Logistic regression models were applied for determining binary outcome variables, including diabetes, LBW, and macrosomia. A p value < 0.05 was set as a cut-off for statistical significance.

Results

Participant characteristics

A total of 3262 pregnant women of Han ethnicity were included in the study, and of these, 21.8% (n = 712) were diagnosed with diabetes (Table 1). Participants with diabetes were on an average significantly older (29.4 years vs. 27.9 years, $p < 0.001$) and shorter length of pregnancy (38.9 weeks vs. 39.2 weeks, $p < 0.001$) than participants without diabetes. Participants with diabetes also had significantly higher fasting glucose, 1-h glucose, and 2-h glucose than participants without diabetes (fasting glucose: 5.10 mmol/L vs. 4.49 mmol/L, respectively, $p < 0.001$; 1-h glucose: 9.53 mmol/L vs. 7.21 mmol/L, respectively, $p < 0.001$; 2-h glucose: 8.10 mmol/L vs. 6.23 mmol/L, respectively, $p < 0.001$) (Table 1).

In addition, participants with diabetes also had significantly higher systolic blood pressure and diastolic blood pressure than participants without diabetes (systolic blood pressure: 121 mmHg vs. 119 mmHg, respectively, $p < 0.001$; diastolic blood pressure: 80 mmHg vs. 78 mmHg, respectively, $p < 0.001$). The prevalence of hypertension in participants with diabetes was 4.6%, which was significantly higher than those without diabetes (1.8%) ($p < 0.001$) (Table 1). The

Table 1 Socio-demographic characteristics and biochemical results of participants by diabetes status

	Diabetes mellitus		*p* value
	Yes (*n* = 712)	No (*n* = 2550)	
Age (years)	29.4 ± 4.6	27.9 ± 3.8	*< 0.001*
Average length of pregnancy (weeks of gestation at delivery)	38.9 ± 1.6	39.2 ± 1.4	*< 0.001*
SP (mm Hg)	121 ± 11	119 ± 11	*< 0.001*
DP (mm Hg)	80 ± 10	78 ± 9	*< 0.001*
Prevalence of hypertension, *n* (%)	33 (4.6)	46 (1.8)	*< 0.001*
Fasting glucose (mmol/L)	5.10 ± 0.84	4.49 ± 0.33	*< 0.001*
1-h glucose (mmol/L)	9.53 ± 1.88	7.21 ± 1.40	*< 0.001*
2-h glucose (mmol/L)	8.10 ± 1.64	6.23 ± 1.04	*< 0.001*
Neonatal birth weight (g)	3402 ± 513	3349 ± 438	*0.011*
Prevalence of LBW, *n* (%)	31 (4.4)	67 (2.6)	*0.017*
Prevalence of macrosomia, *n* (%)	72 (10.1)	148 (5.8)	*< 0.001*
Neonatal APGAR score at 10 min	9.99 ± 0.14	9.99 ± 0.12	0.334

overall prevalence of diabetes and hypertension in participants was 21.8% and 2.4%, respectively.

Neonatal birth weight for participants with diabetes was significantly heavier than those without diabetes (3402 g vs. 3349 g, respectively, $p = 0.011$) (Table 1). In addition, the prevalence of LBW and macrosomia for participants with diabetes was significantly higher than participants without diabetes (LBW: 4.4% vs. 2.6%, respectively, $p = 0.017$; macrosomia: 10.1% vs. 5.8%, respectively, $p < 0.001$) (Table 1). There was no difference in neonatal APGAR score at 10 min between participants with and without diabetes ($p = 0.334$) (Table 1).

Maternal BMI

Obese participants had a significantly higher fasting glucose concentration than overweight participants and participants with a normal BMI (fasting glucose concentration: 4.73 mmol/L, 4.58 mmol/L, and 4.49 mmol/L, respectively) ($p < 0.001$) (Table 2). The prevalence of diabetes in obese participants was significantly higher than in overweight participants and participants with a normal BMI (27.9%, 19.3%, and 15.4%, respectively, $p < 0.001$) (Table 2). Similarly, the prevalence of hypertension in obese participants was significantly higher than overweight participants and participants with a normal BMI (4.6%, 1.2%, and 1.2%, respectively) ($p < 0.001$) (Table 2).

For the neonatal outcomes, newborns born to obese participants were significantly heavier than those born to overweight participants and participants with a normal BMI (3478 g, 3338 g, and 3154 g, respectively) ($p < 0.001$) (Table 2). In addition, the prevalence of LBW in the obese category was significantly lower than those in overweight and

Table 2 Biochemical results of participants by maternal BMI

	Maternal BMI			*p* value
	Normal (*n* = 499)	Overweight (*n* = 1578)	Obese (*n* = 1185)	
SP (mm Hg)	118 ± 11	118 ± 10	123 ± 12	*< 0.001*
DP (mm Hg)	77 ± 9	77 ± 8	80 ± 10	*< 0.001*
Prevalence of hypertension, *n* (%)	6 (1.2)	19 (1.2)	54 (4.6)	*< 0.001*
Fasting glucose (mmol/L)	4.49 ± 0.64	4.58 ± 0.45	4.72 ± 0.62	*< 0.001*
1-h glucose (mmol/L)	7.36 ± 1.75	7.60 ± 1.70	8.03 ± 1.90	*< 0.001*
2-h glucose (mmol/L)	6.38 ± 1.41	6.60 ± 1.34	6.81 ± 1.52	*< 0.001*
Prevalence of diabetes mellitus, *n* (%)	77 (15.4)	304 (19.3)	331 (27.9)	*< 0.001*
Neonatal birth weight (g)	3154 ± 425	3338 ± 429	3478 ± 467	*< 0.001*
Prevalence of LBW, *n* (%)	28 (5.6)	45 (2.9)	25 (2.1)	*0.001*
Prevalence of macrosomia, *n* (%)	75 (5.8)	135 (7.2)	10 (10.4)	0.115
Neonatal APGAR score	9.99 ± 0.15	9.99 ± 0.16	9.99 ± 0.06	0.109

normal BMI categories (2.1%, 2.9%, and 5.6%, respectively) ($p = 0.001$) (Table 2). However, there was no difference in the prevalence of macrosomia among the three different BMI categories ($p = 0.115$) (Table 2). The overall prevalence of LBW and macrosomia was 3.0% and 6.7%, respectively.

Trimesters of pregnancy

The majority of participants were in 2nd trimester (58%), followed by 1st trimester (39%) and 3rd trimester (3%) (Table 3). There was no difference in fasting glucose concentration among 1st, 2nd, and 3rd trimesters (4.62 mmol/L, 4.62 mmol/L, and 4.64 mmol/L, respectively) ($p = 0.935$) (Table 3). Similarly, there was no difference in the prevalence of hypertension among 1st, 2nd, and 3rd trimesters (2.6%, 2.3%, and 2.1%, respectively) ($p = 0.795$) (Table 3). In addition, there was also no difference in the prevalence of diabetes among 1st, 2nd, and 3rd trimesters (23.7%, 20.7%, and 18.8%, respectively) ($p = 0.098$) (Table 3). However, the 1-h glucose and 2-h glucose concentrations in 1st trimester (7.85 mmol/L and 6.74 mmol/L, respectively) were significantly higher than 2nd (7.62 mmol/L and 6.58 mmol/L, respectively) and 3rd trimesters (7.81 mmol/L and 6.58 mmol/L, respectively) (all $p < 0.05$) (Table 3).

Years of study

The prevalence of diabetes in 2016, 2017, and 2018 was 18.9%, 24.3%, and 25.4%, respectively, indicating an increasing trend over the period (Fig. 1). The prevalence of diabetes among participants in 2018 was significantly higher than in 2016 and 2017 ($p < 0.001$). However, there was no significant difference in the prevalence of hypertension among participants over the period ($p = 0.446$). The prevalence of hypertension in 2016, 2017, and 2018 was 2.7%, 2.0%, and 2.7%, respectively (Fig. 1).

Age groups

The prevalence of diabetes in participants aged 40–45 year was the highest (47.6%), followed by 35–39 years (35.7%), 30–34 years (26.3%), 25–29 years (19.0%), and 18–24 years (16.4%) ($p < 0.001$) (Fig. 2). The prevalence of diabetes in participants of advanced maternal age i.e. aged 35–40 years and 40–45 years was 2.584 times and 4.151 times greater than participants aged < 35 years. However, the prevalence of hypertension in participants was not statistically significant among different age groups, although the prevalence of hypertension was the highest in 40–45 years (7.1%), followed by 35–39 years (3.4%), 30–34 years (2.3%), 25–29 years (2.3), and 18–24 years (2.2%) (Fig. 2).

Discussion

Although the WHO does not provide any recommendation on how and/or whether to diagnose diabetes during pregnancy [12], the screening for diabetes is conducted between 24 and 28 weeks of gestation. In our study, although there was no significant difference in the prevalence of diabetes among the three trimesters ($p > 0.05$), the prevalence of diabetes in the 1st trimester (23.7%) was higher than that in the 2nd and 3rd trimesters (20.7% and 18.8%, respectively). Therefore, this indicated that early gestation diabetes screening prior to 24 weeks of gestation may be beneficial in detecting diabetes. In addition, some participants in our study might have pre-existing diabetes or gestational diabetes in whom the glucose intolerance was diagnosed in the early weeks of gestation. A review of the literature reported that approximately 39–66% of pregnant women with diabetes can be identified early prior to 24 weeks of gestation [13, 14].

In our study, the overall prevalence of diabetes was 21.8%, which was similar to the findings reported by Mak et al. [8]. The authors reported that the prevalence of diabetes in pregnant women in western China was 18.3% [8]. A meta-analysis by Gao et al. reported that the pooled prevalence of diabetes

Table 3 Biochemical results of participants by trimesters

	Trimesters			*p* value
	1st ($n = 1286$)	2nd ($n = 1880$)	3rd ($n = 96$)	
SP (mm Hg)	120 ± 11	120 ± 12	121 ± 11	0.358
DP (mm Hg)	78 ± 9	78 ± 9	79 ± 7	0.557
Prevalence of hypertension, *n* (%)	34 (2.6)	43 (2.3)	2 (2.1)	0.795
Fasting glucose (mmol/L)	4.62 ± 0.55	4.62 ± 0.55	4.64 ± 0.61	0.935
1-h glucose (mmol/L)	7.85 ± 1.74	7.62 ± 1.83	7.81 ± 1.72	*0.001*
2-h glucose (mmol/L)	6.74 ± 1.39	6.58 ± 1.44	6.58 ± 1.48	*0.011*
Prevalence of diabetes mellitus, *n* (%)	305 (23.7)	389 (20.7)	18 (18.8)	0.098

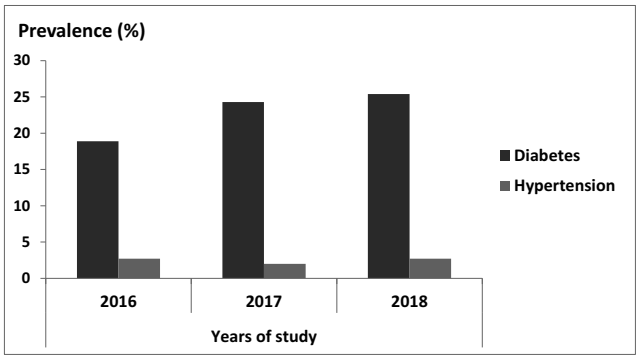

Fig. 1 Prevalence of diabetes and hypertension among pregnant women between 2016 and 2018

among pregnant women in China was 14.8%, according to the criteria recommended by the International Association of Diabetes and Pregnancy Study Groups [15]. In addition, there was also an increasing trend in the prevalence of diabetes in the Chinese population [16–18], suggesting that urgent attention should be drawn on how to control and reduce the prevalence of diabetes in China, especially in pregnant women.

Overall, the prevalence of diabetes in our study was higher than in other developed countries. For example, a meta-analysis of 40 studies with 177,063 participants by Eades et al. reported that the prevalence of diabetes in pregnant women was 5.4% in European countries including the UK, Sweden, France, Finland, Belgium, and Greece [19]. In addition, the prevalence of diabetes in our study was also higher than in other developed countries such as the USA (7.6%) [20] and Japan (6.1%) [21]. When compared with other developing countries, the prevalence of diabetes in our study was also higher than those of Vietnam (20.1%), Malaysia (11.8%), and Thailand (6.1%) [21]. A review of literature has also suggested that a high prevalence of diabetes in pregnant women in developing and less wealthy countries is often due to limited access to maternal health care facilities and low socioeconomic status in populations [21]. However, other factors such as an unhealthy diet, inactive lifestyle, and family history of diabetes will also increase the risk of developing diabetes in pregnant women [22–24]. Therefore, future research studies

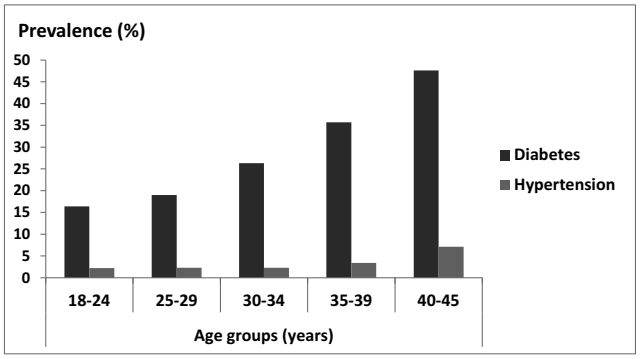

Fig. 2 Prevalence of diabetes and hypertension among pregnant women of different age groups

should assess the factors associated with high prevalence of diabetes among pregnant women in China in order to tackle this significant public health issue.

Our study was consistent with the published literature, which indicated that the prevalence of diabetes in pregnant women increased with increasing maternal age [19]. The prevalence of diabetes had also significantly increased following the implementation of the universal two-child policy when compared with that before the policy implementation [25]. This is a particular concern especially after China had introduced the universal two-child policy in 2015. One possible reason is that the number of pregnancies at advanced maternal age is expected to increase, suggesting that the prevalence of diabetes in pregnant women, especially those of advanced maternal age, would continue to increase as well. In addition, due to the increasing prevalence of overweight and obesity in China [26], this will also have a significant impact on the prevalence of diabetes in pregnant women. Our study also reported the prevalence of diabetes was increasing with BMI, which was consistent in the literature [25, 27]. Therefore, the high prevalence of diabetes among pregnant women in China remains to be a significant public health concern.

In terms of delivery outcomes, our study reported a higher prevalence of macrosomia in participants with diabetes than participants without diabetes (10.1% vs. 5.8%, $p < 0.001$), which was consistent with the findings in another group of Chinese pregnant women [8]. The authors reported that the prevalence of macrosomia was significantly higher in pregnant women with diabetes than in pregnant women without diabetes (6.2% vs. 3.1%, $p = 0.024$) [8]. This is because high glucose concentration in participants with diabetes is associated with an increased neonatal fat deposition and overgrowth, which may lead to macrosomia [28]. In addition, our study also found that the prevalence of LBW was significantly higher in participants with diabetes than participants without diabetes (4.4% vs. 2.6%, $p = 0.017$). This may be due to the complications of diabetic pregnancies including a reduced placental blood flow caused by placental vascular change [29]. In addition, pregnant women with diabetes may practice a strict glycemic control, which may restrict fetal growth [30].

Our study had several strengths including a large sample size of 3262 mother-newborn pairs. In addition, our study was conducted after the implementation of the universal two-child policy by the Chinese government. This allowed us to have a detailed investigation of the prevalence of diabetes and hypertension after the universal two-child policy. One limitation of our study was that we did not screen for pre-existing diabetes in participants. Since our study recruited participants from a hospital and our participant selection was not based on a random basis, our findings might not generalise well to other regions of China because of the potential of selection bias.

This is because to find out the prevalence or screening rate, the ideal methodology is to do random sampling. Therefore, our findings should be interpreted cautiously. Future studies should consider including a larger group of pregnant women and performing a random sampling in order to calculate the prevalence of diabetes and hypertension in pregnant women.

Conclusions

Our study reported a high prevalence of diabetes in this sample of pregnant women. Therefore, in view of the high prevalence of diabetes, screening for diabetes in pregnant women is strongly recommended, regardless of their age, BMI, and gestation weeks. In addition, management and preventive measures of diabetes should also be undertaken in order to reduce the increased risk of developing adverse maternal and delivery outcomes in diabetic pregnant women.

Compliance with ethical standards

The study was approved by the Ethics Committee of the Northern Jiangsu People's Hospital (reference no. 2018063).

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. No animals were used in this study.

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ORIGINAL ARTICLE

Prevalence and risk factors in metabolic syndrome among Temiar in Kelantan

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Abstract

Objective The Malaysian OA live mainly a traditional life of forest gathering. Over the decades, the Malaysian government relocated them, exposing them to lifestyle changes. This study investigated the prevalence of MetS among translocated Temiar OA. The objectives were to compare the prevalence and associated risks with other OA and Malaysian studies to inform authorities of the unintended consequences of translocation.

Study design This was a cross-sectional study of a resettled Temiar community in Kelantan.

Methods The study involved a simple random sampling of 123 resettled Temiar individuals. MetS was diagnosed on a modified NCEP ATP III Guidelines. Anthropometric, dietary, and biochemical information were gathered. Differences were determined using independent *t* tests for continuous variables and chi-squared test for categorical variables. The associations between variables were determined using binary logistic regression.

Results MetS occurred in 39.8% of the subjects. They were younger adults, with a mean age of 38.6 years. Age, BMI, BP, serum adiponectin, and serum resistin predicted MetS development in this population.

Conclusion The prevalence of MetS was higher than reported figures for other OA and ethnic groups in Malaysia with an apparent younger onset. Associated (risk) factors are discussed.

Keyword Metabolic syndrome · Temiar subtribe · Orang Asli · Risk factors · Resistin · Adiponectin

Introduction

Orang Asli (OA) indigenous to Peninsular Malaysia, they comprise about 1% (150, 000) of the Malaysian population [1]. They include three large tribes and several smaller subtribes that are nearly extinct. The large tribes are the ProtoMalays (subtribes: Orang Seletar and Jakun), Senois (subtribes: Temiar, Mahmeri and Semai), and Negritos (subtribes: Jehai, Mendriq, and Batek). They are highly diverse with the majority still living in remote and rural areas.

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Temiar with a population of 30,000 to 40,000 [1] is a subtribe of the Senoi Tribe. The majority live in the central part of Peninsular Malaysia, many within or on the fringes of rainforests, subsisting on agriculture, fishing, hunting, and trading.

Some are now relocated into reservations, with more rapid paces of life, raising concerns of maladaptation, and increasing prevalence of lifestyle-associated diseases such as MetS [2]. They may carry genetic traits that are more suited in a metabolically thrifty rather than the modern "obesogenic" environments [3]. Noteworthy is the low MetS prevalence among OA in their native habitats [4] compared to its higher prevalence among suburban OA [5–7] that parallels prevalence in modern Malaysia, Africa, and India [5, 8] that are nevertheless lower compared to prevalence in developed countries like the USA, UK, Japan, and Europe [9–11].

This study investigated the prevalence of MetS among a relocated Temiar subtribe in Kuala Betis, Gua Musang, Kelantan. Its objective is to inform the authorities in their

efforts to improve the collective lives of these relatively neglected Malaysian community.

Methods

This study involved a simple random sampling of 123 resettled Temiar individuals in Kuala Betis, Gua Musang Kelantan, Malaysia, where they have been relocated over the past three decades to the more developed and urbanized areas in the region. Kuala Betis was one of the largest resettled areas for this population. It consists of 24 villages with more than 500 families and about 2500 villagers. They are given new facilities, new homes with basic amenities, health care services, and various programs by the Malaysian government to improve their quality of life. The majority of them continue with traditional occupations such as hunting and traditional farming.

This study was approved by the UniSZA Human Research Ethics Committee (UHREC). Written permission was also obtained from JAKOA (Jabatan Kemajuan Orang Asli).

Written informed consents were obtained. Before screening recruitment, subjects were told to fast for 8 h.

Metabolic syndrome definition

MetS was defined according to modified NCEP-ATP III [2] criteria (Table 1).

Anthropometric and clinical assessments

Height was measured to the nearest 0.1 cm. Weight was determined on the Omron HBF-375 Body Composition Monitor (Asian Model, Australia) and so were the body mass index (BMI) and body fat (BFA), using the criteria of the World Health Organization [12] and Lohman[13]. Waist circumference (WC) was measured at the level of the umbilicus. Blood pressure (BP) was measured in the sitting position, using Omron HEM-757 (Tables 2 and 3).

Dietary intake was evaluated using 24-h diet recall over 3 days. Food not found in the ProTM software used was added from composition tables and food labels from the Nutrient Composition of Malaysian Foods [14]. Data were analyzed using the Nutritionist ProTM software (Axxya System, US Nutrition Facts). Diet quality was compared with Recommended Nutrient Intakes for Malaysia (RNI) [15] and Recommended Dietary Allowances (RDA) [16].

Biochemicals measurement

Fasting blood glucose was measured using a glucometer (ACCU-CHEK Performa). For other tests, fasting venous blood that was collected from the forearm was centrifuged at 4500 rpm for 10 min and stored at – 20 °C until analysis. Serum was analyzed for lipids, liver enzymes and renal profiles using an automated Olympus AU400 chemistry analyser (Olympus, America Inc, USA).

Serum adiponectin and plasma resistin were measured using a quantitative ELISA assay (CUSABIO Human Adiponectin and Resistin, China). The lowest detection limit for resistin was 0.1 ng/ml with an interassay variability of 5.1% and intraassay variability of 2.8%.

Statistical analysis

All statistics were done using SPSS 22.0 (SPSS Inc., Chicago, IL) (IBM Corporation, Armonk, NY, USA). Categorical variables are presented as frequencies and percentages, and quantitative variables as mean ± standard deviation (SD). Significant differences were determined using an independent *t* test for continuous variables and the chi-squared test for categorical variables. A 95% confidence interval (CI) was included where appropriate. Odds Ratios (ORs) and 95% CI were calculated using binary logistic regression. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Of the 123 subjects, 37 were males, and 86 were females. Their mean age was 40.9 ± 16.60 years and 34.5 ± 11.89

Table 1 Modified NCEP-ATP III. At least any three must be met

Central obesity—WC	Male: ≥ 90 cm, female: ≥ 80 cm
Raised BP	Systolic BP ≥ 130 and/or diastolic BP ≥ 85 mmHg or on treatment for previously diagnosed hypertension
Raised fasting plasma glucose	≥ 5.6 mmol/L or previously diagnosed with T2DM
Raised triglycerides	≥ 1.7 mmol/L or on treatment for lipid abnormality
Raised HDL-C	Male: < 1.03 mmol/L, female: < 1.29 mmol/L or on treatment for lipid abnormality

WC Waist circumference, *BP* blood pressure, *HDL-C* high-density lipoprotein-cholesterol

Table 2 Characteristics of study subjects (n = 123)

Variables	MetS		NonMetS		p value
	n (%)	Mean ± (SD)	n (%)	Mean (SD)	
Sociodemographic characteristics					
Gender					0.057[a] *
Male	10 (20.4)		27 (36.5)		
Female	39 (79.6)		47 (63.5)		
Age (years)		38.61 ± 12.65		35.04 ± 14.25	0.025 [b]*
Number (%) with the time of birth					0.073[a]
Before relocation	14 (28.6)		33 (44.6)		
After Relocation	35 (71.4)		41 (55.4)		
Education level					0.004 [a]*
None/primary	40 (81.6)		42 (56.8)		
Secondary	9 (18.4)		32 (43.2)		
Employment status					0.06 [a]
Unemployed	36 (73.5)		42 (56.8)		
Employed	13 (26.5)		32 (43.2)		
Family history					
HPT					0.211 [a]
Yes	14 (28.6)		14 (18.9)		
No	35 (71.4)		60 (81.1)		
DM					0.011 [a]*
Yes	6 (12.2)		1 (1.4)		
No	43 (87.8)		73 (98.6)		
Anthropometry					
BMI (kg/m^2)		31.6 ± 4.14		22.5 ± 3.19	< 0.001[b]*
Body fat (%)		33.1 ± 8.21		29.6 ± 8.10	0.023[b] *
Fat mass index (kg/m^2)		10.5 ± 10.11		8.1 ± 5.41	0.088[b]
MetS criteria					
WC (cm)		91.5 ± 12.89		74.9 ± 8.3	< 0.001 [b] *
Systolic BP (mmHg)		137.0 ± 21.23		126.7 ± 18.15	0.005 [b] *
Diastolic BP (mmHg)		90.4 ± 13.1		81.3 ± 11.28	< 0.001 [b] *
FBG (mmol/L)		7.2 ± 3.37		5.6 ± 2.02	0.001 [b] *
Fasting TG (mmol/L)		1.9 ± 0.63		1.3 ± 0.2	< 0.001 [b] *
Fasting HDL-C (mmol/L)		0.9 ± 0.35		1.4 ± 0.23	< 0.001 [b] *
Biochemical analysis					
Total cholesterol (mmol/L)		6.6 ± 3.15		4.8 ± 1.95	< 0.001 [b] *
Adiponectin (nmol/L)		25.4 ± 17.93		50.6 ± 22.80	< 0.001 [b] *
Resistin (nmol/L)		35.6 ± 20.16		22.6 ± 17.97[1]	0.002 [b] *

[a] chi-squared test, * $p < 0.05$ versus nonMetS

[a] independent t-test, * $p < 0.05$, versus nonMetS

HPT Hypertension, *DM* diabetes mellitus, *IHD* ischemic heart disease, *BMI* body mass index, *WC* waist circumference, *BP* blood pressure, *FBG* fasting blood glucose, *TG* triglyceride, *HDL-C* high-density lipoprotein

years, respectively. MetS occurred among 39.8% (Table 2). On univariate analysis, age, educational level, employment status, and family history of diabetes and hypertension exhibited associations with MetS (Table 2) and so did BMI and BFC, TC, potassium level, TP, ALT, serum resistin, and adiponectin (Table 4).

On multivariate analyses (i) increasing age, (ii) higher BMI, (iii) higher BP, (iv) serum adiponectin, and (v) higher serum resistin were all found to be independent predictors of MetS (Table 5).

Discussion

This study was prompted by concerns regarding increasing health-care needs and cost of relocated OA community in

Table 3 The association between cardiometabolic risk factors and MetS

Variables	Crude OR (95% CI)	Wald statistics (df)	*p* value
Sociodemographic characteristic			
Age	1.02 (0.99, 1.05)	1.99 (1)	0.159*
Number with the time of birth			
Before relocation	1.00		
After relocation	2.01 (0.93, 4.35)	3.16 (1)	0.075*
Gender			
Male	1.00		
Female	2.24 (0.97, 5.19)	3.54 (1)	0.060*
Education level			
No school	1.00		
Primary education	3.42 (1.37, 8.55)	6.95 (1)	0.008*
Secondary education	3.32 (1.18, 9.37)	5.13 (1)	0.024*
Family history			
DM			
No	1.00		
Yes	10.19 (1.19,	4.48 (1)	0.034*
HPT	87.47)		
No	1.00		
Yes	1.71 (0.73, 4.01)	1.55 (1)	0.214*
Anthropometry characteristic			
BMI (kg/m^2)	2.07 (1.58, 2.71)	27.89 (1)	< 0.001*
BFC (%)	1.18 (1.02, 1.37)	4.87 (1)	0.03*
FMI (kg/m^2)	1.06 (0.98, 1.14)	1.93 (1)	0.17
MetS criteria			
WC (cm)	1.14 (1.09, 1.20)	26.96 (1)	< 0.001*
BP (mmHg)			
< 131/< 86	1.00		
> 130/> 85	2.59 (1.21, 5.54)	6.04 (1)	0.014*
FBG (mmol/L)	1.30 (1.08, 1.58)	7.40 (1)	0.007*
HDL (mmol/L)	0.002 (0.00, 0.02)	28.53 (1)	< 0.001*
TG (mmol/L)	87.82 (16.58, 465.17)	27.68 (1)	< 0.001*
Biochemical analysis			
TC (mmol/L)	1.35 (1.12, 1.64)	9.75 (1)	0.002*
Serum adiponectin (nmol/L)	0.79 (0.72, 0.87)	25.93 (1)	< 0.001*
Serum resistin (nmol/L)	1.12 (1.05, 1.19)	12.25 (1)	< 0.001*

*Factors served as reference category; **$p < 0.05$, statistically significant. *OR* odds ratio, *CI* confidence interval, *DM* diabetes mellitus, *HPT* hypertension, *IHD* ischemic heart disease, *BMI* body mass index, *BFC* body fat composition, *FMI* fat mass index, *WC* waist circumference, *BP* blood pressure, *FBG* fasting blood glucose, *TG* triglyceride, *HDL-C* high density lipoprotein, *TC* total cholesterol

Gua Musang. The MetS prevalence of 39.8% observed was alarming as against Malaysian Malays at 26.4%, Malaysian Chinese at 26.2%, Malaysian Indians at 35.6% [17], and Malaysian OA at 29.6% [6]. Although the prevalence was increasing among the general Malaysian population, at 31.7% [18], it was lower. It is interesting to postulate that relocated Temiars were constitutionally ill-prepared for the new environment and succumbed to MetS with the associated increase in health-care needs and costs.

This study was small, but it is alarming nevertheless, especially if we extend the results to the thousands of relocated OAs. 'The Malaysia Plans', to improve livelihood [19] for the OAs focused on the alleviation of poverty by structured resettlements [20]. Not surprisingly perhaps, the "improved livelihood" precipitated a rise in lifestyle diseases as suggested by the current study and others [21, 22]. In their native environment, 'thrifty genes" that express a "metabolic thrift" protected them against the detrimental consequence of

Table 4 Positive characteristic of MetS

Variables	Crude OR[a] (95% CI)	Adjusted OR[b] (95% CI)	Wald Statistics (df)	*p* value
Serum adiponectin (ng/L)	0.79 (0.72, 0.87)	0.80 (0.66, 0.96)	5.43 (1)	0.029*
Serum resistin (ng/L)	1.12 (1.05, 1.19)	1.24 (0.10, 1.55)	3.69 (1)	0.055
BMI (kg/m^2)	2.07 (1.58, 2.71)	2.76 (1.66, 4.59)	15.38 (1)	<0.001*
BP (mmHg)				
< 131/< 86	1.00			
> 130/> 85	2.59 (1.21, 5.54)	8.81 (1.28, 60.52)	4.90 (1)	0.027*
Age (years)	1.02 (0.99, 1.05)	1.08 (1.00, 1.16)	3.82 (1)	0.051*

[a] Simple logistic regression, [b] Multiple logistic regression

The model reasonably fit well. Model assumptions were met. There were no interaction and multicollinearity problems

starvation [3]. In their new resource-rich environment, the genes may predispose them to obesity and other maladaptive consequences. Alternatively, the shift of humans from prey to predator status (predation release) and random changes in gene frequency (genetic drift) could also have contributed to such maladaptation [23, 24].

The female gender, older age, higher educational level, and family history of DM were associated with a higher prevalence of MetS in our study. The findings among females paralleled previous studies with OA [6] and the Malaysian population [17, 18]. Among the Temiars, the males are more traditionally physically active. Nevertheless, our male subjects had larger waist circumference, but their BMI, systolic and diastolic BP, plasma glucose, triglycerides, and HDL-C levels were lower, the total sum of which probably explains the higher prevalence of MetS among our female subjects.

As expected [10], the prevalence of MetS among our subjects increased with age, although the mean age was lower compared to previous studies. This finding was also probably related to the observation that subjects born after relocation had a higher prevalence of MetS compared to those born before, further suggesting a strong influence of relocation on MetS. A caveat in this observation was the relatively small sample size especially when they were further subdivided according to age groups.

MetS also occurred more commonly among subjects attaining a higher educational level. They probably work in less physically active jobs that predispose to MetS [25]. In more established communities, education was, however, strongly associated with health-related behaviors [26] that reduced risks for MetS [26–28]. Again, the small sample size could have contributed to this discrepant finding in the present study. As in an earlier study [29], our subjects with a family history of DM showed a higher prevalence of MetS, and this may be related to genetic susceptibility, shared environment and common behaviors [30].

The role of diet in the origin of MetS is not well understood [31]. Our study found no association between dietary intake and MetS. A cohort study in Los Angeles suggested an association between low fruit and vegetable consumption and high sweetened beverage consumption with MetS in specific sex-ethnicity populations [32]. As alluded, the small sample size could have contributed to this discrepant finding in the present study. Previous studies have also suggested that excess body fat contributed to MetS [33, 34]. Our subjects with MetS had higher BMI compared to controls. They also had high TG and BP. In a previous study, high normal BP values and hypertension were found in 80% of individuals with MetS [35]. Furthermore, the prevalence of MetS was found higher in hypertensive patients compared to general population [36, 37] with a high frequency of resistant hypertension among individuals with MetS [37].

This study had several limitations, including low response rates and small sample size. It was due to their perception of research involvements that lead to difficulties in recruiting Temiar OA individuals although it was planned to have a larger sample size. Nevertheless, given the overall small population size of the relocated Temiars, our final sample size did probably give a good reflection of the population it represented. Furthermore, there have not been a similar previous study for us to draw upon to exactly estimate the sample size and arguably, the final sample size gave a good approximation. The accessibility of the population to researchers due to remote geographical location and administrative constraints also imposed significant problems as recruitment depended on layered procedures involving OA officials and village heads. There was also a high dropout rate due to inadequate understanding and compliance by subjects with study procedures, although every effort was made to prevent them. The investigators used the Malaysian language to give instructions and some subjects may not have been conversant in the language as it was alien to their mother tongue. Thus, some subjects poorly complied to the requirement for overnight fasting and blood sampling. To validate the study, it is suggested that larger prospective studies are undertaken.

Conclusion

The relocation of the Temiar community increased their prevalence of MetS that also affected younger individuals. Preventive strategies are needed and should target their young to prevent the negative health consequences of relocation for this unique community.

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Authors' contribution All authors participated sufficiently in work and agreed to take public responsibility for appropriate portions of the contents.

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Data availability All data were primary and could be provided if required.

Compliance with ethical standards

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

Informed consent Personal, demographic details, and relevant data of the participants were collected and recorded after getting informed consent.

Ethical approval Research conducted at the Faculty of Medicine, UniSZA in the present study was approved (UHREC/2016/3/012) by the UniSZA Human Ethics Research Committee (UHREC), Universiti Sultan Zainal Abidin (UniSZA; Kuala Terengganu, Malaysia). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the UHREC.

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ORIGINAL ARTICLE

Human gut microbiota and its possible relationship with obesity and diabetes

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Abstract

Background Obesity and diabetes are public health problems that are leading causes of death in the world. Recent surveys suggest that there is a relationship between diabetes and bacterial residents of the gastrointestinal tract.

Objective This case-control study was designed to evaluate the composition of the gut microbiota in patients with type 2 diabetes (T2DM) and obesity compared to the healthy people.

Methods A total of 91 adult subjects (25 patients diagnosed with T2DM, 48 obese patients, and 18 healthy individuals) were included in the study. The gut microbiota composition was investigated by quantitative real-time polymerase chain reaction (qPCR) method using bacterial 16S rRNA gene.

Results The frequency of all bacterial species in the obese group compared to the control group have significantly changed ($p < 0.05$) except *Bacteroides fragilis*, whereas the level of bacterial composition was not changed significantly ($p > 0.05$) in the diabetic patients versus the control ones, except for *Bacteroides* phylum and *Lactobacillus* spp. Moreover, the mean body mass index (BMI) in control, T2DM, and obese groups were 24.28 ± 3.00, 26.83 ± 3.29, and 44.65 ± 3.73, respectively. Our analysis showed a positive correlation between diabetic patients plus obese ones and the number of bacteria ($p < 0.05$).

Conclusions To sum up, these findings show that specific changes in microbial community composition are associated with T2DM and obesity. More extensive, our survey suggests that modulation of the microbiome warrants further investigation as a potential therapeutic strategy for metabolic diseases.

Keywords Gut microbiota · Obesity · Type 2 diabetes mellitus · Real-time PCR

Introduction

Over 10–100 trillion microbes colonize in each part of human body, including the skin, vagina, oronasopharyngeal cavity, and of course gastrointestinal tract [1, 2]. The gastrointestinal microbiota generally refers to the microbial composition in the gut, which contains various types of microorganisms such as bacteria, viruses, archaea, fungi, as well as phages [3]. Among all different bacterial species, which colonized in human guts, five phyla are most abundant, including *Firmicutes*, *Bacteroidetes*, *Verrucomicrobia*, *Actinobacteria*, and *Proteobacteria* [3]. These microorganisms perform variety

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of functions that the human body has no ability to do them by itself. Some studies have suggested that human gut microbiota could play key role in the host immune system, permeability of the intestine and time of pass, increasing the secretion of the metabolic endotoxin (LPS), modulation of neurohormonal function, epithelial cell proliferation, and gut barrier function. Moreover, gut microbes also perform a wide range of bile acid modifications and interfere in cholesterol reduction and in the biosynthesis of some B vitamins and vitamin K, isoprenoids, and amino acids such as lysine and threonine [4, 5]. Therefore, human microbiome can also affect metabolism and may readily lead to the obesity and its related disorders in the host.

Dysbacteriosis, which is known as dysbiosis, is a term for a microbial maladaptation or imbalance on or inside the body. This imbalance has been reported to be associated with diseases, such as malnutrition, inflammatory bowel disease, neurological disorders, rheumatoid arthritis, autism, allergies, and cancer, as well as obesity and diabetes [6–9].

Obesity and type 2 diabetes (T2DM) are global health challenges [3]. Obesity represents the intensity of body fat that results in a higher body mass index (BMI), which may negatively contribute to morbidity and mortality. According to the World Health Organization (WHO) mean BMI guideline [10], generally accepted BMI ranges are underweight, under 18.5 kg/m^2; normal weight, 18.5–25 kg/m^2; overweight, 25–30 kg/m^2; and obese, over 30 kg/m^2. BMI is a major indicator of health, so the high levels of it can increase the risk of various diseases such as cardiovascular disease, diabetes, chronic kidney disease, retinopathy, and several cancers. Additional studies identified that alteration in the equilibrium of the bacterial phyla, especially the low levels of *Bacteroides* and high *Firmicutes* abundances, conduce increased weight gain and obesity [11]. Diabetes is a chronic disease that is correlated with the failure of the pancreas to produce enough insulin relative to body needs, and the body is unable to effectively utilize the insulin it produces [12, 13]. T2DM is also a main cause of renal failure, retinopathy and blindness, and limb amputations that transpire in a situation with decreased blood flow and neuropathy in the feet. Insulin resistance is a critical factor linking obesity that promotes the risk of diabetes, as increasing adipose tissue mass related to insulin resistance [14].

Danish et al. in 2010 showed that the healthy individuals significantly had higher amounts of phylum *Firmicutes* and *Prevotella* spp. compared to T2DM patients [15]. In other studies, Gram-negative bacteria in T2DM patients have developed quite more in intestinal microbiota, principally those parts of the *Proteobacteria* and *Bacteroidetes* phyla [16, 17]. But the question is, how we can link these results about T2DM patients to their BMI? Or better say, how we can explain the association between obesity and T2DM with the imbalance of gut microbial populations? Hence, to achieve a correct answer, we designed this study in our country.

Materials and methods

Study enrollment and collection of specimens

In this study, we collected 91 stool samples from the Institute of Endocrinology and Metabolism Research and Training Center in Tehran, Iran. Among these 91 patients, 25, 48, and 18 of them were T2DM, obesity, and non-diabetic individual patients, respectively, and the mean age of all volunteers was 56 ± 8 years. We matched age, gender, and their current living environment for all 91 participates.

The participants were included using the following criteria: (1) Obese patients with BMI > 40 who have not had diabetes; (2) T2DM patients with glycated hemoglobin (HbA1c) $< 10\%$ whose T2DM was diagnosed less than 5 years; and (3) no subjects had taken antibiotic, probiotic/prebiotic products, or any other medical treatment influencing gut microbiota for 2 months before the beginning of the samples collection. In addition, patients were interviewed for their history of gastrointestinal diseases, dietary habits, and physical activity levels in both case and control groups. Participants who had suffered from gastrointestinal disorders during this period were also excluded from the study.

All participants' stool samples were collected on three occasions by sterile cups instantly after defecation and brought them to the laboratory in 2 h. Fecal samples were immediately stored at 70 °C upon arrival in microbiology laboratory.

Extraction and purification of DNA from stool samples

Total microbial DNAs were extracted from all stool specimens using QIAamp® DNA Stool mini kit (Qiagen Retsch GmbH, Hannover, Germany) according to the manufacturer's protocol. DNA quality and concentrations were determined by Nanodrop spectrophotometer (Nanodrop Technologies, Wilmington, DE, USA) and agarose gel electrophoresis. Whole extracted DNAs were immediately stored at 20 °C.

Design of the oligonucleotide primers and probes

The specific sequences of primers and TaqMan probes are shown in Table 1. Desired specificity of the primer pairs was verified by submitting the sequences to the FASTA database search program provided by the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov) and Probe Match program provided by the Ribosomal Database Project (rdp.cme.msu.edu/ html/). The primers and probes against selected species or group of specific target sequences were synthesized commercially by Pishgam Biotech Co., Iran.

Table 1 16S rDNA gene-targeted specific primers and TaqMan probes used in this study

Target bacteria	Primer Probe[a]	Oligonucleotide sequence	Product size (bp)	Tm	Ref.
F. prausnitzii	Primer F	ATAATGACGGTACTCAACAAGGA	171[b]	59 °C	21
	Primer R	ACAGTTTTGAAAGCAGTTTATGG			
	Probe	ACTTCCAACTTGTCTTCCCGCCTG			
B. fragilis	Primer F	CGAGGGGCATCAGGAAGAA	136	59 °C	21
	Primer R	CGGAATCATTATGCTATCGGGTA			
	Probe	CTTGCTTTCTTTGCTGGCGACCG			
B. longum	Primer F	GTGGCTTCGACGGGTAG	200	59 °C	21
	Primer R	ACGGGTAAACTCACTCTCG			
	Probe	TTGCTCCCCGATAAAAGAGGTTTACA			
G Lactobacillus	Primer F	GTCTGATGTGAAAGCCYTCG CCAGGG	204[c]	60 °C	16
	Primer R	TATCTAATCCTGTTYG YCACCGCTA			
	Probe	CACATGRAGTTCCACT			
G Bifidobacterium	Primer F	GGTTAACTCGGAGGAAGG GTACCGG	85	60 °C	16
	Primer R	CCATTGTAGCA CGTCAGATCATCA			
	Probe	TGCCCCTTACG			
G Fusobacterium	Primer F	GTATGTCRCAAGCGTTATCC AACGCA	100	60 °C	16
	Primer R	ATACRGAGTTGAGC CCTAGACGCG			
	Probe	CTTTACGCCCAAT			
Ph Firmicutes	Primer F	CGAACGGGATTAGATACC	186	60 °C	This
	Primer R	CGAATTAAACCACATACTCC			
	Probe	CCCCGTCAATTCCTTTGAGTTT			
Ph Bacteroidetes	Primer F	GTGGTTTAATTCGATGATACGC CGCT	154	60 °C	This
	Primer R	CGTTATGGGACTTAAG CCTCACGG			
	Probe	CACGAGCTGACG			
Ph Proteobacteria	Primer F	CAAAKACTGACGCTSAGGTG	96	60 °C	This
	Primer R	GGCACAACCTBCAARTCG			
	Probe	AATCCTGTTTGCTCCCCACGCTTTC			
Ph Actinobacteria	Primer F	CCGTTACTGACGCTGAGGAG GCGGGA	141	60 °C	This
	Primer R	TGCTTAACGCG TAGATACCCTGGTA			
	Probe	GTCCACGCCGTA			

[a] Primers F (forward), R (reverse), and probes targeting the 16S rDNA gene

Real-time PCR conditions and optimization

Real-time TaqMan qPCR in Rotor-Gene 6000 real-time PCR cycler (Qiagen Corbett, Hilden, Germany) was used to characterize the bacterial DNA present in the stool samples. Triplicate samples were routinely used for the determination of DNA by real-time PCR, and the mean values were calculated. The real-time qPCR reaction was performed in a total volume of 20 ml including 0.5 ml of forward primer, 0.5 ml of reverse primer, 0.5 ml of TaqMan probe, 12 ml of Probe Ex Taq (Probe qPCR) Master Mix (Takara Bio, Shiga, Japan), 1 ml of template DNA, and 5.5 ml sterilized ultrapure water. The real-time qPCR reaction conditions for amplification of DNA were 95 °C for 30s, followed by 40 cycles of denaturation at 95 °C for 5 s, and annealing/extension at different temperatures associated with any bacteria for 30 s. Negative controls including all the elements of the reaction mixture except template DNA were performed in every analysis. According to our previous study [18], positive control strains used in this study were obtained from the American Type Culture Collection (ATCC).

To construct standard curves for the real-time PCRs, all bacterial standard strains were cultured on BHI agar (Merck, Germany). A suspension was made in BHI broth (Merck, Germany) and DNA was extracted. The DNA concentration was determined 3 times by using the Nanodrop ND-1000 (Nanodrop Technologies, Wilmington, USA), and the mean value was used for further calculations. Standard curves were created according to Applied Biosystems tutorials [19] and normalized to the copy number of the 16S rRNA gene for each species.

Statistical analysis

Statistical analysis was performed with SPSS for Windows, version 18.0 (SPSS, Inc., Chicago, Ill.) and Minitab version 16.2.0. An independent sample *t* test was used to compare the means of different variables between the study groups. Linear correlation between the variables was estimated by Pearson correlation. Ninety-five percent confidence intervals (CI) for sensitivity and specificity were calculated. All data were expressed as mean ± standard deviation, and the real-time

Table 2 Weight and BMI variables in control, diabetic, and obese groups

	Normal	Diabetic			Obese			Diabetic/Obese	
	Mean ± SD	Mean ± SD	Mann-Whitney test		Mean ± SD	Mann-Whitney test		Mann-Whitney test	
			T	Sig.		T	Sig.	T	Sig.
Weight	64.38 ± 6.80	74.27 ± 10.67	− 3.314	0.002	120.5 ± 16.58	16.88	< 0.001	− 10.89	< 0.001
BMI	24.28 ± 3.00	26.83 ± 3.29	− 2.425	0.021	44.6 ± 3.73	19.44	< 0.001	− 17.66	< 0.001

PCR results were presented by Box and Whisker charts, graphically.

Results

Table 2 summarizes the weight and the BMI variations in all the three groups. Pursuant to this table, the means of weight in control, diabetic, and obese groups were 64.38 ± 6.80, 74.27 ± 10.67, and 120.58 ± 16.58, respectively. Furthermore, the means of BMI in these three groups were 24.28 ± 3.00, 26.83 ± 3.29, and 44.65 ± 3.73, respectively.

In this case-control study, real-time PCR analysis was performed to evaluate the differences in composition of fecal microbiota in diabetic, obese, and healthy individuals for *F. prausnitzii*, *B. fragilis*, *B. longum*, *Lactobacillus* spp., *Bifidobacterium* spp., *Fusobacterium* spp., *Firmicutes* phylum, *Bacteroidetes* phylum, *Proteobacteria* phylum, and *Actinobacteria* phylum. Observations related to quantification of bacterial groups are represented in Table 3 and illustrated in Figs. 1 and 2.

According to Table 3, frequency of bacterial species in obese group in comparison with control group are changed significantly ($p < 0.05$) with one exception, *Bacteroides fragilis*. On the other hand, none of bacteria in diabetic group were not changed significantly ($p > 0.05$) versus control group, except *Bacteroides* phylum and *Lactobacillus* spp. Figures 1 and 2 can show us patterns of distribution of fecal microbiota composition in different weight and different groups, respectively. Impressive observations related to quantification of bacterial genera were as follows:

- *Lactobacillus* and *Bifidobacterium* spp: Weight gain significantly reduced *Lactobacillus* spp. copy number between the control and the diabetic vs the obese subjects ($p < 0.001$).
- *Fusobacterium* spp: The quantity of *Fusobacterium* spp. did not have correlation with the weight in the T2DM group and healthy ones ($p < 0.001$), though there was significant changes in *Fusobacterium* spp. frequency between the obese group vs other ones ($p < 0.001$).
- *Bacteroidetes* phylum: Surprisingly, *Bacteroidetes* phylum was significantly more frequent in the diabetic patients compared with the control and obese subjects ($p < 0.001$).
- *Firmicutes*, *Proteobacteria*, and *Clostridium cluster iv* phyla: No significant difference was observed in copy number of *Firmicutes*, *Proteobacteria*, and

Table 3 Different types of bacteria in the control, diabetic, and obese patients

Type of bacteria	Control ($n = 18$)	Diabetic ($n = 25$)			Obese ($n = 48$)		
	Copies/g of fecal	Copies/g of fecal	Levene's test		Copies/g of fecal	Levene's test	
			z	Sig.		*z*	Sig.
B fragilis	7.7E+15 ± 3.3E+16	3.1E+08 ± 8.4E+08	− 0.86	0.384	5.8E+07 ± 1.3E+08	− 1.010	.313
B longum	2.3E+10 ± 2.9E+10	4.2+10 ± 8.5E+10	− 0.032	0.975	2.3E08 ± 5.1E+08	− 6.175	< 0.001
F prausnitzii	7.7E+15 ± 3.3E+16	4.1E+07 ± 1.5E+08	− 0.987	0.319	2.8E+08 ± 4.3E+08	− 3.398	.001
Ph Bacteroidetes	1.8E+10 ± 2.3#+10	8.5E+11 ± 2.9E+11	− 5.330	< 0.001	8.9E+09 ± 1E+10	− 2.441	.015
Ph Firmicutes	5.2E+10 ± 2.8E+10	2.9E+10 ± 2.2E+10	− 0.333	0.739	3.4E+08 ± 1.1E+09	− 6.201	< 0.001
G Bifidobacterium	2.2E+10 ± 2.8E+10	2.3E+10 ± 1.7E+10	− 0.333	0.739	3.4E+08 ± 1.1E+09	− 6.201	< 0.001
Ph Proteobacteria	5.2E+10 ± 2.8E+10	6E+10 ± 4.7E+10	− 0.032	0.975	6.9E+08 ± 1.9E+09	− 6.223	< 0.001
C cluster iv	1.7E+11 ± 1.2E+11	1.3E+11 ± 1.1E+11	− 1.382	0.167	8.6E+08 ± 1.3E+09	− 6.223	< 0.001
G Fusobacterium	4.7E+10 ± 7.9E+10	3.8E+10 ± 4E+10	− 0.934	0.35	1.3E+07 ± 4.6E+07	− 6.235	< 0.001
G Lactobacillus	4.2E+09 ± 3.1E+09	2.5E+10 ± 2.1E+10	− 4.591	< 0.001	2.4E+08 ± 7.7E+08	− 5.770	< 0.001

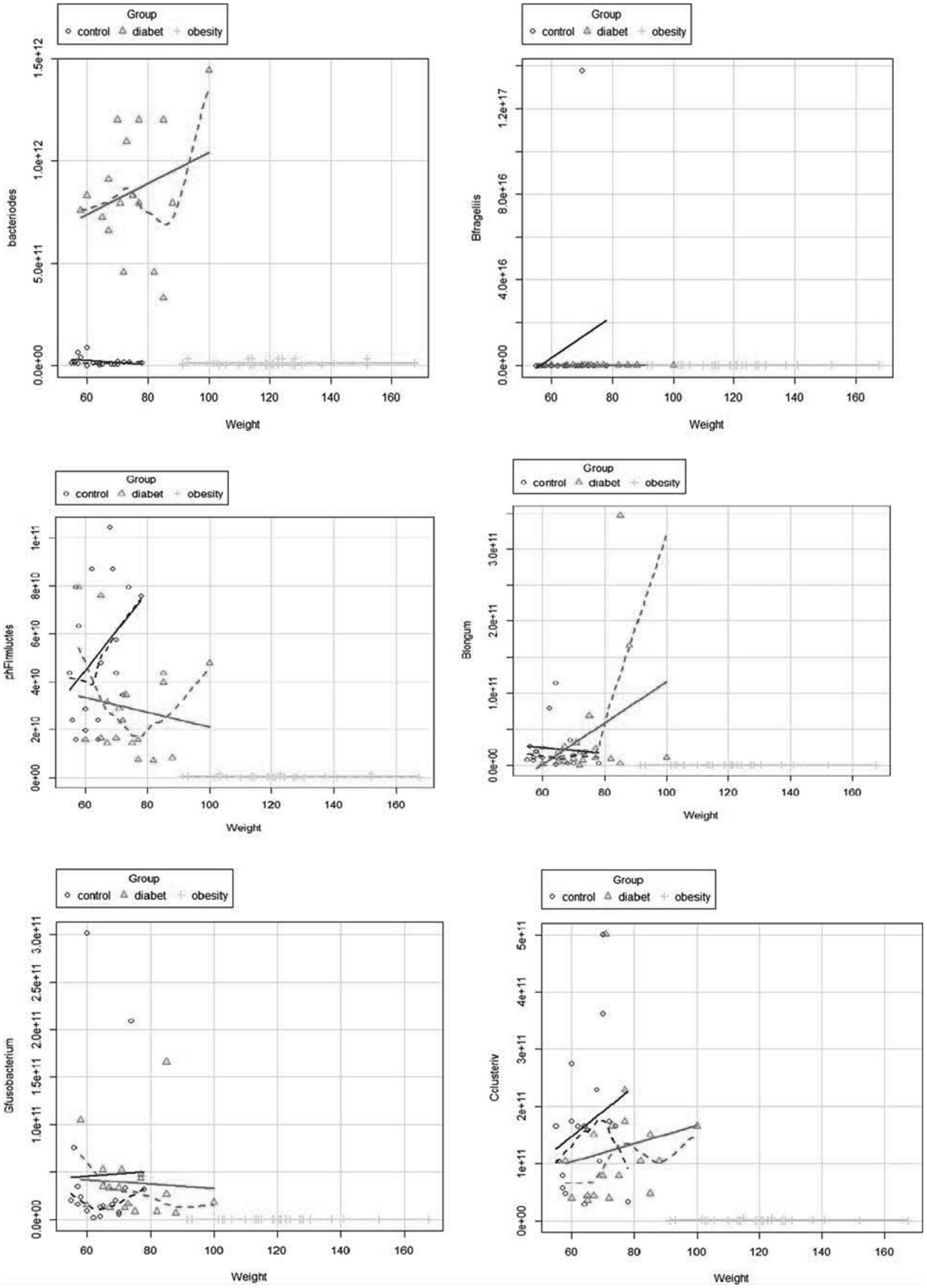

Fig. 1 The scatter plots of various types of microbiota in control, obese, and diabetic patients for different weights

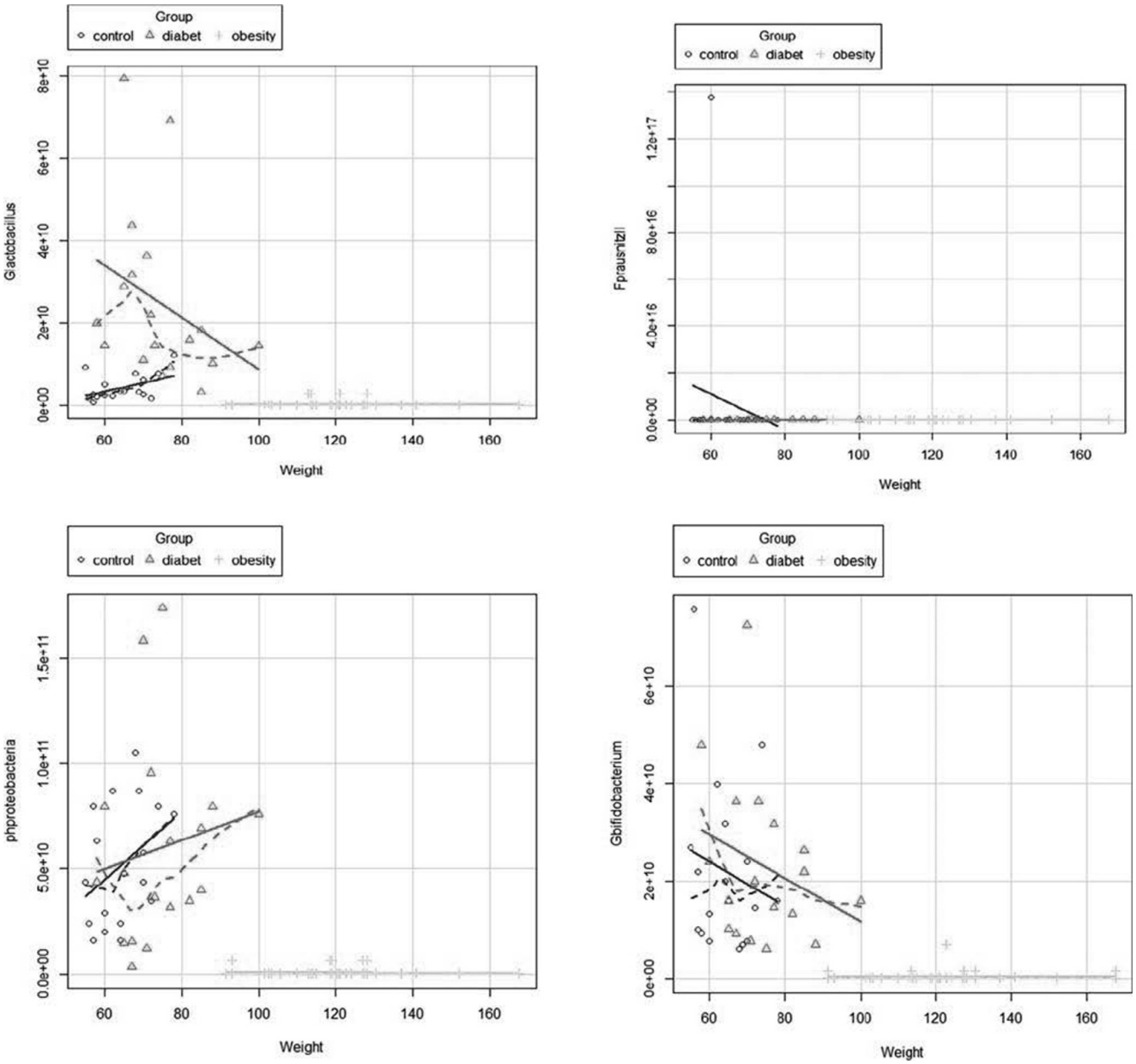

Fig. 1 (continued)

Actinobacteria phyla between the T2DM and the control group, although weight gain significantly reduced copy number of these bacterial phyla in the obese subjects ($p < 0.001$).

Discussion

The current research showed that the intestinal microbiota composition of healthy is heterologous as compared with the diabetic and obese patients. Various studies have shown that changes in compounds of specific genera and intestinal bacterial species in human or animal models may lead to prolonged diseases like diabetes, obesity, IBD, cancer, and autism [20, 21]. The study of Murri et al. on the T1D patients displayed a noteworthy distinction in the *Lactobacillus*, *Bifidobacterium*, *Prevotella*, *Clostridium*, and *Bacteroides* genera levels as well as *Firmicutes*, *Bacteroidetes*, and *Actinobacteria* phyla levels among diabetic and control groups [22]. In the present study, we discovered that the level of *Firmicutes* phylum in healthy subjects was considerably higher than diabetic patients in contrast with the findings of Remely et al. and Larsen et al. [23, 24]. Wu et al. [25] showed a significant higher concentration of *Bifidobacterium* in control groups in comparison with T2DM patients; however, in our study it

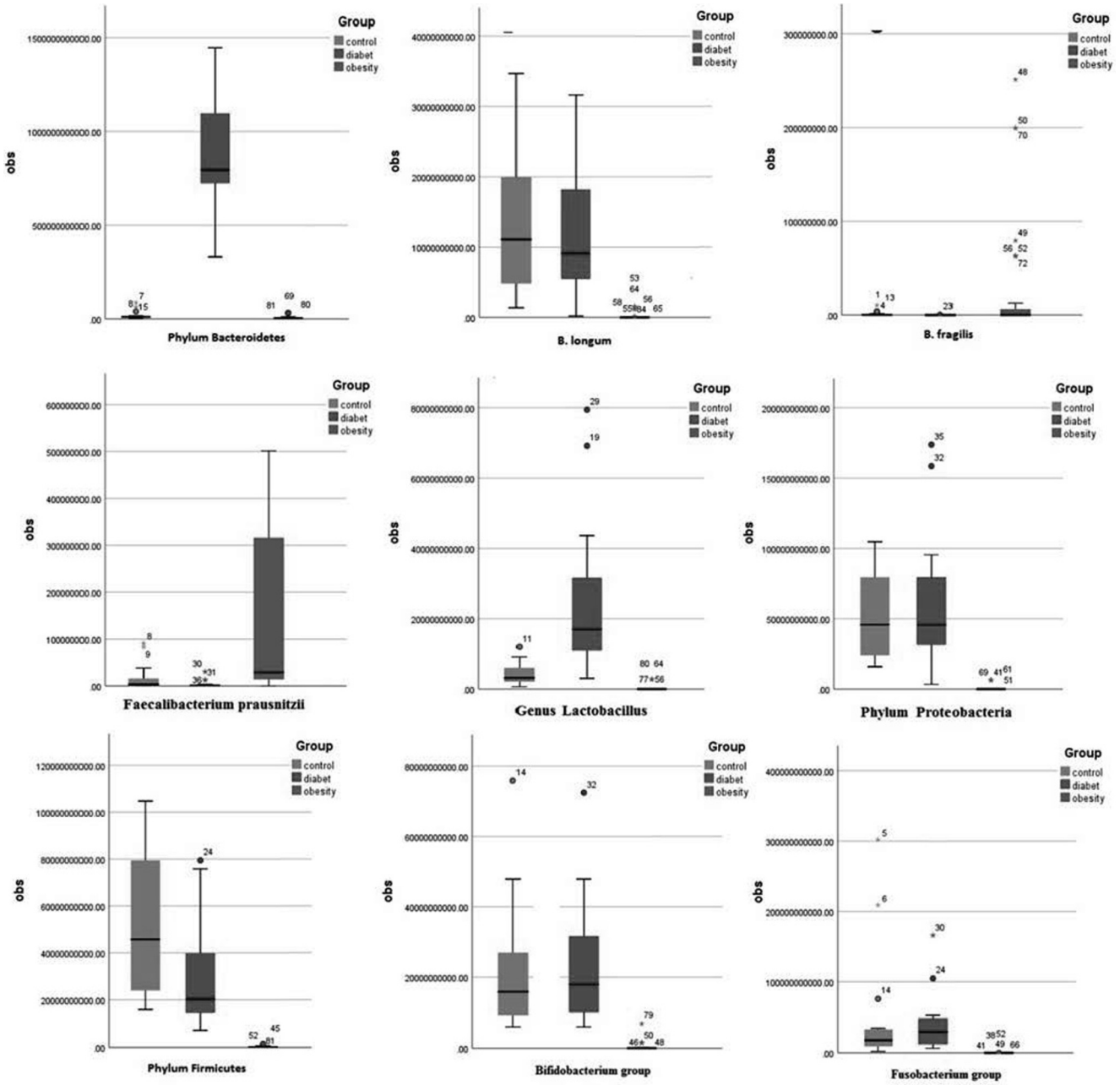

Fig. 2 Number of different types of microbiota in control, diabetic, and obese groups

was higher than T2DM. Also, Remely et al. did not show important dissimilarity in the number of copies of *Bifidobacterium* genus among the control and case individuals [24]. It should be noted that in our previous research, the *Bifidobacterium longum* species concentration belonging to the genus *Bifidobacterium* was not significantly different between diabetic and non-diabetic individuals [26]. We also discovered that the frequency of the *Prevotella* and *Fusobacterium* groups in the diabetic group were reasonably higher than the healthy ones. However, the alterations were not statistically noteworthy. Constantly, Remely et al. [24] and Larsen et al. [23] did not show a significant difference in *Prevotella* level between T2DM patients and healthy subjects. Correspondingly, according to Field et al. [27], *Fusobacterium* was not expressively different in stool specimens collected from T2DM patients related to the controls. Nevertheless, Casarin et al. [28] reported that *Fusobacterium* genus was much lower in the control group than in T2DM patients.

Most likely, T2DM is associated with the substitution in the balance of intestinal microbiota, neither the achievement of a microbe nor a simple change in diversity. For example, Wu et al. [25] investigated the levels of bacterial assortment in

T2DM and non-diabetic patients and showed that there was not any substantial difference between bacterial species in the two groups. Though, they pointed to a meaningful change in the number of bacterial phyla, genera, and species [25]. They believed that the combination of dominant bacteria in the intestinal microbiota of T2DM individuals was not similar to healthy subjects. Regarding previous studies that indicated an association between T2DM and overweight/obesity, we also showed significant correlation between BMI and all the microbial groups, *Bacteroides fragilis*.

Remely et al. [24] and Larsen et al [26] and our results are consistent in overweight individuals, but it contrasts with some studies on the relationship between BMI and this group of bacteria [29, 30]. On the other hand, Million et al. [30], Ignacio et al. [29] showed a positive and noteworthy connection between *Lactobacillus* concentration and BMI in obese subjects, and Saber et al. [31] exhibited a meaningful negative correlation between *Lactobacilli* count and BMI. As with our findings, Million et al. [30], Collado et al. [32] and Remely et al. did not correlate results between *Bifidobacterium* and BMI. In contrast, Ignacio et al. [29] found a negative correlation between BMI and *Bifidobacterium*. Andoh et al. [33] showed a significant positive correlation between *Fusobacterium* and BMI; nevertheless, in the present study, there was no association between this bacterial frequency and BMI in the studied groups. Si et al [34] reported that *Prevotella* spp. have a significant correlation with BMI, but it is not in line with our results. These controversial results about alterations in the composition of intestinal bacteria in T2DM patients and also ambiguous findings in relation between different groups of bacteria and BMI can be explicated by heterogeneity in assorted factors like genetic background, ethnicity, geographical location, environment and occupation, disclosures, medical history, potential underlying diseases/disorders, lifestyle habits, and dietary routines of individuals during studies.

In the present study, we tried to limit the maximum perplexing variables where the members in the T2DM and control group were coordinated by age, sex, race, living environment, and non-interventional medications and food that might affect the outcome (such as various antibiotics, probiotics, and prebiotics). It should be kept in mind that the design of a technical study (i.e., a specific bacterial primer and probe design for a real-time qPCR) is of significant importance in the final output of the study. Thus, some of these heterogeneities may return to the study design. In general, in the present study, we exhibited that T2DM and obese are associated with changes in the gut microbes. Conversely, due to the scheme of this study, we remained restricted to creating a causative connection concerning the changes in the intestinal microbial composition and the disease. Moreover, it is uncertain whether T2DM and obese are created by microbial changes or that it is just a replication of the condition of the disease. This matter should be taken into consideration in longitudinal research.

Conclusion

The outcomes of this study enhance basic knowledge about the gut microbiome in T2DM and obese patients. This survey shows the abundance of different types of bacteria in the gut, which in turn can affect health. In addition, eating habits and probiotics supplements may induce change in the gut microbiota and stabilize microbial communities, which help to prevent or delay T2DM and obese. Nowadays, there is a clear need to continue to explore the roles of the microbiome in obesity and T2DM to facilitate the development of effective therapeutic strategies.

Compliance with ethical standards

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

Ethical statement This project was done based on the ethical guidelines as previously approved by the Iran University of Medical Science, Tehran, Iran (project no: IR.IUMS.REC.1397.1072).

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ORIGINAL ARTICLE

Prevalence of IA-2 antibody in patients suffering from diabetes and their first-degree relatives

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Abstract

Background Type 1 diabetes mellitus (T1DM) is an autoimmune disorder accompanied by activation of auto-reactive B cells, autoantibody production, and consequently insulin-producing beta cell destruction. Some evidences support the value of auto-antibodies such as anti-islet cell antigen (IA-2) auto-antibody in T1DM diagnosis and prognosis. The present study investigated the presence of IA-2 antibody in T1DM patients and their first-degree relatives as well as T2DM patients and healthy people to evaluate the diagnostic and prognostic value of anti-IA-2 in T1DM.

Methods In total 264 cases including 38 T1DM patients, 36 first-degree relatives, 88 T2DM patients, and 102 age-/sex-matched healthy controls participated in this study. After venous blood collection, sera were isolated and the level of IA-2 antibody was measured by ELISA method. Routine hematologic and biochemical tests including complete blood count (CBC), fasting blood sugar (FBS), hemoglobin A1c (HbA1C), urea, creatinine, as well as lipid profile and liver function tests were analyzed.

Results Upregulated level of IA-2 antibody was observed in 47.4 and 5.6% of T1DM and their relatives, respectively; however, the level was significantly higher in T1DM compared to T1DM first-degree relatives ($p < 0.05$). In addition, none of the T2DM patients nor healthy controls were positive for IA-2 autoantibody. There was not any significant correlation between anti-IA-2 levels and total daily dose of insulin and the biochemical and hematological parameters.

Conclusion It seems that the measurement of anti-IA-2 antibody has no value in prediction or management of T1DM. Further studies need to reveal the reason for high anti-IA-2 titer in some patients.

Keywords Type 1 diabetes mellitus · Autoantibodies · IA-2 antibodies · Biomarkers · Iran

Introduction

Type 1 diabetes mellitus (T1DM), which is also known as insulin-dependent diabetes, is caused by a chronic T cell–mediated autoimmune demolition of the insulin-producing pancreatic beta cells [1]. Epidemiological surveys have shown an increasing trend in the incidence and prevalence of type 1 diabetes [2–4]. According to the World Health Organization (WHO), diabetes global prevalence among adults has risen to 8.5% of the population, affecting 422 million people in 2014. Moreover, based on the previous studies, first-degree relatives of individuals with type 1 diabetes have a six times higher risk of developing the disease [5]. Diabetes especially T1DM progresses silently and gradually; therefore, many patients are not aware of their disease until the majority of the beta cells have been destroyed and the symptoms become prominent. The role of the immune system in the pathogenesis of T1DM is not yet fully elucidated, but it is a widely held view that T cell–mediated mechanisms play a major role in the destruction of pancreatic beta (β) cells [6]. This process is probably triggered by environmental stimuli in genetically susceptible subjects which will eventually lead to β-cells' death [7]. The role of antigen-presenting cells especially dendritic cells (DC) is fundamental as they activate CD4+ T cells as well as CD8+ T

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cells by presenting β-cell antigens to them. Activation of CD8+ T cells leads to β-cell destruction through release of cytolytic granules or death signals. Furthermore, activation of CD4+ T cells results in macrophage-mediated killing and activating B cells that consequently differentiate into autoantibody-producing plasma cells; these produced autoantibodies promote autoimmune destructive responses by activation of complement cascade and macrophage-mediated killing of β-cells [8–10]. Regarding the evidences that strongly support the involvement of autoimmunity in pathogenesis of type 1 diabetes [11, 12], one can mention the circulating self-reactive cells and autoantibodies in T2DM [11] and also beliefs in a third type of diabetes, known as latent autoimmune diabetes in adults (LADA) which is a slow-progressing T1DM and difficult to discriminate from T2DM [13]. Considering the role of autoantibodies in the pathogenesis of T1DM and possibly T2DM, several autoantibodies have been identified in patients, including anti-insulin (IAA), anti-glutamic acid decarboxylase 65 (GAD65), anti-zinc transporter 8 (ZnT8), and an anti-islet cell antigen named anti-IA-2 or anti-ICA512. Studies have shown that they may be present for years or even decades before the onset of T1DM [14, 15] and hereof, they may have either a prognostic or diagnostic value [16]. Among different autoantibodies, anti-IA-2 has attracted more attention. IA-2 antigen is a member of receptor-type protein tyrosine phosphatases (RPTPs) family, which is mainly expressed in secretory granules such as insulin-producing β-cells and has critical roles in production, exocytosis, recycling of secretory granules containing insulin, as well as β-cell proliferation [17]. According to some evidences, IA-2 is a major antigen target of islet cell autoantibodies in autoimmune diabetes condition and is present in many of T1DM patients [16]. Considering the prevalence, socio-economic burdens, and the irreversible nature of T1DM, a sensitive and specific biomarker which helps early diagnosis of at-risk individuals would be very helpful in the management of the disease. The aim of this study was to evaluate the serum level of anti-IA-2 autoantibody in a group of T1DM patients, their first-degree relatives, as well as T2DM patients and healthy controls, in search for a diagnostic and/or prognostic marker for T1DM.

Materials and methods

Participants and study design

A total of 264 individuals participated in this descriptive-analytic cross-sectional study, including 38 T1DM, 36 first-degree relatives, 88 T2DM patients, and 102 age-/sex-matched healthy controls. The study was approved by the Ethics Committee of Birjand University of Medical Sciences (BUMS), and all the participants received a written consent form. Both T1DM and T2DM patients were recruited from the registry database of Diabetes Research Center of Birjand University of Medical Sciences. For each T1DM patients, the closest healthy sibling in terms of age was selected and tested if any existed. Healthy controls were selected from university personnel or their families without any record of underlying health conditions. All participants were visited by an expert physician at Diabetes Research Center, and the demographic data were collected by means of a questionnaire. Individuals with a history of any serious health problems, any kinds of addiction, and those who took immunosuppressive drugs were excluded from the study. For all selected cases, a fasting venous blood sample was taken and routine hematologic and biochemical tests including CBC, FBS, HbA1C, cholesterol, LDL, HDL, triglyceride, urea, creatinine, and liver function tests were analyzed.

Measurement of IA-2 serum autoantibody by ELISA

Blood samples were centrifuged and the separated sera were stored at − 20 °C until further analysis. Serum anti-IA-2 autoantibody was measured by a commercial ELISA kit (DLD, Hamburg, Germany) according to the kit's manual. All samples were analyzed in duplicate. The kit's sensitivity and specificity were 66% and 99%, respectively, and the detected limit was from 7.5 to 4000 U/ml.

Statistical analyses

Statistical analysis was performed by using SPSS version 16 software (IBM, Armonk, NY, USA). All data were expressed as mean ± standard deviation (mean ± SD). Statistical analyses for significant differences were performed according to parametric and nonparametric tests where appropriate. Correlation coefficients between the autoantibody level and disease severity performed by Pearson or Spearman tests as appropriate. p value less than 0.05 was considered significant.

Results

A total of 264 individuals were enrolled in this study. Table 1 presents demographic data and laboratory tests' results. Figure 1 and 2 show disease duration and age of onset in T1DM patients.

The correlation between anti-IA2 and other clinical and laboratory parameters including age, disease duration, age at onset, BMI, FBS, HbA1C, TG, cholesterol, LDL, HDL and LFT was not significant (Table 2).

Anti-IA2 antibody was detected in 47.4 and 5.6 percent of T1DM and their relatives respectively but none of T2DM patients or healthy controls was positive for IA-2 autoantibody (Table 3). The mean of anti-IA2 antibody was significantly higher in T1DM than T1DM first degree relatives (665.34 IU/

Table 1 Characterization and laboratory finding in different study groups. The data are expressed as mean ± SD

Groups		T1DM	T1DM relatives	T2DM	Healthy
N		38 (F = 24, M = 14)	36 (F = 16, M = 20)	88 (F = 48, M = 40)	102 (F = 56, M = 46)
Age (year)		12.05 ± 6.52	7.17 ± 4.48	51.89 ± 10.20	31.39 ± 22.61
FBS: (mg/dl, *N*)	< 100	14	36	8	102
	100–126	6	0	6	0
	> 126	18	0	74	0
TG		85.47 ± 22.38	82.44 ± 14.98	90 ± 118.66	118.71 ± 3625
Cholesterol		163.37 ± 33.51	149.50 ± 191.77	191.77 ± 43.98	174.86 ± 20.27
LDL		105.21 ± 32.18	95.17 ± 26.12	114.23 ± 35.09	143.08 ± 100.35
HDL		40.63 ± 13.23	36.83 ± 6.21	38.57 ± 7.32	37.91 ± 5.97
HbA1C (mg/dl, *N*)	< 6.5	2	26	8	102
	6.5–9	16	10	42	0
	> 9	20	0	36	0

ml vs. 222.22 IU/ml, $p < 0.05$). None of T2DM patients or healthy controls was positive for IA-2 autoantibody (Tables 2 and 3).

The correlation between anti-IA-2 and other clinical and laboratory parameters including age, disease duration, age at onset, BMI, FBS, HbA1C, TG, cholesterol, LDL, HDL, and LFT was not significant (Table 4).

Discussion

Type 1 diabetes mellitus (T1DM) is a disorder characterized by the destruction of pancreatic beta cells. Although T cells play a critical role in the pathogenesis of T1DM, there are evidences supporting the role of B cells and their autoantibodies in pathogenesis of T1DM as well [18]. Activated auto-reactive B cells produce autoantibodies and consequently promote autoimmune responses leading to pancreatic beta cell destruction [8, 9]. Some evidence represents the predictive role of these autoantibodies such as anti-IA-2 in T1DM [14, 15].

In the current study, anti-IA-2 antibody was detected in about half of the T1DM patients. Consistent with our results, Hawa et al. reported 44% anti-IA-2 positivity in their T1DM patients [19]. Another study performed in Brazil showed 62.9% positivity for anti-IA-2 in recent-onset T1DM patients [20].

Several studies elucidated the predictive role of anti-IA-2 in developing type 1 diabetes [14, 21, 22]; one of the studies stated that combining ZnT8A with IAA, GADA, and IA-2 assays increases the sensitivity of autoimmune detection [14]. Consistently, the study of Savola et al. reported a 55% predictive value in high levels of anti-IA-2 through 7.7 years duration [23].

In contrast to our findings, Singh et al. showed that 22% of young T1DM patients in north India were positive for anti-IA-

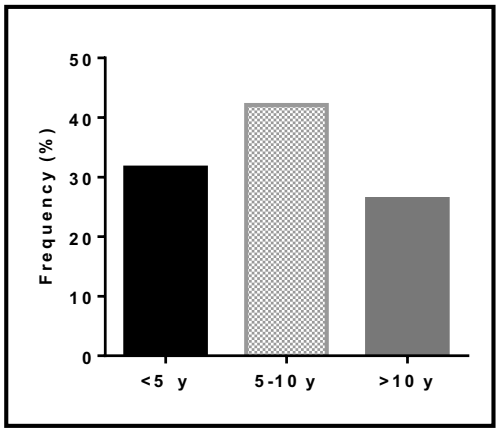

Fig. 1 Duration of disease among T1DM patients

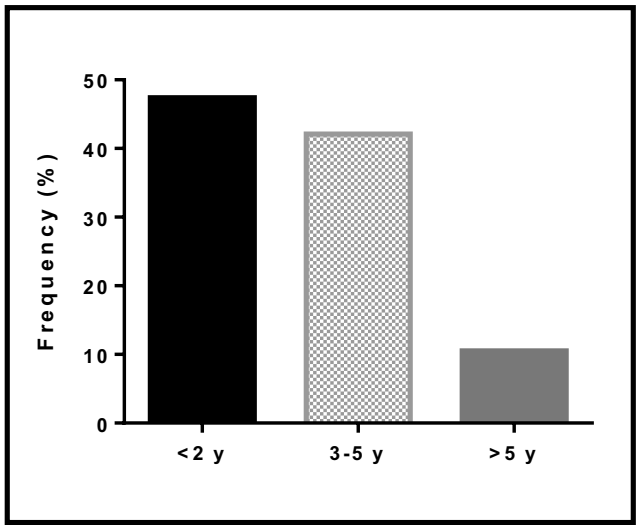

Fig. 2 Age of onset among T1DM patients

Table 2 The correlation between anti-IA-2 and age, duration of disease, and age of onset

	Age	Duration of disease	Age of onset
Level of anti-IA-2	r = −0.16	r = 0.14	r = −0.15
	$p = 0.52$	$p = 0.58$	$p = 0.53$

Table 4 Level of anti-IA-2 in different groups of the study

Level of anti-IA2 Groups	Negative >9 (U/ml)	Low to medium 9–300 (U/ml)	High > 300 (U/ml)
T1DM	% 52.6	% 21.1	% 26.3
First-degree relatives	% 94.4	0	% 5.6
T2DM	% 100	0	0
Healthy control	% 100	0	0

2 [24] and Sanyal et al. reported the 30% seropositivity in their T1DM patients [25].

Several reasons may explain this inconsistency in the frequency of anti-IA-2 antibody and lack of IA-2 antibody in large group of T1DM patients. This can be explained by non-autoimmune pathogenic mechanisms underlying type 1 diabetes, such as genetic defects in beta cells or disorders of the exocrine pancreas [23].In addition, antibody production needs the presence of antigens while by the time of diagnosis, most of the beta cells have been destroyed, and there is little antigen left so the level of autoantibody will be decreased. Furthermore, difference in methodology and kit sensitivity could also be a reason.

We could detect IA-2 antibody in 5.6% of T1DM first-degree relatives. Similar to our findings Laadhar et al. reported 5.2% anti-IA-2-positive subjects among Tunisian T1DM first-degree relatives [26]. Moreover, in another study, anti-IA-2 was positive in about 2.7% of T1DM first-degree relatives [27].

In this study, anti-IA-2 was negative for all T2DM patients and healthy controls. Since T2DM had been introduced as a non-autoimmune disease, the result was compatible with our expectation and questioned the role of autoimmunity in T2DM in spite of some reports indicating the involvement of autoimmune processes in T2DM by observing the presence of some diabetes-related autoantibodies and self-reactive lymphocytes in T2DM [11]. Damanhouri et al. showed that 3 out of 99 T2DM patients were positive for anti-IA2A [28]. Consistently, Hawa et al. reported 3% anti-IA-2 positivity in T2DM patients [19]. Both the studies reported a very low frequency of anti-IA-2 in T2DM which is somehow similar to our results. This difference could be because of our smaller study population and late diagnosis of T2DM in our country which can lead to the reduction of autoantibody titers compared to early phases of the disease [19]. It is also possible that some IA-2-positive cases suffered from LADA (latent autoimmune diabetes in adult) which is very similar to T1DM but appears at older ages and mistakenly considered as T2DM [13].

There was not any significant correlation between IA-2 autoantibody and laboratory parameters including BMI, FBS, HbA1C, TG, HDL, and LDL. The higher level of serum cholesterol and triglyceride in T2DM and healthy groups than T1DM and T1DM relatives is related to difference in age.

The titer of anti-IA2 autoantibody is known to decrease with longer disease duration and varies in different ages [29]. Jinko et al. showed that anti-IA2 negatively correlated with age, with the highest titer in 8–13 years old subjects [30]. Other studies also reported similar findings [19, 23, 28]. In contrast, in the current study, there was no correlation between anti-IA-2 level with disease duration as well as age of onset. Similarly, in a large study on 5020 T1DM patients by Tridgell et al., no significant correlation between disease duration and IA-2 level was found which supports our results [29].

In conclusion, the results of the current study showed that half of T1DM patients had detectable level of IA-2 antibody but there was no correlation between IA-2 antibody and disease-related factors. It seems that measurement of anti-IA2 antibody has little or no value in prediction or management of T1DM. Further studies need to reveal the reason for high anti-IA2 titer in some patients and a few relatives.

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Compliance with ethical standards

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

Table 3 The frequency of positive and negative anti-IA2 in the study groups

	Negative	Positive
T1DM	52.6%	47.4%
T1DM relatives	94.4%	5.6%
T2DM	100%	0%
Healthy controls	100%	0%

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ORIGINAL ARTICLE

The impact of high-fat and high-protein meal of adolescents with type 1 diabetes mellitus receiving intensive insulin therapy on postprandial blood glucose level: a randomized, crossover, breakfast study

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Abstract

Background In addition to carbohydrate count, this study aims to investigate the impact of the determination of bolus insulin doses by fat and protein counts on postprandial blood glucose level for adolescents having type 1 diabetes mellitus.

Methods The study was crossover and randomized; and all of participants were given standard breakfast (insulin dose according to carbohydrate/insulin ratio) for 1 day, and high-fat and high-protein breakfast for 2 days. The insulin dose for one of test meal was determined based on carbohydrate/insulin ratio. In the second application, in addition to carbohydrate/insulin ratios of the adolescents, 1 unit of insulin per what was added for each 200 kcal of energy provided from fat and protein of the meal. Postprandial blood glucose was recorded for 4 h using a continuous glucose monitoring system at intervals of 30 min.

Results The mean blood glucose level between 0 and 240 min following consumption of different meals increased significantly in second application after 150th minute comparing with first application ($p < 0.05$).In addition to this, between 30 and 240 min glycemic response of second application seemed to be higher than those responses in first and third application. The difference among them was not significant ($p > 0.05$).However, the glycemic excursion of 30–0 min in third application was higher than the excursion in first and second applications while the glycemic excursion in first application between 150 and 120 min was higher than in third application ($p < 0.05$).

Conclusions These evidences demonstrated that high-fat and high-protein meal increases the requirement of insulin. Eventually, this study shows that there could be alternative algorithms to carbohydrate-based approach for the determination of the bolus insulin dose.

Keywords Type 1 diabetes mellitus · Postprandial glucose level · High-fat meal · High-protein meal

Highlights • High-fat and high-protein meal raised postprandial blood glucose after 150 min and this meal increased the requirement of insulin in adolescent with type 1 diabetes
• Postprandial glycemia was improved when fat and protein was counted along with carbohydrate in adolescents with type 1 diabetes
• When calculating insulin dose, the amount of fat and protein was considered for glycemic control in adolescents with type 1 diabetes

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Introduction

Maintaining good glycemic control for individuals with diabetes is important in preventing and/or delaying complications such as cardiovascular disease, retinopathy, nephropathy, neuropathy, and amputations [1]. However, it is possible to achieve this by integrating many factors such as measurement of blood glucose level at least 4–5 times per day, the correct interpretation of the blood glucose result, and correct intervention with insulin, nutrition, and exercise management [2]. Nutrition is one of the main components of diabetes care and education, and the main nutrition-related factor in diabetes management is to take a consistent amount of carbohydrates in main and snacks and to avoid changes in the amount of carbohydrate intake [3].

Carbohydrates are the main nutrient that affect postprandial blood glucose level and determine insulin requirement [4]. Because in the intestine, dietary carbohydrates are very rapidly hydrolyzed into sugars [5] and approximately 90% are converted to glucose within 1–2 h after ingestion. Blood glucose levels peak within 60–90 min following a carbohydrate-based meal in individuals with type 1 diabetes mellitus. However, the size of a meal, carbohydrate type, and its macronutrient pattern influence the postprandial glucose excursion [6]. Therefore, the carbohydrate counting method is widely used in the planning of meals for individuals having diabetes mellitus. However, fat and protein have also been shown to impact postprandial glycemia. Foods with high protein or fat content in children and adolescents lead to delayed blood sugar levels (up to 3–6 h after eating) and an increase in insulin requirements. In addition, it may cause a risk of hypoglycemia in the early period (1–2 h) due to delayed gastric emptying and digestion [7, 8]. In studies having been conducted in recent years, with continuous glucose monitoring (CGM), it is emphasized that the meals with the same carbohydrate contents and different contents of fat and protein have different glycemic responses, and the meals with high-fat and high-protein require more insulin comparing with the meals with low fat and protein [8–12]. For this reason, the International Society for Pediatric and Adolescent Diabetes (ISPAD 2018) has suggested that in addition to carbohydrate counts, the effect of proteins and fats on blood sugar should be taken into account in insulin dose calculations [3].

The increase of insulin dose is required in order to control hyperglycemia caused by high-fat and high-protein meals. Bolus doses are recommended to be planned in association with the carbohydrate content of the meal as well as considering the amount of fat and protein of the meal in order to ensure the ideal postprandial glucose control [9].

In the study of Lopez et al., which two algorithms were used for high-fat and high-protein cases on 33 children and adolescents having type 1 diabetes mellitus and using the insulin pump (Pankowska Equation or the Food Insulin Index), blood glucose was monitored by CGM for 5 h [13]. While the risk of hypoglycemia was higher in Pankowska Equation ($p < 0.05$), it was seen there was no difference between those two only when carbohydrate counting and Food Insulin Index Equation were compared. In another study with participants of eleven, it was stated that the meal with high-protein increased the average insulin demand by 50% in order to procure euglycemia in proportion to the meal with low protein [14]. Moreover, in the study investigating the effect of the meal with increased protein content on glycemic response, glycemic fluctuation was reported to increase due to the dose in late postprandial period [15].

However, there has been no simple algorithm easy to use insulin dose calculation for fats and proteins, yet. Therefore, the aim of this study is to evaluate the effect of high fat and high protein on postprandial blood glucose by calculating insulin dose based on protein and fat counting in addition to carbohydrate counting to determine meal plans of people having type 1 diabetes mellitus.

Materials and methods

Study population

In this study which was done in between April 2018 and June 2018, 16 adolescents (8 males and 8 females) who had type 1 diabetes mellitus, whose ages ranged from 14 to 17, who were followed up in the Child and Adolescent Endocrine Policlinic of Ankara University, who have had type 1 diabetes mellitus for more than 1 year, who received an intensive insulin therapy (3 times rapid acting and one long-acting insulin per day), who have carbohydrate counting at least for 6 months, and who have a determined carbohydrate/insulin rate were included. The adolescents with type 1 diabetes mellitus who have been diagnosed with celiac or hyperlipidemia, who have gastric motility problems and other complications related to diabetes mellitus (neuropathy, nephropathy, retinopathy), who have exercised 24 h prior to test meals, who undergo hypoglycemia or ketoacidosis, who were overweight or obese (respectively BMI z score: ≥ 1 SD and ≥ 2 SD), and who are not on the follicular menstrual cycle non-periovulatory phase were not included in the study.

In order to eliminate the variation between individuals, all applications were applied to each individual for 3 consecutive days. At the beginning of the study, randomization was performed to determine the order of application of individuals. However, since the sensor and capillary measurements of 2 participants did not match, 1 participant was excluded from the study because he could not finish the whole meal while 1 participant was excluded from the study because he injected additional dose of insulin before the test meal. Consequently, the study was completed with a total of 12 adolescents with

type 1 diabetes mellitus including 5 males and 7 females. Flow diagram (Fig. 1).

Study design

The study was designed as crossover and randomized. The postprandial glucose response of high-fat and high-protein meal, for which two different prandial insulin regimes were implemented, was compared with standard control meal. Continuous glucose monitoring system sensor (CGMS®; Medtronic) was implanted subcutaneously into the brachium area on the day before the implementation, during which the patients were asked to apply insulin injection to the regions at least 7 cm away from the sensor. Those injection areas were checked whether they were free from hypo- or hypertrophy. The patients were also asked to record capillary fasting blood glucose and blood glucose before sleep for the calibration of the sensor. The sensor was used blinded to the participants and researchers (intermittent CGM). Calibrations during the study (4 h) were performed by the researchers with a single glucometer (Contour Plus®; Bayer) at the beginning and at the second hour.

Each C/I ratio of each patient was validated at the breakfast by measuring the glucose before and 2 h after the meal. C/I ratio was confirmed to be calculated correctly only if the postprandial 2nd hour glucose did not exceed 30–60 mg/dL than the preprandial glucose or the actual blood glucose reading did not exceed 150–180 mg/dL [16].

Dietary intervention

Control and test meals

Each patient was randomly and consecutively subjected to 2 different breakfast meals which were a standard control meal

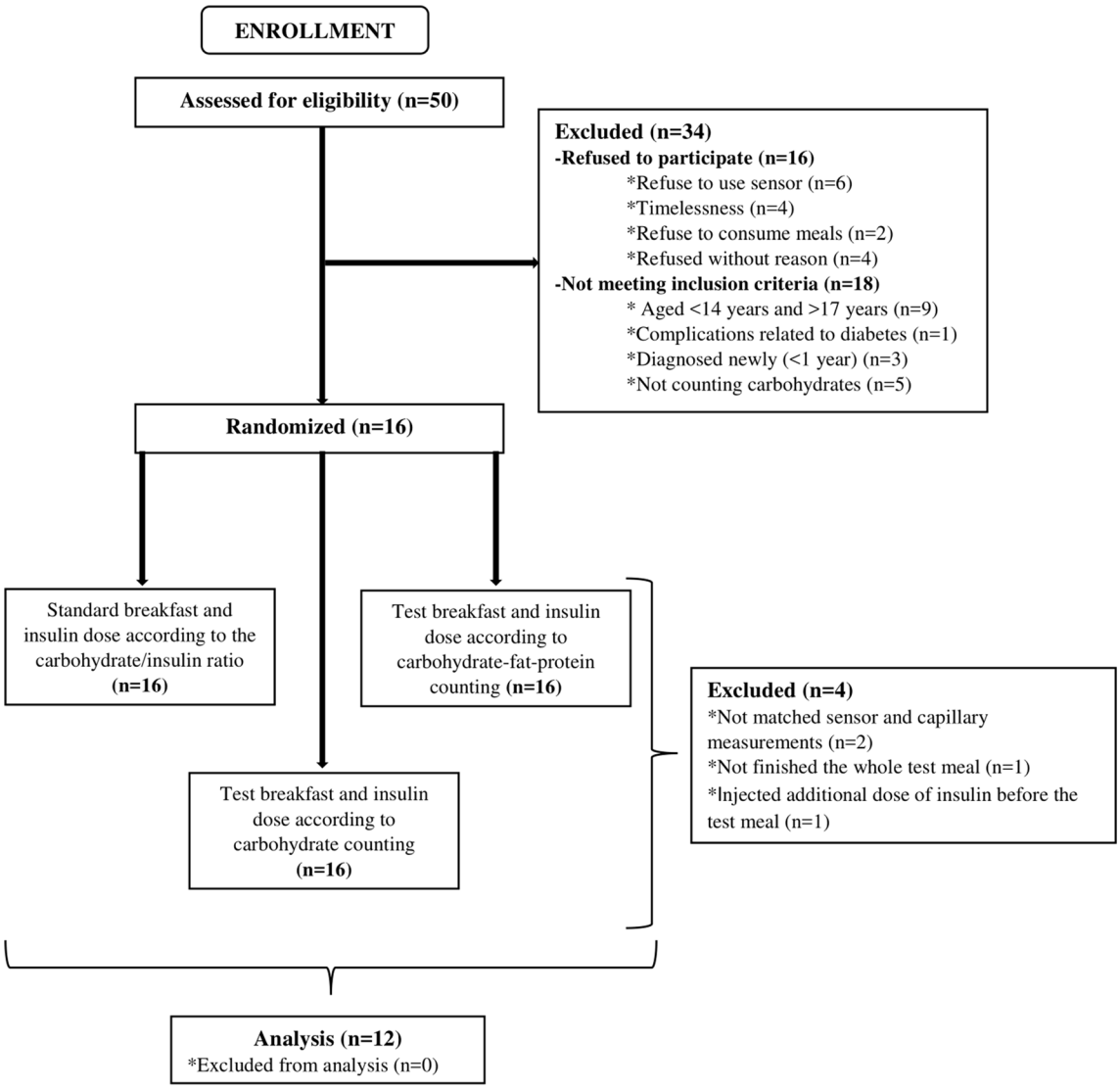

Fig. 1 Flow diagram

on the first day and a high-fat and high-protein test meal on the next 2 days following at least 10 h of fasting on consecutive days. The applications were initiated the day after CGMS sensor was implanted. Every meal was served at 9:00 a.m. The participants were informed and supposed to finish their breakfast within 20 min, not to consume nutrients unless it is a need for the application of hypoglycemia within 4 h after meal consumption, and not to do exhausting physical activity. A proper environment was provided for these statements. The researchers did not intervene meals except for the breakfast and advise to follow their routine nutritional applications.

The content of standard and test meals was identified after a literature survey covering similar researches. Additionally, those were planned as the meal would supply 25% of the daily average energy requirement and were oriented into the Turkish breakfast culture correspondingly. An equal amount of carbohydrate (54 g) was given to each patient in the control and test meals. Yet, the amount of fat and protein was higher in the test meal (fat, 36 g; protein, 42 g) comparing with the control meal (fat, 11 g; protein, 18 g). The content of energy and macronutrient elements in the control and the test meals as well as the mean amount of implemented insulin doses are given in Table 1.

Determination of insulin dosages

The prandial insulin dose in the control meal expressed as the first application was implemented according to the previously determined individual C/I ratio of adolescents with type 1 diabetes mellitus. Likewise, in the test meal of second application, the insulin dose was given based on individual C/I ratio; in the test meal of third application, the 2.5 units of insulin were given in addition to the insulin dose set according to individual C/I ratio. One unit of insulin was added per 200 kcal of energy obtained from fat and protein. A total of 2.5 units of additional insulin were implemented into the test meal for approximately each 500 kcal of energy from fat and protein. Prandial rapid-acting insulin (Lispro**)** was injected into the application area on the arm after the first blood sample was drawn.

At the end of the third day, the CGMS sensor was displanted from the participants and transferred to the computer environment for evaluation of the data. Blood glucose values from CGMS sensor data at 9 measurement times, every 30 min between 0 and 360 min, were recorded in the statistical analysis program. Nevertheless, analyses were performed based on 4 h since hypoglycemia incidents happened after the 240th minute (< 70 mg/dL).

Statistical analysis

The statistical analysis was performed with SPSS for Windows release 15.0.1 (November 2006) (SPSS Inc., Chicago, IL). The regularity of the distribution for each parameter was evaluated using the Shapiro–Wilk test. The comparison among interventions (first, second and third) was performed using the paired-samples *t* test for the specified variables. The level of significance was set in all analyses as $p < 0.05$.

Results

Considering the adolescents having been participated in the study ($n = 12$), 41.7% were male and 58.3% were female. The average age for adolescents was 15.3 ± 1.07. What is more, 50% of the participants were in high school while 50% were in secondary school levels. The duration of having type 1 diabetes mellitus and carbohydrate counting method having been used was 3.7 ± 3.48 and 2.2 ± 1.66 years, respectively. The average $HbA1_c$ (%) value measured lastly was 8.8 ± 1.20 (Table 2).

Table 1 Composition of meals

Parameters	Unit	1st application	2nd application	3rd application
Energy	kcal	387	708	708
Carbohydrate	g	54	54	54
	%	55.8	30.5	30.5
Protein	g	18	42	42
	%	18.6	23.7	23.7
Fat	g	11	36	36
	%	25.6	45.8	45.8
İnsülin application (mean ± SD)	IU	12.1 ± 4.42	12.4 ± 4.23	15.2 ± 4.97

1.application: control meal and insulin dose according to individual carbohydrate/insulin ratio

2.application: test meal and insulin dose according to individual carbohydrate/insulin ratio

3.application: test meal, insulin dose according to individual carbohydrate/insulin ratio, additional 2.5 IU

There existed 5 in the first application and 5 in the third application who got hypoglycemia. There was no incidence of hypoglycemia in the second application.

Examining the postprandial blood glucose levels, the mean blood glucose values at the second application (test meal and insulin dose based on individual C/I ratio) after 150th minutes during the measurement were found to be higher comparing with the first application (the control meal and insulin dose based on individual C/I ratio) ($p = 0.43$; 0.14; 0.19; 0.26, respectively) (Table 3, Fig. 2).

The peak value was seen in between 30 and 60 min in the first application (mean 57.5 ± 29.89 min), in between 90 and 120 min in the second application (mean 95.0 ± 83.72 min) and in between 60 and 90 min in the third application (mean 75.0 ± 81.41 min). Although a new peak value was seen in the second application, the difference was not statistically significant ($p > 0.05$). Similarly, the peak value of the blood glucose was higher in the second application (mean 206.8 ± 59.56 mg/dL) but the difference was not found to be statistically significant ($p > 0.05$). On the other hand, in the second application, slightly the half of 9 measurements (mean 49.0 ± 37.86%) of blood glucose values was above 180 mg/dL ($p > 0.05$). The mean value of the lowest blood glucose during applications existed to be significantly higher in the second application (mean 131.7 ± 47.07 mg/dL) than the first application (mean 92.1 ± 36.34 mg/dL) ($p = 0.03$) (Table 4, Fig. 2).

The effect of the control meal, the test meal, and different insulin regimes on the early, late, and total blood glucose responses are shown in Table 5. The difference between glycemic response after consumption of the control and test meals was not statistically significant ($p > 0.05$). However, the glycemic excursion in the third application (mean − 15.8 ± 17.21 mg/dL) was higher than the first (mean 2.3 ± 10.80 mg/dL) and second (mean 1.7 ± 22.61 mg/dL) applications; whereas the glycemic excursion of 150–120 min in the first application (mean − 17.8 ± 12.37 mg/dL) was higher comparing with the third application (mean − 9.9 ± 13.29 mg/dL) ($p = 0.004$; 0.009; 0.28, respectively) (Table 6).

Discussion

Carbohydrate counting has become a widely used meal planning method as well as application of intensive insulin treatments [17]. This method enables the insulin dose to be adjusted in accordance with the amount of carbohydrates consumed in the main meals and snacks and provides flexibility in the nutrient consumption of individuals with diabetes mellitus [18]. Although, they have fewer impacts on blood glucose level compared with carbohydrates, the content of fat and protein of the meal is expressed to be important in sustaining postprandial normoglycemia [8, 12, 19–21].

The number of studies concerning the determination of insulin dose corresponding to the amount of fat and protein in the meal is quite inadequate [22]. In this regard, Pankowska et al. (2012) asserted the hypothesis that 1 unit of insulin in addition to the insulin dose calculated individually per 100 kcal from fat and/or protein should be administered in the individuals with type 1 diabetes mellitus using insulin pumps. However, this treatment was reported to have caused hypoglycemia especially at the 4th hour [20]. Similarly, in Evans et al. and Lopez et al. studies, the implementation of the Pankowska Equation resulted in lower peak glycemic excursion for between 90–240 min and hypoglycemia. Fat and protein counting methods implemented in this study also experienced hypoglycemia after 240 min [13, 14]. Bell et al. suggested that in person with diabetes receiving intense insulin treatment and using insulin pen, 30–35% of the insulin administered before the meal should be additionally applied at the first hour after the meal for high-fat meal (≥ 40 g/meal).

Table 2 Baseline characteristics of type 1 diabetes adolescents ($n = 12$)

	n (%)
Male/female	5/7 (41.7/58.3)
Secondary school/high school	6/6 (50.0/50.0)
	$\overline{X}$ ±SD (min-max)
Age (years)	15.3 ± 1.07 (14–17)
Diabetes mellitus age (years)	3.7 ± 3.48 (1–10.5)
Height (z score)	− 0.1 ± 0.56 (−1.2–1.0)
BMI (z score)	0.4 ± 0.83 (−1.1–1.5)
Baseline $HbA1_c$ (%)	8.8 ± 1.20 (6.4–10.6)
Duration of using of carbohydrate counting method (years)	2.2 ± 1.66 (0.5–5.0)
Insulin requirement (IU/kg/day)	1.0 ± 0.22 (0.7–1.3)
Proportion of bolus insulin dose in total daily insulin dose (%)	63.3 ± 9.42 (38.9–73.3)

BMI, body mass index; *$HbA1_c$, glycated hemoglobin

Table 3 Mean and standard deviation of blood glucose values (mg/dL) in the measurement times after applications

Minutes after meals	1st application $\overline{X}$ ±SD	2nd application $\overline{X}$ ±SD	3rd application $\overline{X}$ ±SD	p*
0	180.3 ± 52.34	193.1 ± 52.73	207.5 ± 74.73	> 0.05
30	182.6 ± 53.22	194.8 ± 58.91	191.8 ± 74.54	> 0.05
60	175.3 ± 57.40	193.1 ± 68.19	178.8 ± 72.17	> 0.05
90	165.5 ± 62,75	183.9 ± 66.27	168.8 ± 67.83	> 0.05
120	148.8 ± 64.63	176.2 ± 59.24	158.5 ± 69.83	> 0.05
150	131.1 ± 60.89^{a}	165.2 ± 53.03^{b}	148.6 ± 67.73^{ab}	< 0.05**
180	121.4 ± 56.29^{a}	159.5 ± 47.81^{b}	141.5 ± 62.36^{ab}	< 0.05**
210	118.3 ± 52.52^{a}	155.0 ± 49.42^{b}	141.6 ± 59.25^{ab}	< 0.05**
240	127.9 ± 48.05^{a}	150.8 ± 49.16^{b}	138.4 ± 53.76^{ab}	< 0.05**

*Paired-samples t test **$p < 0.05$

1st application: control meal and insulin dose according to individual carbohydrate/insulin ratio

2nd application: test meal and insulin dose according to individual carbohydrate/insulin ratio

3rd application: test meal, insulin dose according to individual carbohydrate/insulin ratio, additional 2.5 IU

[ab] Statistically significant difference between interventions

In insulin pump users, it is recommended to increase the total dose by 30–35% or to implement 50% of it as the double wave bolus in 2–2.5 h. Regarding protein, it was reported that at least 40 g of protein consumed with at least 30 g of carbohydrate would increase total insulin dose by 15–20% [9]. In the study conducted by Bell et al. with 9 adults with type 1 diabetes mellitus at the age from 18 to 75 years, the participants were implemented with the same amount of insulin by being given low-fat and low-protein and high-fat and high-protein meals containing the same amounts of carbohydrate. Then, a model was developed by implementing additional insulin until the targeted postprandial glycemia was achieved for high-fat, high-protein meal. As a result, it was reported that an average dose of 65% (17–124%) more insulin should be implemented for high-fat high-protein meal [10]. Neu et al. gave high-fat high-protein dinner on consecutive days to 15 adolescents with type 1 diabetes mellitus, with a mean age of 16.8 years. While the glycemic response was mean 1400 mg/dL/12 h (± 580) at the standard control meal, it was found to be 1968 mg/dL/12 h (±394) at the test meal. As a result of the study, glucose concentration was established to be significantly higher during 12 h after high-fat high-protein meal [23]. In this study, postprandial blood glucose was significantly increased in the application (second application) in which the insulin was implemented according to individual C/I ratio corresponding to test meal after the 150th minute

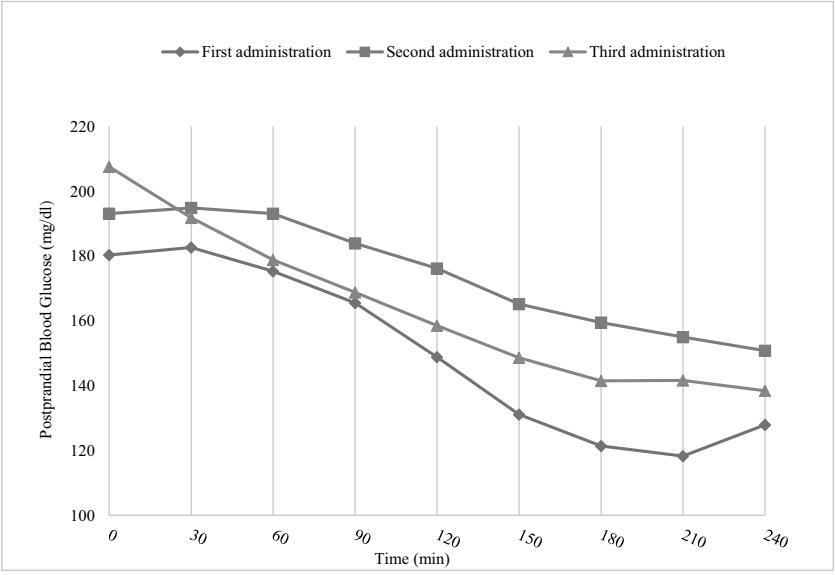

Fig. 2 The postprandial blood glucose profile following control and test meals

Table 4 Mean and standard deviation values of glycemic results

Glycemic outputs	1st application $\overline{X}$ ±SD	2nd application $\overline{X}$ ±SD	3rd application $\overline{X}$ ±SD	p*
Peak value of the blood glucose (mg/dL)	189.8 ± 56.45	206.8 ± 59.56	201.3 ± 67.92	> 0.05
Peak time for the blood glucose (min)	57.5 ± 29.89	95.0 ± 83.72	75.0 ± 81.41	> 0.05
Lowest value of the blood glucose (mg/dL)	92.1 ± 36.34[a]	131.7 ± 47.07[b]	111.2 ± 48.64[ab]	< 0.05**
Proportion of times that blood glucose values were above 180 mg/dL (%)	27.1 ± 36.48	49.0 ± 37.86	30.2 ± 38.60	> 0.05

*Paired-samples t test **$p < 0.05$

1st application: control meal and insulin dose according to individual carbohydrate/insulin ratio

2nd application: test meal and insulin dose according to individual carbohydrate/insulin ratio

3rd application: test meal, insulin dose according to individual carbohydrate/insulin ratio, additional 2.5 IU

[ab] Statistically significant difference between interventions

compared with the standard meal (first application) ($p < 0.05$, Table 3). In order to reduce the risk of hypoglycemia observed in the study of Pankowska et al. [20], 1 unit of additional insulin was implemented in test meal per 200 kcal of energy from protein and fat (third application), and the glycemic response was found to be similar to the first application. The increase of insulin dose in this way caused a lower blood glucose course statistically and clinically. Mean postprandial blood glucose levels were higher in the meal with high-fat and high-protein and without any additional dose of insulin ($p < 0.05$, Table 3). However, even though the area under the curve (glycemic response) seems to be higher in the second application compared with other applications, the difference in between was not statistically significant (Table 5, Fig. 2). These results suggest that the test meal increases postprandial blood glucose compared with the control meal in adolescents with type 1 diabetes mellitus, but there is a need for additional studies to provide normoglycemia.

During the treatment applications, the mean value of lowest blood glucose was found to be significantly higher in the second application comparing with the first application ($p < 0.05$), but no significant difference was found in terms of statistic at the peak values of postprandial blood glucose ($p > 0.05$, Table 4). In the study of Kaya, the effects of fats and proteins on postprandial blood glucose were evaluated, peak blood glucose mean (mean 280.10 ± 62.22 mg/dL) at the treatment of insulin according to C/I ratio corresponding to high-fat and high-protein meal was found to be higher compared with other treatments ($p < 0.05$) [24]. In this study, the mean of time at which postprandial blood glucose reached the peak point was found to be 57.5, 95, and 75 min, respectively ($p > 0.05$, Table 4). Similarly, in the study of Lodefalk et al., 7 adolescents with type 1 diabetes mellitus were given two types of meals with different content of fat and energy (2 g of fat, containing 320 kcal of energy, and 38 g of fat, containing 640 kcal of energy) and with the same content of protein and carbohydrate, and their postprandial blood glucose were monitored during 4 h. As a result of the study, no significant relationship was found between the meals at the peak glucose time [25].

Even though the ratio of individual with postprandial blood glucose level above > 180 mg/dL was the highest in the second application (49%) and the lowest in the first application (27.1%), the difference in between was not statistically significant ($p > 0.05$, Table 4). In spite of the additional dose having been implemented, blood glucose levels having higher course in the third application than in the first application and a downward travel of the blood glucose suggest that the insulin

Table 5 Early and late postprandial glucose response after control and test meals

Area under the curve(mg/dLxmin)	1st application $\overline{X}$ ±SD	2nd application $\overline{X}$ ±SD	3rd application $\overline{X}$ ±SD	p*
Early (0–120 min)	20,636.3 ± 6667.70	22,691.3 ± 7248.99	21,672.5 ± 8434.23	> 0.05
Late (120–240 min)	16,171.5 ± 6635.06	19,283.8 ± 5825.77	17,403.8 ± 7106.63	> 0.05
Total (0–240 min)	37,788.0 ± 12,455.21	41,985.0 ± 12,411.05	39,076.3 ± 14,817.73	> 0.05

*Paired-samples t test **$p < 0.05$

1st application: control meal and insulin dose according to individual carbohydrate/insulin ratio

2nd application: test meal and insulin dose according to individual carbohydrate/insulin ratio

3rd application: test meal, insulin dose according to individual carbohydrate/insulin ratio, additional 2.5 IU

Table 6 Glucose excursions (mg/dL) at 30-min intervals

Interval (min)	1st application $\overline{X}$ ±SD	2nd application $\overline{X}$ ±SD	3rd application $\overline{X}$ ±SD	p*
30–0	2.3 ± 10.80[a]	1.7 ± 22.61[a]	−15.8 ± 17.21[b]	< 0.05**
60–30	−7.3 ± 16.40	−1.7 ± 18.65	−12.9 ± 11.81	> 0.05
90–60	−9.8 ± 18.75	−9.2 ± 12.22	−10.0 ± 14.30	> 0.05
120–90	−16.7 ± 12.54	−7.8 ± 11.36	−10.3 ± 16.08	> 0.05
150–120	−17.8 ± 12.37[a]	−11.0 ± 15.38[ab]	−9.9 ± 13.29[b]	< 0.05**
180–150	−9.7 ± 16.95	−5.7 ± 15.32	−7.1 ± 14.81	> 0.05
210–180	−3.1 ± 20.72	−4.5 ± 13.34	0.1 ± 31.54	> 0.05
240–210	0.0 ± 19.22	−4.3 ± 12.02	−3.2 ± 11.42	> 0.05

*Paired-samples t test **$p < 0.05$

1st application: control meal and insulin dose according to individual carbohydrate/insulin ratio

2nd application: test meal and insulin dose according to individual carbohydrate/insulin ratio

3rd application: test meal, insulin dose according to individual carbohydrate/insulin ratio, additional 2,5 IU

[ab] Statistically significant difference between interventions

implemented for fat and protein needs to be applied as dispensing dose instead of bolus. In similar studies, it is suggested that high-fat and/or high-protein meals increase the requirement of insulin in 42–125 [10, 21]. In the study conducted by Wolpert et al., 7 individuals with type 1 diabetes mellitus using insulin pump were given high-fat (60 g) and low-fat (10 g) meals at the dinner containing the same amount of carbohydrates and proteins on different days, and the content of morning and lunch meals as well as physical activity levels were fixed. The blood glucose level was monitored by CGM for 18 h following the consumption of test meal. As a result of the study, it was revealed that the high-fat evening meal requires more insulin compared with low fat evening meal ($p = 0.01$), the C/I ratio at high-fat meal at the dinner was lower ($p = 0.01$), and the impact of diet fat on insulin requirement showed individual differences ($p = 0.03$). It was reported that a meal containing high-fat causes hyperglycemia after 5th hour and requires insulin [12]. However, in another study conducted with 17 individuals with type 1 diabetes mellitus with a similar method, it was observed that majority of individuals had blood glucose in the normoglycemic range (70–180 mg/dL) within 180 min following high-fat and high-protein meals [26]. Such broad spectrum of increasing requirement was considered to be stemmed from individual differences [10].

In the study of Smart et al., it was though the glucose excursion of high-fat and high-protein test meal was also stated to be higher [8]. In this study, the glycemic excursion of 30–0 min at third application was higher compared with first and second applications; the glycemic excursion of 150–120 min at first application was higher compared with third application ($p < 0.05$, Table 6). The studies conducted in the person without diabetes and with type 1 diabetes have shown that saturated fats cause deeper insulin resistance compared with monounsaturated and polyunsaturated fatty acid [27, 28]. In this study, the breakfast meal contained predominantly unsaturated fatty acids (test meal 41% of saturated fat, 59% of unsaturated fat). One of the reasons for the consequences that are not similar to the literature was considered to be this situation. On the other hand, further studies are needed to be conducted to determine the effects of diets with different fatty acid patterns on glycemic control in individuals having type 1 diabetes mellitus.

The results of this study indicated that the fat and protein content of the meal may cause postprandial hyperglycemia in individuals with type 1 diabetes mellitus. In an intensive insulin therapy, which is commonly used in the management of type 1 diabetes mellitus, there are limitations to the current carbohydrate-based approach used to calculate the bolus insulin dose. Therefore, more studies are needed to develop and validate alternative insulin dose algorithms for high-fat and high-protein meals.

As a result, the presence of hypoglycemia cases in the first and third applications, but no hypoglycemia in the second application, proves that high fat and high protein meals increase the need of insulin. The mean postprandial blood glucose levels after high-fat and protein meal in the adolescents with type 1 diabetes mellitus who receive intensive insulin treatment were significantly higher in terms of statistics after 150 min compared with control meal. This study reveals a supportive evidence that the amount of protein and fat in addition to carbohydrate should be taken into account in determining the insulin dose. However, the results of studies evaluating the effects of dietary fat and protein on blood glucose levels and insulin requirements are inconsistent, the method and quality of studies are significantly different, making it difficult to develop an algorithm for fat and protein counting. Hence, further studies are required to explore the glycemic

impact of fat and protein more thoroughly. Therefore, in order to prevent hyperglycemia after high-fat and high-protein meals, it is considered that people with diabetes mellitus should be evaluated individually. On the other hand, in the training of carbohydrate counting, patients and their families should be informed about adequate and balanced meals to be preferred rather than consuming high-fat and high-protein meals. Higher fat and higher protein meals appear to need additional insulin and thus need to be evaluated on an individual basis.

High-fat and high-protein meal raised postprandial blood glucose after 150 min and this meal increased the requirement of insulin in adolescent with type 1 diabetes mellitus. Postprandial glycemia was improved when fat and protein was counted along with carbohydrate in adolescents with type 1 diabetes mellitus. Calculating insulin dose, the amount of fat and protein was considered for glycemic control in adolescents with type 1 diabetes mellitus.

Limitations There are some limitations in the study. Firstly, the only meal having intervened was the breakfast, and routine medical nutrition therapy was expected to continue for other meals. However, commitment to nutritional therapy was questioned at the beginning of the study exclusively. Secondly, while determining the individual C/I ratio, the record of the nutrient consumption was requested from the adolescents. However, incorrect or incomplete disclosure of these records was ignored.

In addition, most of the studies on this subject have been performed in people with type 1 diabetes mellitus using insulin pump, and individuals using insulin pen participated in this study. Therefore, the insulin implemented for high-fat and high-protein meals since bolus is not as the spreading dose. Furthermore, blood glucose values before initial application are not in the euglycemia range. This is because the participants are in adolescence, and their compliance to treatment is poor. The difficulty in finding volunteer participants in this study is the reason for the high glucose level in 0 min. Although the initial blood glucose level was not in the optimal range, no statistically significant difference was found between the applications, and the effect of the applications was evaluated. However, the data of this study provided clinically important findings in Turkey as a developing country.

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Compliance with ethical standards

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

Ethical approval The study was conducted in accordance with the Helsinki Declaration and was approved by the local Ethics Committees. After the approval (69545805-044-E.22189) required for the study was obtained from Ankara University, Faculty of Medicine, Cebeci Research and Application Hospital; the study was executed with the Ethics Committee Approvals received from Ankara University Clinic Studies Ethical Committee (18-1163-17) and from Turkish Republic Ministry of Health Turkey Pharmaceuticals and Medical Devices Agency (93189304-514.04.01-E.245193). All study performed as appropriate to Helsinki declaration and our institution ethical rules

Statement of informed consent All the patients and their parents were informed about the study and their consent was written obtained.

Transparency declaration The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The reporting of this work is compliant with CONSORT guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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ORIGINAL ARTICLE

Real-world outcomes of insulin pump compared to multiple daily injection therapy in adult type 1 diabetes mellitus patients in a Mediterranean scenario

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Abstract

Aim To analyze the real-life outcomes of insulin pump therapy, as compared to multiple daily injection (MDI) treatment, in adult type 1 diabetes mellitus (T1DM) patients from a tertiary diabetes care hospital in a Mediterranean scenario.

Materials and methods Observational cross-sectional study regarding all T1DM patients on insulin pump therapy compared (1:1) with MDI-treated patients selected through simple random sampling from our database. Primary efficacy outcome was to describe glycated hemoglobin A_{1c} (HbA_{1c}) differences.

Results Ninety patients were analyzed (male 53%). Mean age was 40.0 ± 14.4 years, and T1DM duration was 19.7 ± 11.8 years. Duration of continuous subcutaneous insulin infusion (CSII) therapy was 5.6 ± 3.9 years, and most frequent indication (47%) for CSII treatment was $HbA_{1c} \geq 53$ mmol/mol (7%). More patients treated with CSII used interstitial glucose monitoring compared with MDI patients (73% vs. 20%, $p < 0.001$). Self-monitoring of blood glucose (SMBG) daily frequency was higher among insulin pump–treated patients compared with patients receiving MDI therapy (5.0 ± 2.2 times/day vs. 3.8 ± 3.2 times/day, $p = 0.048$). Glycated hemoglobin was lower among patients on insulin pump therapy compared with MDI-treated patients (54 ± 10 mmol/mol vs. 60 ± 13 mmol/mol, 7.1 ± 0.9% vs. 7.6 ± 1.2%; $p = 0.038$). Besides, patients on insulin pump showed less hypoglycemia frequency (6% vs. 11%, $p = 0.006$) and suffered less from frequent hypoglycemia (20% vs. 42%, $p = 0.02$).

Conclusions Patients using insulin pump therapy had a better glycemic control relative to the injection therapy cohort in a real-world Mediterranean scenario.

Trial registration Clinical Trials NCT03793283.

Keywords Real-world · Insulin pump · Continuous subcutaneous insulin infusion · Multiple daily injection therapy · Continuous glucose monitoring · Treatment · Type 1 diabetes

Introduction

Over the last two decades, the use of continuous subcutaneous insulin infusion (CSII) has markedly increased [1–3]. CSII safely improves metabolic control and quality of life in patients with type 1 diabetes mellitus (T1DM) [4, 5]. Most recent meta-analysis showed a modest significant 0.37% reduction in glycated hemoglobin A_{1c} (HbA_{1c}) with lower incidence of nocturnal hypoglycemia in patients treated with CSII compared to multiple daily injections (MDI) [6]. Despite the incremental use of insulin pumps among T1DM patients, only a minority achieved glycemic goals [7].

Randomized controlled trials (RCTs) that evaluated CSII compared to MDI are based on selected population, for a short period of time and under very specific conditions [8–10]. Therefore, they do not reflect the actual routine use of these therapies. Real-life studies are deemed necessary to validate information gathered from RCTs in order to add data in the real-world setting. Both studies have limitations and should be complementary.

So far, few real-world studies with CSII compared with MDI have been conducted [2, 11, 12], particularly in the Mediterranean area [13]. In fact, the wider view comes from the Swedish National Diabetes Register where the group treated with insulin pump therapy showed some clinical benefits including less frequent fatal cardiovascular disease and all-causes mortality [2].

In our knowledge, no study has specifically compared real-life use and clinical effects of CSII with MDI in adult T1DM patients in the Mediterranean area. Here, we present the results from a Spanish tertiary diabetes care hospital.

Materials and methods

This was a cross-sectional analysis of data extracted from the electronic medical record (EMR) system at Ciudad Real Health Public Area (Castilla-La Mancha Health Public System, Spain) [14].

The study was conducted from 1 January 2018 to 31 December 2019. All adult (≥ 18 years of age) patients diagnosed of T1DM treated with CSII or MDI for ≥ 6 months from our electronic database were eligible. All T1DM patients on insulin pump therapy were compared (1:1) with MDI-treated patients selected through simple random sampling from our database. All patients received the same diabetes educational program focus on dietary needs. Primary efficacy outcome was to describe between-group HbA_{1c} differences (method certified through the National Glycohemoglobin Standardization Program). Secondary efficacy outcomes were to identify between-group differences in daily hypoglycemia frequency; frequent hypoglycemia (defined as ≥ 10% interstitial glucose values < 3.9 mmol/L [70 mg/dL]); median capillary blood glucose; interstitial glucose monitoring compliance (flash or real-time continuous glucose monitoring [RT-CGM]), calculated as the amount of actual sensor use over expected sensor use of 100%; median interstitial glucose; glycemic variability (coefficient of variation of capillary blood and interstitial glucose); self-monitoring of blood glucose (SMBG) daily frequency; severe hypoglycemia frequency (any glycemic value < 3.9 mmol/L [70 mg/dL] requiring assistance from another person to treat) during the last year of follow-up; anthropometric variables (weight, size, and body mass index); insulin use (doses and basal/bolus proportions); diabetes quality of life (DQOL) assessed through the Spanish version of the Diabetes-related Quality Of Life (EsDQOL) questionnaire; presence of unawareness hypoglycemia evaluated by using the Clarke questionnaire; and safety-related adverse events including diabetes ketoacidosis (DKA), hospitalization due to T1DM decompensation, or death.

Flash glucose monitoring was partially funded during 2018 by Castilla-La Mancha Public Health Service. Flash public financing was limited to blinded, planning pregnancy, or pregnant T1DM patients. RT-CGM was reimbursed directly by the Ciudad Real University Hospital according to the Spanish Diabetes Association recommendations [15].

Quantitative variables are expressed as means and standard deviation (SD); qualitative variables are presented as total numbers and percentages. A paired Student *t* test or a Wilcoxon signed-rank test was used for the analysis of differences. Comparisons between proportions were analyzed using a chi-squared test. In order to evaluate the risk factors associated with HbA_{1c} levels, multiple linear regression analysis was carried out. Variables included were those with an effect described in the bibliography and with biological plausibility or whose result in the bivariate analysis was $p < 0.2$. Significance was taken at $p < 0.05$. Statistical analyses were performed using the SPSS software (version 24.0 for Windows; IBM, Armonk, NY, USA) and graphics with R 3.6.1 (R Statistics, Vienna, Austria).

Results

Ninety adult T1DM patients from our electronic database were analyzed. All patients ($n = 45$) on insulin pump therapy and forty-five patients treated with MDI were included in the study. The patients showed a mean age of 36.9 ± 11.0 years and T1DM duration of 18.6 ± 10.7 years. All patients were Caucasian. CSII users were more frequently females (78% vs. 44%, $p = 0.001$) with longer T1DM duration (21.1 ± 7.6 years vs. 16.2 ± 12.5 years, $p = 0.029$) and never exposed to tobacco (69% vs. 45%, $p = 0.019$) compared with patients treated with MDI. Duration of CSII therapy was 5.6 ± 3.9 years. Main indication (47%) for CSII treatment was $HbA_{1c} \geq 53$ mmol/mol (7%); other frequent reasons for CSII therapy were problematic hypoglycemia (22%), high glycemic variability (16%), and gestation or planning gestation (9%). Rest of demographics and anthropometric characteristics are shown in Table 1.

More patients treated with CSII used interstitial glucose monitoring compared with MDI patients (73% vs. 20%, $p < 0.001$). Self-financed flash glucose monitoring was the interstitial glucose monitoring system received in all MDI patients ($n = 9$). However, RT-CGM was the most frequent option ($n = 30$) for insulin pump–treated patients. In fact, only three patients on insulin pump used self-financed flash glucose monitoring. Mean use of glucose sensors was 80.1%. We did not detect differences between flash and RT-CGM user adherences (79.8% vs. 81.0%, $p = 0.467$). All patients combining CSII plus RT-CGM were treated with sensor-augmented pump therapy including the predictive low-glucose insulin suspend function (Medtronic Minimed 640G).

SMBG daily frequency was higher among insulin pump–treated patients compared with patients receiving MDI therapy (5.0 ± 2.2 times/day vs. 3.8 ± 3.2 times/day, $p = 0.048$). In fact, a SMBG daily frequency greater than 5 times a day was detected in a higher proportion of CSII-treated patients (42.2% vs. 20.0%, $p = 0.025$). Flash glucose monitoring scanning daily frequency was 11.2 ± 8.3 times/day, with no differences between patients treated with CSII or MDI (5.8 ± 4.3 times/day vs. 13.6 ± 8.7 times/day, $p = 0.104$).

Glycated hemoglobin was lower among patients on insulin pump therapy compared with MDI-treated patients (54 ± 10 mmol/mol vs. 60 ± 13 mmol/mol, 7.1 ± 0.9% vs. 7.6 ± 1.2%; $p = 0.038$). Only 41% percent of the patients achieved HbA_{1c} levels < 53 mmol/mol (7%), with no differences between CSII and MDI treatment (49% vs. 33%, $p = 0.134$). Besides, patients on insulin pump showed less hypoglycemia frequency

Table 1 Demographics and anthropometric characteristics of the patients

	CSII (n = 45)	MDI (n = 45)	Total (n = 100)	p
Sex (male/female), number (%)	10/35 (22/78)	25/20 (56/44)	35 (39)/55 (61)	0.001
Age (years), mean ± SD	36.6 ± 13.0	37.2 ± 8.6	36.9 ± 11.0	0.796
Diabetes duration (years), mean ± SD	21.1 ± 7.6	16.2 ± 12.5	18.6 ± 10.6	0.029
Body mass index (kg/m^2), mean ± SD	25.5 ± 3.3	25.0 ± 3.8	25.3 ± 3.5	0.476
Educational level, number (%)				
• Primary education	1 (1)	7 (8)	8 (9)	0.058
• Secondary education	8 (9)	10 (11)	18 (20)	0.598
• General certificate of education	14 (16)	13 (14)	27 (30)	0.818
• University	22 (24)	15 (17)	37 (41)	0.134
Type of rapid analog insulin				
• Lispro	5	8	13	0.42
• Aspart	40	37	77	0.65
• Glulisine	0	0	0	NA
Tobacco use, number (%)				
• Never smoker	31 (69)	20 (45)	51 (57)	0.019
• Former smoker	8 (18)	6 (13)	14 (15)	0.561
• Current smoker	6 (13)	19 (42)	25 (28)	0.02
Chronic diabetes complications, number (%)				
• Microvascular	15 (33)	9 (20)	24 (27)	0.153
• Macrovascular	0 (0)	1 (1)	1 (1)	0.315
• Overall	15 (33)	9 (20)	24 (27)	0.153

CSII, continuous subcutaneous insulin infusion; *MDI*, multiple daily injections; *SD*, standard deviation; *NA*, not applicable

(6% vs. 11%, p = 0.006) and suffered less from frequent hypoglycemia (20% vs. 42%, p = 0.02). Rest of glycemic outcomes can be observed in Table 2.

Interstitial glucose monitoring users showed lower HbA_{1c} levels compared with those patients using exclusively self-monitoring of blood glucose (53 ± 9 vs. 61 ± 13 mmol/mol; 7.0 ± 0.8% vs. 7.7 ± 1.2%, p = 0.001). In addition, percentage of hypoglycemia was lower among subjects using interstitial glucose monitoring (5.9 ± 6.1% vs. 11.2 ± 9.2%; p = 0.003). Furthermore, interstitial glucose monitoring–treated patients were administered higher number of daily insulin boluses (4.9 ± 1.7 vs. 3.3 ± 1.1, p < 0.001).

In multivariate analysis, HbA_{1c} result was associated with sex (males), higher level of studies and diabetes duration, greater proportion of bolus insulin, and interstitial glucose monitoring system use (Image 1). The set of variables explains 31.8% of the variability of HbA_{1c} levels. Level of studies (university studies, OR = − 0.48 [− 0.683, − 0.277], p < 0.001) and interstitial glucose monitoring use (OR = − 0.517, [− 0.918, − 0.116], p = 0.012) were significant factors associated with HbA_{1c} levels. Glycated hemoglobin result was not related to other baseline characteristics, insulin dose, or reason for CSII indication.

Insulin requirements were smaller in CSII-treated patients compared with MDI patients (0.5 ± 0.1 UI/kg/day vs. 0.7 ± 0.3 UI/kg/day, p < 0.001). Insulin pump–treated patients showed higher daily bolus frequency (5.1 ± 1.5 bolus/day vs. 3.0 ± 0.7 bolus/day, p < 0.001). In fact, more patients in the CSII group were receiving five or more daily insulin bolus (51.1% vs. 2.2%, p < 0.001). However, the proportion of basal and bolus insulin was similar between both groups of treatment (data not shown).

Other diabetes management differences were found between CSII- and MDI-treated patients. Active carbohydrate count was more frequently performed by insulin pump users compared with MDI-treated patients (43% vs. 15%, p < 0.001). Furthermore, basal and bolus insulin adjustments were conducted more often by CSII-treated patients (89% vs. 64%, p = 0.016; and 91% vs. 64%, p = 0.01, respectively).

Diabetes-related QOL was similar between both groups of treatment (CSII 83.6 ± 19.2 vs. MDI 88.8 ± 17.0, p = 0.184). Better satisfaction (lower score) was reported in the EsDQOL questionnaire by insulin pump–treated patients compared with the MDI group (29.4 ± 8.4 vs. 33.6 ± 8.5, p = 0.021). Rest of the EsDQOL scores are shown in Table 3.

Safety-related adverse event frequencies were similar between both groups of treatment (CSII 3.8 ± 14.1 events/100 patients/year vs. MDI 1.2 ± 6.2 events/100 patients/year, p =

Table 2 Glycemic outcomes

	CSII (n = 45)	MDI (n = 45)	Total (n = 100)	p
HbA_{1c} (mmol/mol, %), mean ± SD	54 ± 10, 7.1 ± 0.9	60 ± 13, 7.6 ± 1.2	57 ± 12, 7.4 ± 1.1	0.038
Median capillary blood glucose (mmol/L, mg/dL), mean ± SD	9.2 ± 2.0, 166 ± 36	8.9 ± 2.2, 161 ± 39	9.1 ± 2.0, 163 ± 36	0.531
Median interstitial glucose (mmol/L, mg/dL), mean ± SD	8.5 ± 1.2, 153 ± 21	8.6 ± 1.3, 155 ± 24	8.6 ± 1.2, 154 ± 21	0.851
Capillary blood glucose coefficient of variation (%)	41	46	43	0.017
Interstitial glucose coefficient of variation (%)	37	33	36	0.405
Hypoglycemia frequency (% patients)	6	11	9	0.006
Severe hypoglycemia frequency (number episodes/year)	0.3	0.8	0.5	0.234
Unawareness hypoglycemia (% patients)	29	40	34	0.267

SD, standard deviation

0.259). DKA and hospitalization frequencies due to glycemic decompensation after T1DM diagnosis were also similar among CSII- and MDI-treated patients (3.8 ± 14.1 events/100 patients/year vs. 1.2 ± 6.2 events/100 patients/year, p = 0.260; and 3.4 ± 14.1 events/100 patients/year vs. 0.8 ± 5.9 events/100 patients/year, p = 0.264, respectively). Two patients on insulin pump treatment had suffered high frequent DKA and subsequent hospitalizations since T1DM debut (first patient, twenty-four episodes; second patient, fourteen episodes). After initiation of insulin pump therapy in both patients in 2011, one episode of DKA and hospitalization was detected in the first patient and the second patient did not suffer more safety-related adverse events.

Discussion

The main result of our investigation was that glycemic control was better among adult T1DM CSII-treated patients compared to the MDI cohort in a real-world Mediterranean scenario. In this case-control context, insulin pump treatment was associated with lower HbA_{1c} levels without an increase in hypoglycemia frequency. Moreover, we detected some benefits over hypoglycemia, with less hypoglycemia frequency and frequent hypoglycemia in CSII-treated patients. In our knowledge, this is the first study showing real-life use and clinical benefits of CSII treatment compared with MDI therapy in adult T1DM patients in the Mediterranean area.

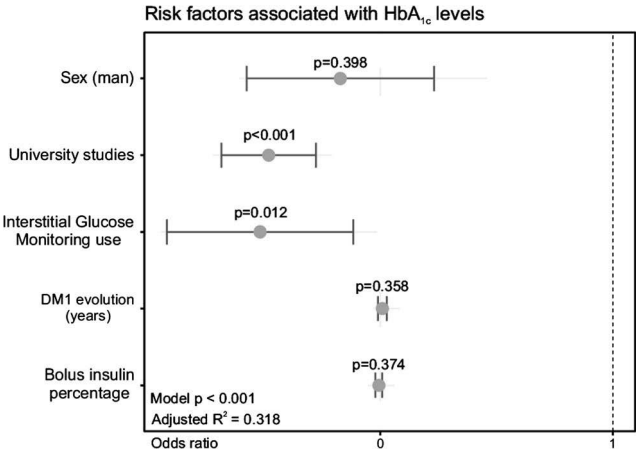

Image 1 Risk factors associated with HbA_{1c} levels

Up to the moment, only two great studies compared glycemic control between CSII and MDI among adult T1DM patients [2, 12]. The wider view came from the Swedish National Diabetes Register with no differences in HbA_{1c} between CSII therapy and MDI treatment (53 mmol/mol vs. 64 mmol/mol, 7.9% vs. 8.0%; p = 0.8) [2]. However, insulin pump users had a significant lower HbA_{1c} compared to MDI-treated patients (60 mmol/mol vs. 64 mmol/mol, 7.6% vs. 8%; $p < 0.001$) in the Central Denmark Region [12]. Other smaller observational studies had shown comparable controversial HbA_{1c} results, with lower [16] or similar [11, 17–19] levels in CSII-treated patients compared with patients on MDI therapy. Our present data showed better HbA_{1c} levels in the CSII group compared with the MDI group (53 ± 9 vs. 61 ± 13 mmol/mol; 7.0 ± 0.8% vs. 7.7 ± 1.2%, p = 0.001). Mean glycated hemoglobin level among adult T1DM insulin pump users was at least similar to median HbA_{1c} described in our whole region (Castilla-La Mancha, Spain) during 2018 (57 ± 10 mmol/mol, 7.4% ± 0.9%) [3].

Most recent systematic review and meta-analysis showed no significant difference in minor or severe hypoglycemic events between CSII and MDI in individuals with T1DM [6]. Real-world information about hypoglycemic results of CSII compared with MDI is scarce. This end point was not consistently reported [2, 12, 13, 16, 17], or different scales were used to define hypoglycemia [11]. In the METRO prospective study, the proportion of patients with one or more daily hypoglycemia or severe hypoglycemia decreased more in the CSII group compared to MDI at 2 years of follow-up [18]. Nevertheless, no severe hypoglycemic frequency difference was found between CSII and MDI in the COMISAIR study [20, 21]. Our present study showed less hypoglycemic frequency and frequent hypoglycemia among insulin pump

Table 3 Diabetes-related quality of life

EsDQOL	CSII (n = 45)	MDI (n = 45)	Total (n = 100)	p
Satisfaction	29.4 ± 8.4	33.6 ± 8.5	31.5 ± 8.6	0.021
Impact	33.0 ± 8.7	33.5 ± 8.7	33.2 ± 7.8	0.790
Social/vacational concern	12.6 ± 5.1	12.7 ± 4.6	12.6 ± 4.8	0.930
Diabetes-related concern	8.9 ± 2.4	9.0 ± 2.8	9.0 ± 2.6	0.935
Total	83.6 ± 19.2	88.8 ± 17.0	86.2 ± 18.2	0.184

Data expressed as mean ± SD

EsDQOL, Spanish version of the Diabetes-related Quality Of Life questionnaire; *SD*, standard deviation

users compared with patients on MDI therapy. However, we did not observe severe hypoglycemic frequency differences between the CSII and MDI groups. Our study size was not estimated to detect severe hypoglycemia differences due to the epidemiological characteristics of a real-world scenario study.

Interstitial glucose monitoring systems (flash or RT-CGM) as a stand-alone device or in combination with CSII (sensor-augmented pump, SAP) lead to improvements in HbA_{1c} with reduced risk of hypoglycemic events [22–30]. SAP with suspend before low option reduces both HbA_{1c} and hypoglycemic frequency [31–36]. These results are in consonance with our study where interstitial glucose monitoring (with an 80% sensor adherence) was associated with an additional 8-mmol/mol (0.7%) HbA_{1c} reduction together with 53% of hypoglycemia.

Our last set of analysis was aimed at assessing the influence of CSII compared with MDI on DQOL. This revealed that CSII-treated patients showed similar DQOL to the MDI group in the EsDQOL questionnaire. To date, available studies have only provided weak and/or insufficient evidence to sustain that DQOL improves with insulin pump treatment [17, 19]. Hoogma et al. described that CSII was not associated with decreased quality of life [17]. Here, we only detected a significant better score in the satisfaction section in accordance with our previous report [19].

A strength of this study is that although it is not a randomized controlled trial, it analyzes real-world outcomes over a duration of time on CSII of 5.6 years in a Mediterranean area. CSII duration was not reported by most authors in real-world studies [12, 13, 16]. The COMISAIR and the METRO studies performed a 1-year and a 2-year follow-up, respectively [18, 20]. The Swedish National Diabetes Register described a mean follow-up of 6.8 years, although their results may not be applicable to the Mediterranean scenario [2]. Another strenght of this study is that it came from a population where CSII patients were compared with a random sampling algorithm which minimizes a potential selection bias in the MDI group. Finally, the cohorts were managed by one team, so management protocols and education are the same for all subjects included in the study. However, our study is subject to a series of limitations. Mainly, the external validity of these results is limited because the monocenter study population may not be representative of all adult T1DM treated in all public health areas in the Mediterranean. Moreover, our study was not a RCT; therefore, subjects were already on insulin pumps before the study without any wash out period, and there could be confounding factors not taken into account.

Conclusions

CSII-treated patients had improved glycemic control compared to the injection therapy cohort. This better control included lower HbA_{1c} and less hypoglycemia frequency. Real-world data are necessary to help determine the benefits, cost-effectiveness, and burden of new diabetes technologies as they are incorporated into clinical care.

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Compliance with ethical standards

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

Ethical approval The protocol was approved by the reference Castilla-La Mancha Public Health Institute Ethic Committee. All participants provided written informed consent. The protocol was publicly registered through Clinical Trials (NCT03793283).

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ORIGINAL ARTICLE

The efficacy of once-daily liraglutide as an add-on to oral antidiabetic agents on weight reduction and glycemic control in obese patients with inadequately controlled type 2 diabetes: a retrospective analysis in relation to liraglutide dose escalation within a 7-month treatment period

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Abstract

Background This study aimed to evaluate the efficacy of once-daily liraglutide as an add-on to oral antidiabetics (OADs) on glycemic control and body weight in obese patients with inadequately controlled type 2 diabetes (T2D).

Methods A total of 27 obese T2D patients who received 7 months (0.6 mg/day for the first month, 1.2 mg/day for 3 months, and 1.8 mg/day for 3 months) of liraglutide treatment as an add-on to OADs were included. Data on body weight (kg), fasting plasma glucose (FPG, mg/dL), postprandial glucose (PPG, mg/dL), and HbA1c (%), were recorded.

Results Liraglutide doses of 1.2 mg/day and 1.8 mg/day were associated with significant decreases in body weight (by 8.0% and 11.9%, respectively, $p < 0.01$ for each) and HbA1c (by 20.0 and 26.5%, respectively, $p < 0.01$), while all liraglutide doses yielded significant reductions in FPG (p ranging from < 0.001 to < 0.01) and PPG (p ranging from < 0.001 to < 0.01). Glycemic parameters showed a significant reduction from the 1.2 mg/day dose to the 1.8 mg/day dose ($p < 0.01$ for each), whereas no further reduction in body weight was noted.

Conclusion Our findings indicate favorable efficacy of liraglutide as an add-on to OADs in weight reduction and improving glycemic parameters in obese patients with inadequately controlled T2D. Once-daily liraglutide treatment was associated with significant weight loss and improved HbA1c levels only at 1.2-mg and 1.8-mg doses, while a 1.8-mg dose compared with a 1.2-mg dose seemed to enable a further improvement in glycemic control but not in weight loss.

Keywords Type 2 diabetes mellitus · Glycemic control · HbA1c target · Obesity · Body weight · Liraglutide · Dose titration · Iraq

Introduction

Despite the availability of a variety of treatment options, a considerable proportion of patients with type 2 diabetes (T2D) worldwide have suboptimal glycemic control with failure to achieve glycated hemoglobin (HbA1c) targets [1], and this is more common in Arabian Gulf countries or the Middle East and North Africa (MENA) region [2–4] than in the USA or European countries [1].

In a past study conducted in 2008 with 3395 T2D patients from Iraq, poor glycemic control (HbA1c ≥ 7%) was noted in 2571 (75.7%) patients, and most of the patients stated that the current health situation in Iraq (i.e., no drug supply at the primary health care center or a drug shortage, drug or

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laboratory expenses, or migration after war) was the cause of their poor glycemic control [5]. Nonetheless, rates for poor glycemic control remained unchanged in the following years in Iraq and were reported to be 83.6% ($n = 337$, HbA1c: 10.1%, duration of diabetes: 8.7 years) in 2013 [6] and 82% ($n = 100$, HbA1c: 8.4%, duration of diabetes: 8.0 years) in 2018 [7]. This seems notable given that consistent with worldwide trends for the prevalence of diabetes mellitus [8], diabetes has reached an epidemic status in Iraq over the last decade, with a dramatic (115%) increase from 19.58/1000 in 2000 to 42.27/1000 in 2015 [9].

Glucagon-like peptide 1 (GLP-1) is an incretin hormone responsible for glucose-dependent stimulation of insulin secretion and the inhibition of glucagon secretion, while it also delays gastric emptying and induces satiety, leading to decreased energy intake and weight reduction [10, 11]. In this regard, GLP-1 analogs with receptor agonist (RA) activity have emerged as effective antidiabetic treatments; they are recommended by recent guidelines to be preferred following metformin, particularly in adults with T2D and additional CV risk factors, given their potential to meet the criteria of optimal T2D treatment involving patient-oriented treatment goals (i.e., reduced risk of weight gain, hypoglycemia and CV complications) beyond glycemic control [12, 13].

Liraglutide is a long-acting GLP-1RA with an effect on both fasting glucose (via enhanced glucose-dependent insulin secretion and reduced glucagon secretion in the fasting state) and postprandial glucose (via enhanced postprandial insulin secretion and the inhibition of glucagon secretion) [14, 15]. Accordingly, along with its unique therapeutic potential enabling glycemic control with no risk of hypoglycemia and the additional benefit of weight loss, liraglutide is considered a preferable noninsulin injectable agent both in obesity and in T2D [15–17].

Liraglutide was approved by the FDA in January 2010 as a once-daily injection for patients with uncontrolled T2D despite lifestyle changes and metformin monotherapy, while after the demonstration of CV benefits in high-risk patients by the LEADER trial, it was also approved by the FDA for reducing 3-point major adverse cardiac events [14, 18].

This study was designed to evaluate the efficacy of once-daily liraglutide as an add-on to oral antidiabetics (OADs) in escalated doses of 0.6 mg, 1.2 mg, and 1.8 mg through a 7-month treatment period on glycemic control and body weight reduction in obese patients with inadequately controlled T2D in Iraq.

Methods

Study population

A total of 27 obese T2D patients (mean age: 48 years, ranging from 32 to 68 years, 51.9% were males) who received 7-month liraglutide treatment as an add-on to OADs due to failure to achieve glycemic control and weight reduction on previous OADs (metformin with or without dipeptidyl peptidase-4 inhibitors (DPP-4i) or glimepiride) were included in this retrospective study conducted between January 2017 and August 2017.

While the present study was exempt from the requirements of ethical approval because of its retrospective design, the study was conducted in full accordance with local Good Clinical Practice guidelines and current legislation, and permission was obtained from our institutional ethics committee for the use of patient data for publication purposes.

Liraglutide treatment

The trial consisted of a 1-month starting dose (0.6 mg/day) period and two consecutive 3-month escalation periods for 1.2 mg/day and 1.8 mg/day doses of once-daily subcutaneous liraglutide therapy. Accordingly, the study period included an overall 7-month liraglutide treatment, with a starting dose of 0.6 mg/day to avoid nausea and vomiting for the first 1 month, escalation to 1.2 mg for the next 3 months, and a final escalation to the maximum permissible dose of 1.8 mg daily for 3 months.

Assessments

Data on patient demographics (age, sex) and the duration of diabetes were recorded at baseline. Data on body weight (kg) and glycemic parameters, including fasting plasma glucose (FPG, mg/dL), postprandial glucose (PPG, mg/dL), and HbA1c (%), were recorded at baseline and at three consecutive visits conducted at month 1 (after 1 month of the 0.6 mg/day treatment), month 4 (after 3 months of the 1.2 mg/day treatment), and month 7 (after 3 months of the 1.8 mg/day treatment) of liraglutide treatment. Changes from baseline in body weight and glycemic parameters were evaluated for the 0.6 mg, 1.2 mg, and 1.8 mg daily doses, while changes in these parameters from the 1.2-mg dose were also evaluated during the 1.8-mg dose treatment period.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Changes over time are evaluated by dependent group t test or Wilcoxon test depending on the distribution pattern of continuous variables. Data were expressed as the "mean (standard deviation, SD)," minimum-maximum and percent (%) where appropriate. $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

The mean patient age was 48 years (range, 32 to 68 years), and males composed 51.9% of the study population. The duration of diabetes was less than 5 years in 51.9% of patients, while 18.5% of patients had suffered from diabetes for more than 10 years (Table 1).

The baseline average values for body weight and HbA1c were 113.9 kg (ranging from 80 to 180 kg) and 9.8% (ranging from 7.5 to 14.0%), respectively (Table 1).

Effect of 7-month liraglutide treatment on body weight and glycemic parameters

For body weight, a significant decrease from baseline was noted with liraglutide doses of 1.2 mg/day and 1.8 mg/day (by 8.0% and 11.9%, respectively, $p < 0.01$ for each) but not with the initial dose of 0.6 mg/day (Table 2).

For HbA1c, a significant decrease from baseline was noted with liraglutide doses of 1.2 mg/day and 1.8 mg/day (by 20.0 and 26.5%, respectively, $p < 0.01$) but not with the initial dose of 0.6 mg/day (Table 2).

For FPG (by 33.4%, 34.2%, and 49.5% reduction at 0.6-mg, 1.2-mg, and 1.8-mg doses, respectively, p ranged < 0.001 to < 0.01) and PPG (by 24.5%, 28.0%, and 39.3% reduction at 0.6-mg, 1.2-mg, and 1.8-mg doses, respectively, p ranged < 0.001 to < 0.01), a significant reduction from baseline was evident for all doses of liraglutide starting from the initial dose of 0.6 mg/day (Table 2).

When the change from the 1.2 mg/day dose to the 1.8 mg/day dose was evaluated, all glycemic parameters showed a significant reduction ($p < 0.01$ for each), whereas no further reduction was noted in body weight (Table 2).

Table 1 Baseline characteristics

	Baseline characteristics
Age (year), mean (SD, min–max)	48 (19, 32–68)
Gender, *n* (%)	
Female	13 (48.1)
Male	14 (51.9)
Body weight (kg), mean (SD, min–max)	113.9 (26.6, 80–180)
Duration of diabetes, *n* (%)	
< 5 years	14 (51.9)
5–10 years	8 (29.6)
> 10 years	5 (18.5)
HbA1c (%), mean (SD, min–max)	9.8 (1.9, 7.5–14.0)
FPG (mg/dL), mean (SD, min–max)	251.6 (89.0, 110.0–421.0)
PPG (mg/dL), mean (SD, min–max)	282.0 (92.0, 147.0–520.0)

FPG fasting plasma glucose, *PPG* postprandial glucose

Discussion

Our findings indicate significantly improved HbA1c, FPG, and PPG values as well as a significant reduction in body weight after the implementation of once-daily liraglutide as an add-on to OAD therapy in obese patients with inadequately controlled T2D. Our findings emphasize the efficacy of liraglutide on weight loss and HbA1c reduction only after the patients were titrated to a 1.2-mg daily dose and that there was no further reduction in body weight but continued improvement in glycemic parameters when patients were uptitrated to the highest daily liraglutide dose of 1.8 mg/day.

Data from randomized trials of liraglutide indicate the favorable efficacy and safety profile of liraglutide when used as a monotherapy or as an add-on to other treatments (i.e., metformin, sulfonylurea, thiazolidinedione, and basal insulin) in T2D patients [19–21].

In the current study, once-daily liraglutide improved the HbA1c from 9.8% at baseline to 7.8% at the 1.2-mg dose (reduced by 20.0%) and to 7.2% (reduced by 26.5%) at the 1.8-mg dose treatment periods, each lasting for 3 months. Similarly, in a past study conducted in an Arab population of T2D patients, the authors reported a reduction in HbA1c from 8.3 to 7.7% at the 3rd month and to 7.6% at the 6th month of liraglutide therapy [22]. In a meta-analysis of 9 randomized controlled trials (RCTs) of 2981 patients receiving liraglutide as an add-on to metformin, the authors concluded that there was an association of liraglutide with significantly decreased HbA1c compared with placebo (by − 0.36%), while subgroup analysis revealed a significant reduction in HbA1c at a dose of liraglutide of 1.8 mg/day (by − 0.47%) and 1.2 mg/day (by − 0.35%) but not at a dose of 0.6 mg/day (by − 0.09%) [23]. Our findings also revealed no significant improvement in HbA1c from baseline with a 0.6-mg dose of liraglutide, while the HbA1c reductions obtained by 1.2 mg (by 20.0%) and 1.8 mg (by 26.5%) doses of liraglutide were significant compared with pretreatment values.

Data from the SCALE trial of 846 T2D patients from 9 countries regarding 56-week, once-daily 3.0 mg liraglutide ($n = 423$), 1.8 mg liraglutide ($n = 211$), or placebo ($n = 212$) as an add-on to OADs (metformin, thiazolidinedione, sulfonylurea) revealed significantly higher efficacy of a 3.0-mg vs. a 1.8-mg dose of liraglutide on glucose-related measures, including a reduction in HbA1c and FPG levels and achieving a target HbA1c level of ≤ 6.5% [15]. Similarly, continued improvement in HbA1c, FPG, and PPG parameters was observed with increasing liraglutide doses in our cohort, and the highest glycemic efficacy was achieved after patients were uptitrated to the highest daily liraglutide dose of 1.8 mg.

Table 2 Efficacy of once daily liraglutide treatment in 0.6-mg, 1.2-mg, and 1.8-mg doses on body weight and glycemic parameters

	Pre-treatment visit (Baseline)	Post-treatment visits		
		Month 1 1-month (0.6 mg/day)	Month 4 3-month (1.2 mg/day)	Month 7 3-month (1.8 mg/day)
Body weight (kg)				
Visit value, mean (SD)	113.9 (26.6)	112.8 (27.0)	104.8 (27.5)	100.3 (23.4)
Change from baseline	Absolute (kg); %	1.1; 0.9	9.1; 8.0	13.6; 11.9
	p value	> 0.05	*< 0.01*	*< 0.01*
Change from 1.2 mg/day dose	absolute (kg); %			4.5; 4.3
	p value			0.3
HbA1c (%)				
Visit value, mean (SD)	9.8 (1.9)	8.9 (1.3)	7.8 (1.5)	7.2 (0.7)
Change from baseline	Absolute (%); %	1.0; 10.2	2.0; 20.0	2.6; 26.5
	p value	0.058	*< 0.01*	*< 0.01*
Change from 1.2 mg/day dose	absolute (%); %			0.6; 7.7
	p value			*< 0.01*
FPG (mg/dL)				
Visit value, mean (SD)	251.6 (89.0)	167.9 (53.4)	165.3 (69.7)	127.0 (35.2)
Change from baseline	absolute (mg/dL); %	84; 33.4	85.7; 34.2	124.6; 49.5
	p value	*< 0.001*	*< 0.01*	*< 0.01*
Change from 1.2 mg/day dose	absolute (mg/dL); %			38.3; 23
	p value			*< 0.01*
PPG (mg/dL)				
Visit value, mean (SD)	285.5 (92.0)	215.8 (74.1)	205.4 (66.5)	173.0 (44.5)
Change from baseline	absolute (mg/dL); %	70; 24.5	80.1; 28.0	112.3; 39.3
	p value	*< 0.001*	*< 0.01*	*< 0.01*
Change from 1.2 mg/day dose	absolute (mg/dL); %			32.3; 15.7
	p value			*< 0.01*

Values in italic indicate statistical significance ($p < 0.05$)

FPG fasting plasma glucose, *PPG* postprandial glucose

Indeed, the superiority of liraglutide 1.8 mg/day over placebo in improving glycemic control was also reported by the LIRA-ADD2SGLT2i trial in T2D patients with inadequately controlled HbA1c despite treatment with sodium-glucose co-transporter-2 (SGLT2) inhibitors with or without metformin [24]. The authors also noted the glycemic efficacy of liraglutide in T2D patients to be clinically important given the achievement of a target of HbA1c < 7.0% and ≤ 6.5% by more than half and one-third of patients, respectively, as well as the maintenance of good glycemic control without severe hypoglycemia or weight gain in half of patients [24]. The PIONEER-4 trial compared oral semaglutide (dose escalated to 14 mg), liraglutide (dose escalated to 1.8 mg), or placebo in T2D patients, and the findings in the liraglutide arm included a mean − 1.1% change from baseline in HbA1c and − 3.1 kg weight loss at week 26 [25]. In the SUSTAIN 10 trial, which aimed to reflect real-world clinical practice by comparing the most commonly prescribed doses for once-daily liraglutide (1.2 mg) vs. once-weekly semaglutide (1.0 mg) in Europe, 30-week liraglutide therapy in patients with T2D uncontrolled by 1–3 OADs was reported to reduce mean HbA1c (baseline 8.2%) by 1.0% and mean body weight (baseline 96.9 kg) by 1.9 kg, while semaglutide was superior to liraglutide in improving glycemic control and reducing body weight [26].

Our findings revealed significant reductions in FPG (85 mg/dL (4.7 mmol/L), 84.7 mg/dL (4.8 mmol/L), and 124.6 mg/dL (6.9 mmol/L), respectively) and PPG (70 mg/dL (3.9 mmol/L), 80.1 mg/dL (4.4 mmol/L), and 112.3 mg/dL (6.2 mmol/L), respectively) with 0.6-, 1.2-, and 1.8-mg doses of liraglutide. This seems to indicate the achievement of a more favorable glycemic efficacy with liraglutide in our cohort compared with the LEAD-2 trial, which revealed lower decreases from baseline in FPG (1.1 mmol/L, − 1.6 mmol/L, and − 1.7 mmol/L) and in PPG (− 1.7 mmol/L, − 2.3 mmol/L, and − 2.6 mmol/L) for 0.6 mg, 1.2 mg, and 1.8 mg liraglutide, respectively [27]. This seems notable given that long-acting GLP-1RAs are considered to be noninsulin injectable agents that target both FPG and PPG and, therefore, to show a greater

HbA1c reduction with no risk of hypoglycemia and the additional benefit of weight loss [12, 13, 16, 17].

In a model-based meta-analysis of 76 publications on the glycemic efficacy of 90-day DPP-4i, GLP-1RA, and SGLT2i as add-on treatments to metformin monotherapy in T2D patients, long-acting GLP-1RAs including liraglutide (FPG reduction by − 22.1% and HbA1c reduction by − 16.3%) were concluded to provide better glycemic control [28]. In fact, given that liraglutide was used as an add-on to either metformin alone or metformin plus insulin secretagogues (i.e., DPP-4 inhibitors and sulfonylureas) in our cohort, it should also be noted that higher efficacy of liraglutide has been suggested when used as an add-on to metformin alone than when used as an add-on to insulin secretagogues, particularly in reducing cardiovascular risk in T2D patients [29].

Data from the meta-analysis of 9 RCTs with 2981 patients receiving liraglutide as an add-on to metformin revealed that liraglutide lowered body weight more than the placebo (by − 2.13 kg), while subgroup analysis revealed significantly reduced body weight at all three dosages, including 1.8 mg/day (by − 2.07 kg), 1.2 mg/day (by − 2.21 kg), and 0.6 mg/day (by − 1.90 kg) [23]. Data from a meta-analysis of 5 RCTs involving 1440 T2D patients revealed significantly lower HbA1c with 1.2 mg (by 0.31%) and 1.8 mg (by 0.38%) liraglutide than with sitagliptin as an add-on to metformin, while only the 1.8 mg liraglutide group had significant body weight loss (by − 1.12%) [30]. Data from the SCALE trial of 846 T2D patients from 9 countries comparing 56-week, once-daily 3.0 mg liraglutide ($n = 423$), 1.8 mg liraglutide ($n = 211$) and placebo ($n = 212$) as an add-on therapy to 0–3 OADs (metformin, thiazolidinedione, sulfonylurea) revealed significantly higher weight loss with 3.0 mg liraglutide (6.0%, 6.4 kg) than with 1.8 mg liraglutide (4.7%, 5.0 kg) or placebo (2.0%, 2.2 kg) [15].

In the current study, only 1.2 mg (by − 9.1 kg, 8%) and 1.8 mg (by − 13.6 kg, 11.9%) doses of liraglutide were associated with significant weight loss when compared with baseline, and no further reduction in body weight was noted when the dose was titrated from 1.2 to 1.8 mg. Past studies indicated an association of a 1.8-mg dose of liraglutide with a 4–6-kg reduction in body weight and a greater proportion of patients achieving a 5–10% loss of weight with liraglutide than with placebo [31], while liraglutide versus placebo was also reported to reduce body weight by 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg for doses of 1.2 mg, 1.8 mg, 2.8 mg, and 3 mg, respectively [32]. A similar trend of liraglutide-dependent weight loss from baseline to the 3rd month and 6th month of therapy was also reported in a past study in an Arabic T2D population (from 96.0 to 94.8 kg and to 94.5 kg, respectively) [22].

The amount of weight loss obtained via 1.2-mg and 1.8-mg doses of once-daily liraglutide in our obese T2D patients seems much higher than those reported by other studies in T2D patients. This may be attributed to the fact that the T2D patients enrolled in the current study were highly motivated to lose weight and keen to adhere to lifestyle interventions, and their socioeconomic status was favorable enough to afford out-of-pocket expenses.

In fact, poor glycemic control in younger age groups of diabetes patients has been considered to be associated with lower adherence to a diabetes care plan and lifestyle changes due to the active occupational and social life in this age group [33, 34]. In this regard, given the relatively young age of our patients, with at least half of them having suffering from diabetes only for less than 5 years, the efficacy of liraglutide in our study population also seems to indicate the likelihood of obesity rather than early-stage diabetes (with no as-yet apparent diabetes-related complications) to be considered a major complaint by patients, leading to the adoption of a better self-care practice towards improved adherence to lifestyle interventions. Another important factor to be considered is the achievement of favorable outcomes in our T2D patients despite challenging circumstances due to vast destruction of the Iraqi health system infrastructure after the 2003 War, resulting in the restrictions in the provision of essential care [35] and poor practice of daily diabetes self-management protocols with strong adverse impact of stressful life factors (i.e., a lack of clean water and electricity and political instability) and the unavailability of educational programs in Iraq [36, 37].

In addition, it should be noted that higher doses of liraglutide (3.0 mg vs. 1.8 mg) were reported to be associated with better scores of weight-related quality of life along with a significant improvement in participants' physical function, while improvements in quality of life and treatment satisfaction are suggested to reinforce desired behavior via better adherence to treatment and lifestyle interventions [15]. Moreover, for the same degree of weight loss, liraglutide treatment was also reported to be associated with a greater improvement in β-cell function and more remarkable reduction in visceral fat than a standardized lifestyle intervention protocol in T2D patients [38, 39].

Certain limitations to this study should be considered. First, due to the retrospective single-center design of the present study, establishing causality between the drug and the observed effects is not possible. Second, the lack of data on certain patient-reported outcome measures related to quality of life or treatment satisfaction is another limitation, which would otherwise extend the knowledge achieved in the current study.

In conclusion, our findings indicate favorable efficacy of liraglutide as an add-on to metformin-based OADs in weight reduction and improved glycemic parameters, including HbA1c, FPG, and PPG, in obese patients with inadequately controlled T2D. Once-daily liraglutide treatment was associated with significant weight loss and improved HbA1c levels only at 1.2-mg and 1.8-mg doses, while a 1.8-mg dose compared with a 1.2-mg dose seems to enable a further

improvement in glycemic control but not in weight loss. Accordingly, our findings support the utility of once-daily liraglutide as an add-on to OADs as an effective option to promote weight loss along with glycemic control in obese T2D patients and emphasize the likelihood of higher doses to enable better glycemic control with similar weight loss.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval While the present study was exempt from the requirements of ethical approval because of its retrospective design, the study was conducted in full accordance with local Good Clinical Practice guidelines and current legislation, and permission was obtained from our institutional ethics committee for the use of patient data for publication purposes.

Consent to participate This is a retrospective study.

Consent for publication Permission was obtained from our institutional ethics committee for the use of patient data for publication purposes.

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ORIGINAL ARTICLE

Glycemic control rate of type 2 diabetes mellitus in Chinese adults: a multi-centered, retrospective, cross-sectional study

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Abstract

Objectives This study aims to clarify the current status of glycemic control in type 2 diabetes mellitus (T2DM) patients in China.

Methods This study was a multi-centered, retrospective, cross-sectional study based on electronic medical records. Individuals with T2DM who were admitted to a hospital between January 1, 2018, and December 31, 2018, and had either a fasting blood glucose or HbA1c tests results were included to assess the glycemic control. T2DM patients with fasting blood glucose < 7.0 mmol/L or/and HbA1c < 7.0% were defined as having adequate glycemic control.

Results A total of 19,926 patients from 44 hospitals were included in this study. Among them, male patients were 9796 (49.2%). The mean age of T2DM patients was 62.0 ± 12.9 years and the mean duration of diabetes was 3.0 ± 3.0 years. Totally, 30.7% T2DM patients achieved the adequate glycemic control with fasting blood glucose < 7.0 mmol/L, 44.3% with HbA1c < 7.0%, and 23.0% with both fasting blood glucose < 7.0 mmol/L and HbA1c < 7.0%. T2DM patients with longer duration, admitting to secondary hospitals, and living in the southern and undeveloped regions had lower glycemic control rate.

Conclusions In China, only 23.0% of T2DM patients achieved adequate glycemic control target (both fasting blood glucose < 7.0 mmol/L and HbA1c < 7.0%). Glycemic control should be strengthened for T2DM patients with longer duration, admitting to secondary hospitals, and living in the southern and undeveloped regions.

Keywords Type 2 diabetes · Glycemic control rate · Fasting blood glucose, HbA1c

Background

The prevalence of type 2 diabetes mellitus (T2DM) in China has dramatically increased from 0.67% [1] in 1980 to 11.6% [2] in 2010 with the aging and lifestyle changes. At present, the number of T2DM patients in China has exceeded 110 million [2]. T2DM-related complications including retinopathy, kidney disease, and neuropathy are the significant causes of increased disability and mortality in T2DM patients. At present, T2DM has become the public health problem in China [3, 4].

The main purpose for T2DM treatment is to achieve adequate glycemic control, thereby delaying or reducing the occurrence of complications. Poor glycemic control can cause a variety of acute and chronic complications [5], seriously affecting the quality of life of T2DM patients and bringing heavy psychological and economic burden for them. A number of studies have demonstrated that glycemic control is critical to reduce the risk of cardiovascular diseases [6, 7]. Investigating the status of glycemic control will provide an important basis for the T2DM prevention and control strategies in China.

The Chinese Diabetes Society (CDS) recommends < 7.0 mmol/L for fasting blood glucose control and < 7% for HbA1c for T2DM patients. On July 15, 2019, China issued the "Healthy China Action (2019-2030)" which sets continuous improvement in glycemic control rate in T2DM patients as one of its strategic goals [8]. A large-scale study investigated the prevalence and control of diabetes in 98,658 Chinese adult populations in 2010, demonstrating that the adequate glycemic control could be achieved in 39.7% of treated

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diabetes patients [2]. Between 2010 and 2012, T2DM glycemic control rate was 32.6% in 9065 T2DM outpatients from 26 Chinese medical centers [9].

To provide an important basis for the development of T2DM prevention and control plans and to achieve the strategic goals of T2DM set by the "Healthy China Action (2019–2030)", it is necessary to carry out relevant research to investigate the glycemic control status of T2DM patients in China. Therefore, based on the electronic medical records (EMRs) of outpatients and inpatients, this study analyzed the glycemic control rate of T2DM patients from January 1, 2018, to December 31, 2018, in China, providing an important basis for the prevention and control of T2DM.

Methods

Study design

This study was a multi-centered, retrospective, cross-sectional study based on EMRs of inpatients and outpatients with T2DM from January 1, 2018, to December 31, 2018. The EMRs of study population were derived from SuValue database which includes EMRs of > 90 million unique patients from 161 hospitals across 18 provinces in China [10]. The glycemic control rate indicators for this study are fasting blood glucose or HbA1c. Patients with fasting blood glucose < 7.0 mmol/L or/and HbA1c < 7.0% were defined as adequate glycemic control. Authorization for SuValue database was obtained when the database was constructed, so ethics approval or written informed patient consent was exempt for this study.

Inclusion and exclusion criteria

Inclusion criteria include the following: T2DM patients aged 18 years or older, either outpatients or inpatients; having fasting blood glucose or HbA1c test results between January 1, 2018, and Dec 31, 2018; oral or injectable antidiabetic agents had been used for at least 6 months prior to the available last readings of fasting blood glucose or HbA1c test results. Exclusion criteria include the following: patients on emergency admission within 2 weeks prior to the available last readings of fasting blood glucose or HbA1c test results; pregnant women with gestational diabetes mellitus. The flowchart of data inclusion and exclusion is shown as Fig. 1.

Data collection

Sociodemographic information (sex, age), data on T2DM diagnosis, laboratory examinations, comorbidities/complications, and medications were collected for all patients by chart review. All available last readings of HbA1c, fasting blood glucose, low-density lipoprotein, triglyceride, and total cholesterol were extracted from EMRs. Comorbidity information of hypertension, ischemic stroke and myocardial infarction, and complication information of nephropathy, retinopathy, neuropathy, lower extremity arterial disease, and foot disease were extracted. Patients without the records of comorbidities or complications were defined as none. Medication information of biguanides, sulfonylurea, glinides, alpha-glucosidase inhibitor, thiazolidinediones, and insulin were extracted.

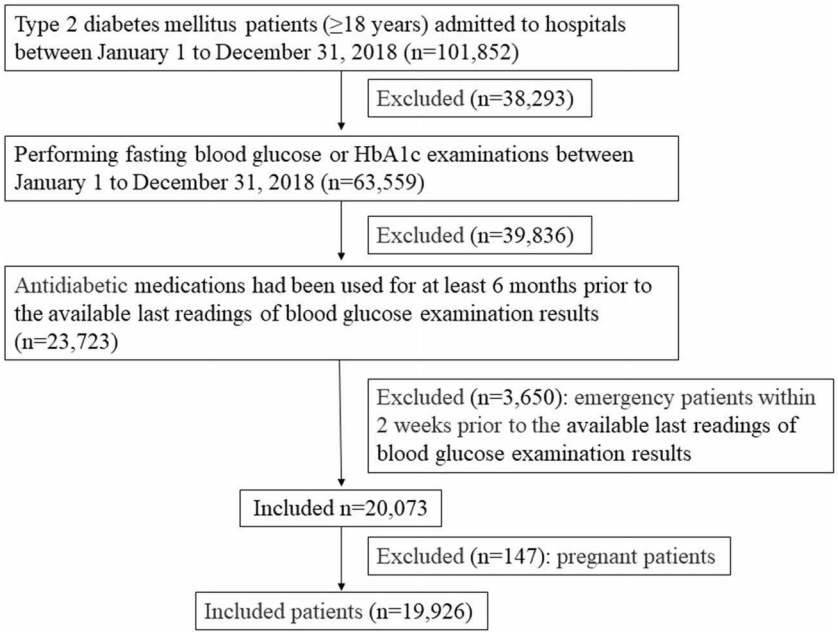

Fig. 1 Flowchart of data inclusion and exclusion

Operational definition

The diagnosis of T2DM was defined according to the guidelines for the prevention and treatment of T2DM in China [11]. Age was categorized into 18–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, and ≥ 70 years. T2DM duration since diagnosis was categorized as < 5 years, 5–10 years, and > 10 years. Regions where patients resided in were stratified by two geographic regions (northern and southern regions) with Qinling-Huaihe Line as the demarcation line in China [12]. Regions where patients resided in could also be stratified by 3 socioeconomic strata (developed areas, medium-developed areas, and underdeveloped areas) according to local gross domestic product published in the local government website. Hospitals were stratified by two levels (secondary and tertiary hospital). The categories for medications were single oral antidiabetic agent, insulin only, combination of oral antidiabetic agents, and combination of oral antidiabetic agents and insulin.

Statistical analysis

Data analysis was performed using SPSS 20.0 software. Data were expressed as mean ± standard deviation or percentage, where appropriate.

Results

Demographic data

Between January 1, 2018, and December 31, 2018, a total of 63,559 patients with T2DM had fasting blood glucose or HbA1c test results in 44 hospitals. Finally, a total of 19,926 patients were included in this study (Table 1). Among them, male patients were 9796 (49.2%). The mean age of patients was 62.0 ± 12.9 years and the mean duration of diabetes was 3.0 ± 3.0 years. Geographically, there are 18,055 (90.6%) and 1871 (9.4%) patients in the southern and northern regions, respectively. There are 16,809 (84.4%), 1261 (6.3%), and 1856 (9.3%) patients in developed regions, medium-developed regions, and underdeveloped regions, respectively. There were 11,833 (59.4%) and 8093 (40.6%) patients admitting to secondary and tertiary hospitals, respectively. Characteristics of included T2DM patients are shown in Table 1.

Glycemic control rates

A total of 5702 (30.7%) T2DM patients had their fasting blood glucose controlled to a concentration of less than 7 mmol/L and 7700 (44.3%) T2DM patients had their HbA1c controlled of less than 7.0%. Only 1972 (23.0%) T2DM patients had both their fasting blood glucose and HbA1C controlled less than 7 mmol/L and 7.0%, respectively (Table 2).

Subgroup analysis of glycemic control rates

T2DM patients with longer T2DM duration had lower proportion of controlled diabetes (fasting blood glucose < 7.0 mmol/L, HbA1c < 7%, and both) than T2DM patients with shorter T2DM duration. T2DM patients with comorbidity/complications had higher proportion of controlled diabetes (fasting blood glucose and both fasting blood glucose and HbA1c) than T2DM patients without comorbidity/complications. T2DM patients living in the southern regions had lower proportion of controlled diabetes (fasting blood glucose, HbA1c, and both) than T2DM patients living in the northern regions. T2DM patients admitting to secondary hospitals had lower proportion of controlled diabetes (HbA1c and both fasting blood glucose and HbA1c) than T2DM patients admitting to tertiary hospitals. T2DM patients living in the underdeveloped regions had lower proportion of controlled diabetes (HbA1c and both fasting blood glucose and HbA1c) than T2DM patients living in the developed regions Table 2.

Discussion

This was a multi-centered, retrospective, cross-sectional study of glycemic control in T2DM patients who were admitted to a total of 44 hospitals between January 1, 2018, and December 31, 2018. Our study showed that 44.3% of T2DM patients achieved adequate glycemic control (HbA1c < 7%) and 30.7% achieved for fasting blood glucose< 7 mmol/L while only 23.0% achieved for both indicators. T2DM patients with longer T2DM duration, without comorbidities or complications, admitting to secondary hospital, and living in the undeveloped regions had lower proportion of poor glycemic control.

In this study, 44.3% patients achieved adequate glycemic control with HbA1 < 7% in China, which was higher than 39.7% and 32.6% between 2010 and 2012 in China in previous reports [2, 9]. A cross-sectional study in the Netherlands showed that 161 (36%) T2DM patients achieved HbA1c < 7% [13]. Besides, 30.7% T2DM patients had adequate glycemic control with fasting blood glucose < 7 mmol/L in this study, which was higher than previous report of 25.5% in China [14]. There were several reasons contributing to these results. First, the Chinese government attach the importance of glycemic control and issued the "Healthy China Action Plan (2019–2030)" with the goal of improvement in glycemic control for diabetic patients in 2019 []. As early as 2009, China issued the "National Basic Public Health Service Regulations (2009 Edition)," focusing on the health management of T2DM [15]. In 2017, the National Health Commission of China promulgated the "National Basic Public

Table 1 Demographic characteristics of the type 2 diabetes mellitus patients in this study

Variables	Total (n = 19,926)
Male, n (%)	9796 (49.2%)
Age (year)	62.0 ± 12.9
Fasting blood glucose (mmol/L)	9.5 ± 4.4
HbA1c (%)	7.7 ± 1.9
Duration of diabetes (year)	3.0 ± 3.0
Triglyceride (mmol/L)	2.1 ± 2.1
Total cholesterol (mmol/L)	4.9 ± 1.3
Low density lipoprotein cholesterol (mmol/L)	2.8 ± 1.0
Serum creatinine (μmol/L)	186.8 ± 993.4
Diabetes comorbidity	
Hypertension, n (%)	8629 (43.3%)
Ischemic stroke, n (%)	3576 (17.9%)
Myocardial infarction, n (%)	3983 (20.0%)
Diabetes complications	
Diabetic nephropathy, n (%)	2435 (12.2%)
Diabetic retinopathy, n (%)	1142 (5.7%)
Diabetic neuropathy, n (%)	3300 (16.6%)
Myocardial infarction, n (%)	512 (2.6%)
Regions	
Southern, n (%)	18,055 (90.6%)
Northern, n (%)	1871 (9.4%)
Hospital grade	
Secondary hospital, n (%)	11,833 (59.4%)
Tertiary hospital, n (%)	8093 (40.6%)
Economic development	
Developed, n (%)	16,809 (84.4%)
Medium-developed, n (%)	1261 (6.3%)
Underdeveloped, n (%)	1856 (9.3%)
Medications	
Single oral antidiabetic agent	
Biguanide	1549 (7.8%)
Sulfonylurea	520 (2.6%)
Glinide	208 (1.0%)
Alpha glycosidase inhibitor	589 (3.0%)
Thiazolidinedione	116 (0.6%)
Insulin only	1143 (5.7%)
Combination of oral antidiabetic agents	
Metformin + sulfonylurea	2526 (12.7%)
Metformin + glinide	387 (1.9%)
Metformin + thiazolidinedione	190 (1.0%)
Metformin + alpha glycosidase inhibitor	1018 (5.1%)
Metformin + alpha glycosidase inhibitor + sulfonylurea	1533 (7.7%)
Combination of oral antidiabetic agents and insulin	
Metformin + insulin	1182 (5.9%)
Sulfonylurea + insulin	124 (0.6%)
Glinide + insulin	192 (1.0%)
Alpha glycosidase inhibitor + insulin	852 (4.3%)

Data are presented as mean ± standard deviation (SD) for continuous variables, and number of subjects (n) and percentage (%) for categorical variables. *HbA1c*, glycosylated hemoglobin

Table 2 Glycemic control rate among type 2 diabetes mellitus patients

	Fasting < 7.0 mmol/L, % (*n*)	HbA1c < 7.0%, % (*n*)	Fasting < 7.0 mmol/L and HbA1c < 7.0%, % (*n*)	Fasting < 7.0 mmol/L and HbA1c > 7.0%, % (*n*)	Fasting > 7.0 mmol/L and HbA1c < 7.0%, % (*n*)
Overall	30.7% (5706)	44.3% (7700)	23.0% (1972)	7.9% (679)	20.0% (1718)
Age (year)					
18–29	26.9% (28)	32.4% (34)	15.0% (9)	10.0% (6)	23.3% (14)
30–39	30.8% (165)	44.6% (208)	24.9% (64)	4.3% (11)	17.5% (45)
40–49	27.6% (719)	45.2% (1039)	23.2% (282)	4.3% (52)	22.6% (275)
50–59	28.8% (1305)	45.0% (1841)	22.6% (466)	7.0% (144)	21.5% (444)
60–69	30.5% (1673)	43.7% (2271)	22.7% (562)	7.8% (193)	19.9% (491)
≥ 70	34.1% (1816)	44.2% (2307)	23.6% (589)	10.9% (273)	18.0% (449)
Diabetes duration (year)					
< 5	33.1% (4180)	45.9% (5311)	25.0% (1542)	7.8% (483)	20.1% (1240)
5–10	25.9% (1433)	41.2% (2227)	17.9% (416)	8.2% (190)	19.7% (456)
> 10	22.3% (93)	39.0% (162)	14.9% (14)	6.4% (6)	23.4% (22)
Diabetes comorbidities/complications					
Yes	35.8% (2568)	41.9% (3074)	24.8% (912)	9.7% (358)	17.0% (625)
No	27.5% (3138)	46.0% (4626)	21.7% (1060)	6.6% (321)	22.4% (1093)
Diabetes comorbidity					
Hypertension	34.7% (2718)	45.3% (3503)	24.8% (898)	9.2% (333)	19.1% (689)
Ischemic stroke	38.0% (1235)	41.7% (1392)	26.1% (437)	11.5% (192)	15.9% (266)
Myocardial infarction	37.5% (1316)	42.3% (1574)	26.8% (460)	10.8% (185)	16.4% (281)
Diabetes complications					
Diabetic nephropathy	32.4% (700)	38.8% (897)	22.4% (245)	12.0% (131)	14.7% (161)
Diabetic retinopathy	30.7% (324)	35.2% (390)	18.5% (110)	13.8% (82)	15.3% (91)
Diabetic neuropathy	29.1% (857)	34.6% (1081)	19.3% (314)	10.2% (166)	14.9% (242)
Diabetic foot disease	27.4% (127)	40.7% (191)	20.6% (43)	6.2% (13)	20.6% (43)
Regions					
Southern regions	30.0% (5082)	44.2% (6914)	22.5% (1722)	7.6% (586)	20.3% (1554)
Northern regions	38.2% (624)	45.0% (786)	27.5% (250)	10.2% (93)	18.0% (164)
Hospital grade					
Secondary hospitals	31.3% (3440)	40.0% (3922)	21.8% (1238)	8.2% (465)	19.2% (1092)
Tertiary hospitals	29.8% (2266)	49.8% (3778)	25.4% (734)	7.4% (214)	21.6% (626)
Economic development					
Developed regions	30.8% (4793)	44.8% (6639)	23.5% (1631)	7.8% (542)	19.3% (1341)
Medium-developed regions	25.2% (291)	42.8% (395)	18.5% (117)	5.5% (35)	28.1% (177)
Underdeveloped regions	33.8% (622)	40.8% (666)	22.2% (224)	10.1% (102)	19.9% (200)
Medications					
Single oral antidiabetic agent					
Biguanide	44.3% (642)	67.8% (890)	38.2% (248)	3.8% (25)	28.6% (186)
Sulfonylurea	39.4 (198)	62.8% (311)	32.6% (71)	6.4% (14)	28.9% (63)
Glinide	44.7% (93)	59.7% (117)	40.7% (37)	3.3% (3)	23.1% (21)
Alpha glycosidase inhibitor	54.0% (308)	71.1% (371)	40.5% (105)	6.2% (16)	22.0% (57)
Thiazolidinedione	58.2% (64)	83.5% (86)	48.0% (24)	4.0% (2)	36.0% (18)
Insulin only	28.8% (280)	29.3% (304)	15.9% (78)	12.7% (62)	10.8% (53)
Combination of oral antidiabetic agents					
Metformin + sulfonylurea	28.6% (701)	46.8% (906)	20.9% (195)	8.3% (77)	22.4% (209)
Metformin + glinide	31.6% (115)	52.0% (160)	29.6% (42)	7.0% (10)	18.3% (26)
Metformin + thiazolidinedione	38.9% (72)	75.4% (135)	43.0% (34)	3.8% (3)	35.4% (28)

Table 2 (continued)

	Fasting < 7.0 mmol/L, % (*n*)	HbA1c < 7.0%, % (*n*)	Fasting < 7.0 mmol/L and HbA1c < 7.0%, % (*n*)	Fasting < 7.0 mmol/L and HbA1c > 7.0%, % (*n*)	Fasting > 7.0 mmol/L and HbA1c < 7.0%, % (*n*)
Metformin + alpha glycosidase inhibitor	33.4% (323)	54.7% (469)	26.9% (111)	7.0% (29)	26.0% (107)
Metformin + alpha glycosidase inhibitor + sulfonylurea	21.7% (312)	44.3% (564)	18.2% (122)	5.1% (34)	24.3% (163)
Combination of oral antidiabetic agents and insulin					
Metformin + insulin	26.1% (260)	22.4% (249)	13.7% (74)	11.9% (64)	9.1% (49)
Sulfonylurea + insulin	33.3% (41)	30.1% (31)	12.5% (7)	14.3% (8)	16.1% (9)
Glinide + insulin	30.1% (50)	33.3% (58)	14.3% (12)	15.5% (13)	11.9% (10)
Alpha glycosidase inhibitor + insulin	27.3% (213)	32.0% (257)	16.1% (69)	12.9% (55)	14.5% (62)

Health Service Regulations (Third Edition)," [16] providing 4 times a year of fasting blood glucose tests for T2DM patients for free. Maybe the national strategies promote the adequate glycemic control among T2DM patients. Second, the professional ability of the medical staff has been improved in recent years. For example, CDS has been tracking new technologies, new methods, and new evidence in the field of diabetes, and has published and updated T2DM prevention and treatment guidelines based on the latest research progress. In addition, CDS has been promoting academic exchanges and improving academic level by various means. Finally, better diabetes education and self-management of T2DM patients also contribute to adequate glycemic control, which have been shown to be associated with the better glycemic control [17].

In this study, T2DM patients with longer duration of diabetes had lower glycemic control rate. This result was consistent with previously published studies [18–21]. The reason may be related to the progressive loss of pancreatic beta cell function [22]. The glycemic control rate of patients with diabetes comorbidity/complications was higher than that of patients without diabetes comorbidity/complications. Patients who do not have diabetes comorbidity/complications may pay more attention to the glycemic control. Overall, the glycemic control rate among patients in the northern region is slightly higher than that in the southern region. T2DM patients living in the developed regions had higher glycemic control rate than in the underdeveloped regions, which were similar with previous report that proportion of patients with adequate glycemic increased from undeveloped regions, intermediate-regions, and developed regions (35.6%, 37.8%, and 42.8%) [2]. The reasons may be due to the differences in the diabetes awareness, economic status, and educational levels in various regions. The glycemic control rate among patients in tertiary hospitals was slightly higher than that in secondary hospitals, which may be due to the professional level of different grades of hospitals. Overall, glycemic control at all levels of hospitals still needs to be improved. The profession and health education of the medical staff should be strengthened, and the medical cooperation at all levels of hospitals should be established to achieve the goal of improvement in glycemic control.

There were several limitations in this study. First, some factors that may influence the glycemic control were not available on the EMRs such as weight, lifestyle, and medication adherence. Second, no patient in the primary hospital met the inclusion and exclusion criteria. Third, laboratory test methods of patients in the hospitals may be different across different laboratories, which may affect the results. Fourth, data collected for this study were from EMRs. Some patients with diabetes are unaware of the presence of complications or comorbidities, or due to the unstructured data, the study may not fully extract the complication or comorbidity information, which may result in bias.

Conclusions

The glycemic control rate of patients with fasting blood glucose < 7.0 mmol/L in China was 30.7% and the rate of patients with HbA1c < 7.0% was 44.3% while the rate of patients with both fasting blood glucose was < 7.0 mmol/L and HbA1c < 7.0% was only 23.0%. T2DM patients with longer duration, without comorbidity/complications, admitting to secondary hospitals, and living in the southern and undeveloped regions had lower glycemic rate control. The current status of glycemic control in T2DM patients in China provides an important basis for the prevention and management of T2DM.

Author contributions HSM and LY designed the study, analyzed the data, and wrote the first draft of the manuscript. HSM, LY, YL, JL, and HZ revised it critically for important intellectual content and approved the final version.

Data availability The dataset will be available upon request unless there are legal or ethical reasons for not doing so.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

Healthcare seeking behavior and glycemic control in patients with type 2 diabetes attending a tertiary hospital

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Abstract

Purpose To assess the relationship between healthcare seeking behaviors and glycemic control in patients with type 2 diabetes.
Methods A secondary data analysis was conducted among patients with type 2 diabetes from a randomized controlled trial conducted in a tertiary hospital, Bangladesh. Data on health center use, healthcare providers visited, self-monitoring of blood glucose, blood pressure, foot care, and physical activity were collected through structured questionnaires. Uncontrolled diabetes was defined as HbA1c ≥ 7%. Multivariable logistic regression models were performed.
Result Of the 265 patients (mean age 50.3 ± 9.9 years; 49.8% females), the majority (71.3%) had uncontrolled diabetes. More than one-third (34.9%) of the participants did not visit their physician or a healthcare center during the previous 3-months. Only 12.4% of participants checked their blood glucose, and 35.8% checked their blood pressure during the last week. Participants who did not visit a physician or a healthcare center during the past 3 months had twice the odds of having uncontrolled diabetes, compared with those who visited during the same period [OR 2.12, 95% CI (1.02–5.14), $p = 0.04$].
Conclusion Regular consultation with a physician or visiting a healthcare center might help to improve glycemic control in patients with type 2 diabetes in Bangladesh.

Keywords Healthcare seeking behavior · Type 2 diabetes · Blood pressure · Self-management · Healthcare provider · Bangladesh

Introduction

Non-communicable diseases, including diabetes, cardiovascular diseases, chronic respiratory diseases, and cancers, are significant health burden globally causing 41.1 million deaths in 2017 [1], and affecting millions of people in low- and middle-income countries (LMICs) [1, 2]. The International Diabetes Federation estimated that in 2019, there were 463 million adults with diabetes globally, which is projected to rise to 700 million by 2045 [3]. In 2019, an estimated 4.2 million global deaths were due to diabetes and related complications [3]. Diabetes is a costly condition with direct and

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indirect costs of USD 760 billion and 1.31 trillion, respectively [3]. In Bangladesh, diabetes has become an epidemic with increasing prevalence over the last few decades and imposes a substantial financial burden on the health systems [4, 5]. A study analyzing data from the 2011 Bangladesh Demographic and Health Survey reported that the overall prevalence of diabetes and pre-diabetes among the adult population was 10% and 23% respectively, with a higher prevalence of diabetes in urban areas compared with rural areas (15.3 vs. 8.3%) [6]. If this increasing trend continues, Bangladesh will be one of the highest diabetic populous countries in the world.

Evidence suggests that healthcare seeking behaviors of patients are directly related to disease incidence, prevalence, control, and complications [7]. Previous studies in Bangladesh reported a high proportion of diabetes-related health problems, depression, and poor quality of life among patients with type 2 diabetes attending an urban hospital [8–10]. Healthcare seeking behavior is essential for planning diabetes care and management upon diagnosis so that complications can be minimized. National and international diabetes care guidelines recommend maintaining optimum blood glucose levels of HbA1c < 7%. However, this is often difficult to achieve with medications alone as glucose levels are influenced by participants' behaviors. Healthcare seeking behavior can affect glycemic control in people with diabetes. The negative impact of delayed healthcare seeking behavior for diabetes includes late diagnosis, delayed treatment, and poor health outcomes, thereby increasing healthcare expenditure and suffering [4].

Healthcare seeking behavior is not just an isolated event but rather part and parcel of personal, family, and community identity that results from an evolving mix of personal, social, cultural, and experiential factors. The process of responding to illness and seeking care involves multiple steps. It is influenced by peoples' perceptions about a disease within the context of traditional and cultural beliefs and attitudes [11]. It concerns factors that enable or prevent people from making healthy choices about their lifestyles and adoption of medical care [12]. Understanding healthcare seeking behavior is essential to determine the utilization of healthcare services, identify most vulnerable patients, and support those with most significant needs. However, information regarding healthcare seeking behavior among patients with diabetes is limited in Bangladesh. Therefore, we conducted this study to assess the healthcare seeking behavior and its relationship with glycemic control among patients with type 2 diabetes and identify any gender disparity.

Methods

Study design and population

A secondary data-analyses was performed from the baseline data of participants enrolled in the "Mobile phone intervention for diabetes" (MPID) study, a randomized controlled trial for measuring the effectiveness of mobile phone intervention for diabetes in Bangladesh. The study protocol has been published previously [13]. Briefly, 265 patients with type 2 diabetes attending the Bangladesh Institute of Health Science (BIHS) Hospital in Dhaka, Bangladesh, were enrolled between September 1, 2013, and July 30, 2014. All consecutive patients meeting the following inclusion criteria were included in the trial: adults (aged ≥ 18 years), diagnosed with type 2 diabetes within the last 5 years according to the WHO standards by a BIHS attending physician, on oral medication therapy, living in Dhaka city, had access to a mobile phone and were willing to return for a follow-up visit after 6 months. Patients with severe co-morbidities, type 1 diabetes, gestational diabetes, and not ready to perform HbA1c tests were excluded. The BIHS hospital is a tertiary level hospital offering quality outpatient and inpatient services to patients from all socioeconomic classes in Dhaka city and surrounding neighborhoods. All patients registered with the BIHS receive one-time complementary health education and counseling for 20–30 min by trained health educators on diet and lifestyle, eye examination by an ophthalmologist, dental check-up by a dentist, and lifelong subsidized blood tests at BIHS laboratory.

Data collection procedure

Data collection took place at the outpatient department of BIHS hospital by the study team consisting of a research physician, a research officer, and three research assistants. The principal and senior investigators trained the data collection team for 2 weeks on study design and objectives, interview techniques and skills, anthropometric measurements, and research ethics. A draft questionnaire was developed in English and translated into Bengali using back-translation by two independent bi-lingual researchers (SMSI and TB) according to WHO guidelines. The questionnaire was pre-tested in an outpatient department of another hospital among 30 diabetic patients and was modified based on their feedback and suggestions.

Variables and measurements

Glycemic control

Blood tests for fasting blood sugar, 2-h postprandial sugar, and glycated hemoglobin (HbA1c) were measured at the BIHS laboratory following standard protocol. Diabetes was defined according to WHO guideline as (venous) fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl), or random plasma glucose ≥ 11.1 mmol/l (200 mg/dl), or plasma glucose 2 h after a 75 g oral load of glucose ≥ 11.1 mmol/l (200 mg/dl). Uncontrolled diabetes or poor glycemic control was defined

as HbA1c > 7% according to the American Diabetes Association criteria.

Health seeking behaviors

Participants reported about the frequency of self-monitoring practices of blood glucose, history of visiting a healthcare facility and providers 3-months preceding the survey completion, adherence to physicians' advice, foot care, physical activity, weight, blood pressure monitoring, and current history of tobacco use.

Sociodemographic and other variables

The following variables were included in the questionnaire: age, sex, education, occupation, monthly income, marital status, and distance of the healthcare center from home in kilometers. Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, using standard protocols [13]. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meter square (in kg/m^2) and categorized as: underweight (< 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), and overweight/obese (≥ 25 kg/m^2) as recommended by WHO for Asian populations [14]. Blood pressure (BP) was measured using a digital blood pressure monitor (Omron, SEM-1, Omron Corp, Japan) twice in both arms at 5-min interval and after the patient had rested for 10 min. The average value of the two readings was considered. Hypertension was defined as an average systolic BP (SBP) ≥ 140 mmHg or an average diastolic BP (DBP) ≥ 90 mmHg, based on the average BP measurements, or if the patient was taking any BP-lowering medication.

Data analysis

Data were checked for errors and missing values manually after collection by the data collector and re-checked by the research officer. We used the EpiInfo software for data entry with customized built-in forms for range and consistency checking to avoid data entry errors. Each variable was tested for normality. Data were presented as frequency and percentage for categorical variables and mean ± standard deviation (SD) and median (interquartile range; IQR) for continuous variables. We performed Chi-square tests, *t* tests, and Fishers' exact test for comparing the group difference between males and females as appropriate. Logistic regression was performed adjusting for potential confounders (age, sex, education, marital status, and distance of health center from home) to examine if health seeking behavior had attributed to uncontrolled diabetes. Odds ratios (OR) with 95% confidence intervals (CI) were presented. A p value < 0.05 was considered significant. Data analysis was performed using SPSS version 17 for Windows (SPSS Corporation, Chicago. IL, USA).

Ethical consideration

Written informed consent was obtained from each participant before enrollment, and the aims and objectives of the study were explained. Respondents were informed about their right to refuse and withdraw from the study at any time, which will not hamper the services they receive at BIHS hospital or elsewhere. Data were collected following the Helsinki Declaration and Bangladesh Medical Research Council guidelines of ethical conduct. Permission was granted from the Director of BIHS hospital for using their facility for data collection. The ethical and research review committee of the International Center for Diarrheal Diseases Research, Bangladesh (icddr,b) approved the study protocol.

Results

A total of 265 patients with type 2 diabetes on oral therapy participated in this study. Table 1 shows the sociodemographic characteristics of the study participants. The mean ± SD age of patients was 50.3 ± 9.9 years, and 49.8% were females. The majority of the participants were married. The median (IQR) income per month was 30,000 (30,000, 40,000) BDT [1 USD = 80 BDT, 2015]. Almost one-third (33.6%) of the participants completed college education (graduate, postgraduate diploma), 12.8% higher secondary education (year-12), 29.1% secondary education (year-10), 14.7% primary education (year-5), and 9.8% had no formal education. About half of the participants were homemakers (46.9%). More than half of the participants had hypertension (57.7%), which was significantly higher among females compared with males (65.2% vs. 50.4%, $p = 0.015$). Two out of three participants (64.5%) had overweight/obesity, with more females overweight/obese than males (70.5% vs. 58.6%).

Table 2 shows the healthcare seeking behavior of the participants by gender. About 65% of the participants visited their physician or healthcare center during the past 3 months. The majority (87.5%) of the participants had no problem remembering their physician's appointment or visit the healthcare center as per their physician's advice. Only 12.4% of participants checked their blood glucose weekly at home, while 30.6% and 57.0% of participants checked their blood glucose monthly and at every 2–3 months or more, respectively. However, a vast majority of the participants did not take care of their feet (62.6%), measure blood pressure (64.2%), and weight (70.6%) during the last week before the interview. More than 70% of the participants reported walking regularly for 30 min per day in the previous week before the interview.

Table 1 Characteristics of the study participants ($N = 265$)

Variables	*n* (%)
Age, mean ± SD (50.3 ± 9.9 years)	
Sex	
Male	133 (50.2)
Female	132 (49.8)
Religion	
Muslim	251 (94.7)
Non-Muslim	14 (5.3)
Educational status	
No formal education	26 (9.8)
Primary education	39 (14.7)
Secondary education	77 (29.1)
Higher secondary education	34 (12.8)
Graduate and higher education	89 (33.6)
Occupation	
Homemaker	120 (46.9)
Government or private sector	65 (25.4)
Business	41 (16.0)
Retired	26 (10.2)
Unemployed	4 (1.6)
Monthly income (household), median (IQR) BDT	30,000 (30,000, 40,000)
≤ 30,000 BDT	132 (51.6)
> 30,000 BDT	124 (48.4)
Marital status	
Married	236 (89.1)
Single	29 (10.9)
Glycemic status	
Controlled (HbA1c < 7%)	76 (28.7)
Uncontrolled (HbA1c > 7%)	189 (71.3)
Hypertension	
Present	153 (57.7)
Absent	112 (42.3)
Body mass index	
Underweight (< 18.5 kg/m^2)	1 (0.4)
Normal (18.5–24.9 kg/m^2)	93 (35.1)
Overweight/obese (≥ 25 kg/m^2)	171 (64.5)

N may not equal to 265 due to missing values. Single refers to those participants not currently married and includes "never married," "separated/divorced," and "widowed"

BDT Bangladeshi Taka [1 US$ = 80 BDT, 2015], *HbA1c* glycated hemoglobin, *IQR* inter-quartile range, *SD* standard deviation

Just over 14% of the participants reported being current tobacco users with more males (23.3%) than females (4.6%).

Table 3 presents the unadjusted and adjusted binary logistic regression models to determine possible factors associated with uncontrolled diabetes. The adjusted logistic regression models showed that those who did not visit a physician or healthcare center during the past 3 months had more than two times the odds of having uncontrolled diabetes compared with those who had visited a physician or health center during that period (OR 2.12, 95% CI 1.02–5.14, $p = 0.044$).

Discussion

This is the first published study in Bangladesh, to the best of our knowledge, measuring the healthcare seeking behavior and its relationship with glycemic control among patients with type 2 diabetes. The results of the study suggest that a high number of patients with type 2 diabetes in an urban area in Bangladesh had uncontrolled diabetes and poor adherence to self-monitoring blood glucose, blood pressure, weight, and foot care. Participants who did not visit a physician or healthcare center during the past 3 months had more than two times the odds of having uncontrolled diabetes, compared with those who visited during the same period. A recent study demonstrated that personal healthcare access is linked to quality improvement [15]. Our results suggest that regular visits to physicians and self-monitoring of blood glucose along with blood pressure, foot care, and weight might help to control diabetes.

A previous study in Bangladesh reported a high non-adherence rate of blood glucose monitoring (37%), diet (44.8%), foot care (43.2%), and exercise (33.2%) [16]. In our study, the non-adherence rate of foot care was much higher since our patients were relatively new cases and might be less aware of the disease and its complications. On the other hand, the inadequacy of the services for patient counseling for foot care, lifestyle modification, and follow-up could not be assessed in this study, which might affect diabetes care. Another study in Bangladesh demonstrated that 70% of the diabetic patients had non-adherence of foot care, and 25% had non-adherence of exercise [17]. Several studies have also reported that diabetic patients had low adherence to treatment behavior and inadequate blood glucose monitoring [18, 19]. Other studies have shown that certain factors such as gender, age, racial group, income, educational level, and presence of chronic disorder can predict appropriate health seeking behavior [20, 21].

The current management of diabetes in Bangladesh is more physician-centered, rather than patient-centered. Patients with type 2 diabetes need to be treated by a holistic approach through dietary adjustment, exercise, medication, education, and self-care besides regular follow-up with their physicians. Healthcare-seeking behavior is influenced by peoples' perceptions about a disease within the context of traditional and cultural beliefs and attitudes [11]. Positive attitude towards health seeking behavior is vital to prevent disease. In contrast, the negative impact of delayed health seeking response leads to late diagnosis, delayed treatment, and poor health outcomes

Table 2 Health seeking behavior of the patients with type 2 diabetes, by sex ($N = 265$)

Variables	Male, *n* (%)	Female, *n* (%)	Total, *n* (%)	*p* value
Self-monitoring of blood glucose at home				
Weekly	19 (14.3)	14 (10.6)	33 (12.4)	0.154
Monthly	46 (34.6)	35 (26.5)	81 (30.6)	
Every 2–3 months or later	68 (51.1)	83 (62.9)	151 (57.0)	
Visited a physician or health center (last 3 months)				
Yes	79 (61.2)	91 (68.9)	170 (65.1)	0.192
No	50 (38.8)	41 (31.1)	91 (34.9)	
Problems to remember physician's appointments as per physician's advice				
Never/rarely	112 (84.8)	119 (90.1)	231 (87.5)	0.193
Sometimes	20 (15.2)	13 (9.9)	33 (12.5)	
Feet care (last week)				
Yes	56 (42.1)	43 (32.6)	99 (37.4)	0.109
No	77 (58.0)	89 (67.4)	166 (62.6)	
Walk (30 min/day) for at least 5 days (last week)				
Yes	104 (78.2)	84 (63.6)	188 (70.9)	0.009
No	29 (21.8)	48 (36.4)	77 (29.1)	
Measure blood pressure (last week)				
Yes	47 (35.3)	48 (36.4)	95 (35.8)	0.862
No	86 (64.7)	84 (63.6)	170 (64.2)	
Measure weight (last week)				
Yes	43 (32.3)	35 (26.5)	78 (29.4)	0.299
No	90 (67.7)	97 (73.5)	187 (70.6)	
Tobacco use (current smoker)				
No	102 (76.7)	124 (95.4)	226 (85.9)	< 0.001
Yes	31 (23.3)	6 (4.6)	37 (14.1)	

[22]. Thus, proper health education and patient empowerment through mass-media and social-media campaigns to take control of their chronic conditions are critical for diabetes management.

Our findings suggest overall poor self-management and less frequent consultation with physicians among the participants. In contrast, similar studies conducted in other countries have shown an appropriate level of health seeking behavior among diabetic patients. For example, a study in Malaysia among people with diabetes showed that 85.9% of the participants reported health seeking behavior. This was significantly associated with respondent's age, presence of other illness, positive family history of diabetes, the distance of health facilities from participants home, perceived family support, and history of early treatment-seeking at diagnosis and duration of disease [21]. A similar study in Australia among patients with type 2 diabetes found that the majority of the patients (92%) visited a general practitioner in the past 6 months and had their HbA1c test done, and 29% had visited a practice nurse for managing diabetes and related conditions [23]. In our study, only 64% visited a physician or health center during the past 3 months. Still, service from other healthcare professionals (i.e., diabetes educator, podiatrist) for diabetes management is generally not available. Besides, compared with males, females reported significantly less physical activity and tobacco use.

The traditional physician-centric healthcare delivery system in Bangladesh appears to be inadequate to meet the demands for patients with diabetes, and innovations in diabetes care are needed. Information technology is increasingly being used in the healthcare sector in Bangladesh [24], which could support patients with diabetes and other chronic diseases to improve healthcare seeking behavior and care [25, 26]. In a randomized controlled trial in Bangladesh, we reported that mobile phone text messaging improved glycemic control in patients with type 2 diabetes in Bangladesh, and the intervention was cost-effective [27, 28]. Another study showed that patients in Bangladesh were willing to pay a modest fee for receiving text messages for diabetes [29]. A survey among patients with type 2 diabetes in Dhaka city reported that more than half of the participants had moderate to inadequate knowledge of diabetes [27, 30]. Participants' knowledge and perception of diabetes are key factors determining their adherence to medications and, thereby, diabetes management [31]. Mobile phone text messaging might help to increase knowledge about the disease, improve self-management, and play a role in healthcare seeking behavior in diabetic patients [26, 28].

Table 3 Logistic regression models for factors associated with uncontrolled diabetes

Variables	Unadjusted OR (95% CI)	*p* value	Adjusted OR* (95% CI)	*p* value
Self-monitoring of blood glucose at home				
Weekly	(Ref)		(Ref)	
Monthly	0.81 (0.36–1.82)	0.61	1.67 (0.62–4.54)	0.31
Every 2–3 months or later	1.32 (0.71–2.43)	0.38	1.34 (0.54–3.32)	0.53
Visited a physician or health center (last 3 months)				
Yes	(Ref)		(Ref)	
No	1.66 (0.93–2.98)	0.09	2.12 (1.02–5.14)	0.04
Foot care (last week)				
Yes	(Ref)		(Ref)	
No	0.97 (0.56–1.68)	0.91	1.0 (0.52–1.90)	0.99
Walk (30 min/day) for at least 5 days (last week)				
Yes	(Ref)		(Ref)	
No	0.65 (0.37–1.15)	0.14	0.56 (0.29–1.09)	0.09
Measure blood pressure (last week)				
Yes	(Ref)		(Ref)	
No	0.83 (0.47–1.46)	0.53	0.69 (0.35–1.38)	0.30
Measure weight (last week)				
Yes	(Ref)		(Ref)	
No	0.97 (0.54–1.74)	0.91	1.12 (0.54–2.30)	0.77
Tobacco use				
Never	(Ref)		(Ref)	
Former (stopped > 6 months)	0.53 (0.18–1.61)	0.26	0.38 (0.10–1.36)	0.14
Current (in last 6 months)	1.17 (0.59–2.32)	0.65	1.26 (0.60–2.64)	0.54

*Adjusted for self monitoring blood glucose, h/o visit to a physician or health center, caring of foot, walking, measuring weight, monitoring of blood pressure, and using tobacco

Limitations

This study was conducted at a single tertiary level hospital in an urban area of Bangladesh. Thus, the findings may have limited generalizability; especially, the results may not reflect the views of rural patients and those living in hard-to-reach areas with limited access to healthcare services. It is possible that our study participants had a better education, received better healthcare, and were more likely to seek support from healthcare providers to manage their diabetes and related conditions. Furthermore, our participants might be better motivated as they had volunteered to participate in our clinical trial. The level of health seeking behavior in this relatively motivated group suggests that health seeking behavior might be lower among the general diabetic population in Bangladesh. Health seeking behavior of the patients was self-reported; as such, the chance of bias could not be ruled out. Besides, we did not have data on the frequency of physician and healthcare center visits. The cross-sectional design in data collection restricts the presumption of any causal relationship between health seeking behavior and glycemic control. Further population-based longitudinal studies in both urban and rural areas of Bangladesh are needed for a more substantial evidence base.

Conclusion

This study revealed that health seeking behavior among diabetic patients in urban areas of Bangladesh is inadequate, which may result in uncontrolled diabetes in the majority of the participants. Improving health seeking behaviors, including a regular visit to a physician and healthcare center, might help to improve glycemic control and overall diabetes care in Bangladesh. Health policymakers and practitioners need to identify and effectively address the barriers to behavior change related to diabetes control among newly diagnosed patients.

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Authors' contributions SMSI obtained funding and developed the study concept and protocol. TB was responsible for the data collection and contributed to the first draft. TB and SMSI performed the data analysis. SMSI, AN, and SBZ interpreted the data and contributed to the manuscript for improving the scientific contents. RU, TT, ZC, and MAM reviewed the manuscript and contributed intellectually. LN and AN

provided overall supervision and final comments. All authors have read the final manuscript and agreed for submission.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

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

Ethical approval The study protocol was approved by the ethical and research review committee of the International Center for Diarrheal Diseases Research, Bangladesh (icddr,b).

Consent to participate Written informed consent was obtained from each participant before enrollment and the aims and objectives of the study were explained.

Consent for publication The participants consented for their data to be used in scientific communications, including publication in journals.

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ORIGINAL ARTICLE

Could the appropriate anti-diabetic therapy be mixed insulin in dialysis patients?

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Abstract

Background A good glycemic regulation should be provided to reduce mortality and morbidity in patients with end-stage renal failure due to diabetes mellitus. However, the use of insulin therapies in patients with renal failure is troublesome due to the increased rate of side effects. In our study, we investigated the frequency of hypoglycemia and its symptoms in patient groups receiving intensive and mixed insulin therapies.

Materials and methods This prospective study included 89 hemodialysis patients with DM-related stage 5 chronic kidney disease who were followed up in a nephrology clinic of a university hospital between January 2013 and August 2015. Our study group was divided into two groups as those receiving intensive insulin therapy and mixed insulin therapy. Group 1 and group 2 consisted of 46 patients and 43 patients, respectively. Hypoglycemia (glucose < 70 mg/dl) was investigated in patients with HbA1c levels that decreased below 7% after treatment, and the symptoms were evaluated according to the hypoglycemic scale. The results between the groups were evaluated using chi-square and Student's *t* test

Results A total of 89 patients were included in the study. HbA1c was 6.83% in the group receiving intensive insulin therapy and 6.95% in the group receiving mixed insulin therapy ($p > 0.05$). Hypoglycemia was detected in 27 patients (58.7%) in the intensive insulin therapy group and 14 patients (32.6%) in the mixed insulin therapy group. There was a significant level of hypoglycemia in the group receiving intensive insulin therapy ($p < 0.05$). In our study, the group receiving intensive insulin therapy had higher frequency and severity of common hypoglycemia symptoms such as confusion, sweating, weakness, dysphasia, palpitations, blurred vision, and feeling hungry.

Conclusion There was a higher frequency of hypoglycemia under intensive insulin therapy in patients undergoing dialysis due to chronic kidney failure, which suggests that mixed insulin therapy is the ideal treatment to avoid hypoglycemia in this group of patients.

Keywords Diabetes mellitus · Hypoglycemia · Insulin therapy · Dialysis · Kidney failure

Background

Type 2 diabetes mellitus is a chronic disease characterized by hyperglycemia, resulting from partial deterioration in both insulin resistance and secretion [1]. Type 2 DM increases proportionally with increasing prevalence of obesity [2]. This disease, which is more common today, is an important cause of mortality and morbidity due to its complications that develop over the years. Diabetic nephropathy is one of these complications. Increasing prevalence of diabetes mellitus (DM) increased the frequency of follow-up of patients with diabetic nephropathy. In fact, DM is the most common cause of end-stage renal failure in many geographical regions [3, 4]. However, if blood glucose levels are not regulated after the

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onset of clinical signs of kidney failure, other micro and macrovascular complications develop or progress. Therefore, strict clinical follow-up is important in patients with diabetic nephropathy. For example, cardiovascular complications are the major cause of mortality in patients with end-stage renal failure due to diabetic nephropathy, thus requiring effective treatment modality [5]. In addition, poor control of blood sugar levels is associated with comorbidities such as diabetic foot ulcers, peripheral vascular diseases, and increased risk of infection [6, 7]. An effective treatment improves the patient's quality of life as well as controlling these complications. However, the kidneys, which have an important role in insulin metabolism, are dysfunctional in end-stage kidney disease. Ultimately, complications in patients with chronic kidney disease due to diabetic nephropathy make regulation of blood sugar levels important; on the other hand, it causes difficulties in the use of insulin for an effective therapeutic purpose. Hypoglycemia comes first among these difficulties. The increasing number of hypoglycemia episodes increases mortality. In addition, both hypoglycemia and hypoglycemic symptoms can prevent effective treatment and cause the patient to stop treatment [8, 9]. As the increased risk of hypoglycemia and the symptoms of hypoglycemia affect the patient's performance, it can be difficult to determine the therapeutic insulin dose, treatment options, and target blood glucose value. Therefore, there is no consensus regarding the follow-up of diabetic patients with chronic renal failure in the treatment recommendations reported by the diabetes study groups. Therefore, it is controversial which treatment option is better. The absence of episodes and symptoms of hypoglycemia is important for therapeutic choice.

We also investigated the relationship between our therapeutic preference and the development of hypoglycemia and hypoglycemia symptoms in patients whose HbA1c levels were kept lower than 7 through an effective treatment regimen. Our patients were divided into two groups: mixed insulin and intensive insulin groups. Although there are many studies comparing the superiority of these two treatment regimens to each other in diabetic patients, there are very few literature studies on this subject in the population with chronic renal failure (CRF).

Our aim in this study is to compare the presence of hypoglycemia and the frequency of symptoms of hypoglycemia among preferred insulin regimens to reach target HbA1c levels in diabetic patients who develop end-stage renal failure.

Methods

This prospective study included patients with DM-related stage 5 chronic kidney disease who were hospitalized in a nephrology clinic of a university hospital between January 2013 and August 2015. Our study group was divided into two groups: intensive insulin therapy and mixed insulin therapy. Intensive insulin therapy was defined as basal insulin once a day and three doses of fast-acting insulin a day with meals. Mixed insulin therapy was defined as fast and medium-acting insulin administered twice a day in the morning and evening. In all patients, HbA1c value was targeted to be 7% or less during at least 3 months follow-up with current treatment protocols. Subsequently, we evaluated the frequency of hypoglycemia and the presence and severity of symptoms based on the hypoglycemic scale.

In the study, group 1 consisted of patients receiving intensive insulin therapy with target HbA1c levels, and group 2 consisted of patients receiving mixed insulin therapy. Blood glucose levels < 70 mg/dl were accepted as hypoglycemia [9]. The presence and severity of symptoms were evaluated using the face-to-face interview method by referring to the scale in the study of V. Macaulay et al Based on this scale, the presence of confusion, sweating, drowsiness, weakness, dizziness, difficulty in speaking, palpitations, decreased concentration, tremor, double vision, blurred vision, feeling hungry, nausea, anxiety, fatigue, tingling in the tongue, and headache were questioned. As the severity of symptoms increased, the score increased from 1 to 7 points [10].

Biochemical (Abbott C16000 Device) and hematological (Flow cytometry CELL-DYN Ruby System) analyses were performed. HbA1c levels were calculated using high-performance liquid chromatography (HPLC) on Agilent 1100 automated system. In addition, BioSystems SA kits were used. With this method, the normal level of HbA1c is between 4.4 and 5.7%. Blood glucose levels were monitored 4 times a day using Clever Chek device and strips.

Data were analyzed using SPSS Statistics 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics for continuous variables were expressed as mean, standard deviation, and minimum and maximum values, whereas they were expressed as numbers and percentages for categorical variables. Categorical variables were compared with chi-square test, while continuous variables were compared with Student's t test. A p value less than 0.05 was considered statistically significant.

Results

A total of 89 patients (61 female and 28 male) were included in the study. The number of patients and hypoglycemia percentages of the groups are shown in Table 1.

Group 1 consisted of 46 patients receiving intensive insulin therapy, whereas group 2 consisted of 43 patients receiving mixed insulin therapy. While the duration of diabetes was 23.8 years in group 1, it was 23.9 years in group 2 ($p > 0.05$). The mean age of group 1 was 58.4 years and of group 2 was 62 years ($p > 0.05$). The rate of hypoglycemia in male

Table 1 Effects of intensive insulin therapy and mixed insulin therapy on hypoglycemia

Number of patients	89	
• Mixed insulin	43	
• Intensive insulin	46	
Hypoglycemia		$p < 0.05$
• Mixed insulin	14(32.6%)	
• Intensive insulin	27(58.7%)	

patients was higher than in female patients (female/male: 26/15) ($p < 0.05$).

Fifty-four percent of patients had hypoglycemia(48/89). The average age of patients with and without hypoglycemia was 59.60 years and 60.72 years, respectively ($p > 0.05$).

The results of the analysis in Table 2 show the absence of a significant difference between HbA1c levels of patients who received mixed insulin therapy and those who received intensive insulin therapy ($p = 0.74$).

Treatment modality and hypoglycemic symptom type in both the groups are given in Table 3.

Discussion

Our study found that mixed insulin therapy is the preferred insulin therapy to achieve target values without causing hypoglycemia in diabetic patients with end-stage renal failure. The low risk of hypoglycemia of mixed insulin therapy may pave the way that medium-acting insulin preparations may be the treatment of choice in advanced stage renal failure. Diabetes is the most important cause of chronic kidney disease in many geographical regions [11, 12].

Diabetic nephropathy is defined as kidney damage as a result of microangiopathy [13] and is an important cause of diabetes-induced morbidity and mortality [14]. Due to the high prevalence of diabetes and the reduction in cardiovascular deaths through effective treatments, the frequency of end-stage renal failure (ESRD) due to diabetes is higher worldwide [15]. Moreover, diabetic patients make up 40% of patients who need renal replacement therapy [16]. In this population where oral antidiabetics cannot be used, insulin treatment is the most optimal treatment modality. In this treatment method, fast- (analog), short- (regular; crystallized), medium- (Neutral Protamine Hagedorn; NPH) and long-acting insulins and mixtures thereof can be used. However, regulation of insulin therapy is very difficult due to the elimination of insulin through the kidneys. Therefore, hypoglycemia is almost inevitable while providing a strict glycemic control in patients with diabetes, and hypoglycemia is an important cause of mortality and morbidity independent of diabetes (8).

Table 2 The effectiveness of insulin treatment modality on HbA1c levels

HbA1c	*N*	Mean %	*p*
Mixed insulin	43	6.95	0.743
Intensive insulin	46	6.83	

It is the experience of many relevant clinicians to monitor the presence and symptoms of hypoglycemia while regulating glucose levels with insulin therapy in patients with CKD. However, there are studies in the literature on insulin regimens, glucose regulation and hypoglycemia more frequently in intensive care patients. In this regard, Berghe et al. showed higher rates of glucose regulation and a mortality rate that decreased from 8 to 4.6% in a study of 1548 patients admitted to intensive care after cardiovascular surgery. However, in the study, no evaluation has been made on hypoglycemia [17]. A subsequent study of the same researchers showed higher frequency of hypoglycemia in the intensive insulin treatment group. Another result of this study is higher mortality rates in patients with hypoglycemia [18]. In a study of 537 patients with sepsis in an intensive care unit, Brunkhorst et al. showed better regulation of glucose levels in the intensive insulin group, and hypoglycemia in 17% and 4% of patients in the intensive insulin and conventional groups, respectively, with a statistically significant difference [19]. In a study on a large patient population, Preiser et al. detected higher rates of hypoglycemia in the group receiving intensive insulin treatment [20]. This study is comparable to the NICE-SUGAR study in which the cut-off value of hypoglycemia is considered as 40 mg/dl [21]. In a multicenter study conducted in 26 centers, Griesdale et al. found higher rates of hypoglycemia and mortality in the intensive insulin group in patients in 14 centers [22]. All these studies have shown that the rate of hypoglycemia is higher in those under intensive insulin therapy. Hypoglycemia causes an increase in mortality rates as well as disruptions in the treatment process. In our study on a special group of patients, such as those with chronic kidney disease, hypoglycemia developed in 27 (58.7%) of the patients in the intensive insulin treatment group and 14 (32.6%) of the conventional treatment group, with a statistically significant difference. Six of those who received intensive insulin therapy stopped treatment after the study, and this was not the case in the conventional treatment group.

Another aim of our study was to investigate the symptoms of hypoglycemia. Our study investigated the incidence of all symptoms and their correlation with the groups. The cutoff value of hypoglycemia was accepted as a blood glucose level below 70 mg/dl [9]. The study of MacAulay et al. [10] was taken as reference for the evaluation of hypoglycemic symptoms. Accordingly, patients with hypoglycemia had higher rates of confusion, sweating, drowsiness, difficulty in speaking, palpitations, decreased concentration, tremors, blurred

Table 3 Distribution of common hypoglycemic symptoms by insulin treatment modality

	Intensive treatment (27 patients)	Mixed treatment (14 patients)
Confusion	21 (77.7%)	8 (57.1%)
Sweating	22 (81.4%)	6 (42.8%)
Weakness	25 (92.5%)	12 (85.7%)
Difficulty speaking	19 (70.3%)	9 (64.2%)
Palpitation	23 (85.1%)	11 (78.5%)
Blurred vision	20 (74%)	7 (50%)
Feeling hungry	25 (92.5%)	12 (85%)

vision, and feeling hungry. In the study of MacAulay et al. [10], the severity of symptoms was scored between 1 and 7 points. The most common symptoms in our study were feeling of hunger, fatigue, and weakness. In our study, the group receiving intensive insulin therapy had higher frequency and severity of common hypoglycemia symptoms such as confusion, sweating, weakness, dysphasia, palpitations, blurred vision, and feeling hungry.

There were higher rates of hypoglycemia and hypoglycemia symptoms in the group receiving intensive insulin therapy to achieve target HbA1c levels. This can lead to disruptions in the treatment of diabetic patients with chronic kidney disease.

Limitations of our study

The limitations of our study included the selection of patients with a stable hemodynamic status and targeted HbA1c values and the exclusion of patients receiving oral antidiabetic therapy.

In conclusion, we need an effective treatment modality for limiting other complications of diabetes and effective regulation of blood glucose levels in patients with end-stage renal failure due to diabetic nephropathy. However, intensive insulin therapy has been associated with higher rates of hypoglycemia episodes and symptoms. Although there are very few studies on the subject in the literature, it seems that more optimal results can be obtained with mixed insulin therapy in the population of patients with chronic renal failure.

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Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Vehbi Demircan, Yaşar Yıldırım, Emre Aydın, Ali Veysel Kara, Fatma Yılmaz Aydın, Zülfükar Yılmaz, Ali Kemal Kadiroğlu, Alpaslan Kemal Tuzcu, and Zafer Pekkolay. The first draft of the manuscript was written by Vehbi Demircan, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

Compliance with ethical standards

Dicle University Faculty of Medicine Ethics Committee, Diyarbakir, Turkey, has approved the study protocol (422/2015). The methods and procedures of the study comply with the ethical standards of the Declaration of Helsinki.

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.

Consent to participate Written informed consent was obtained from the patients.

Consent for publication Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Code availability Not applicable.

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ORIGINAL ARTICLE

Prevalence of peripheral neuropathy among type 2 diabetes mellitus patients in a rural health centre in South India

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Abstract

Background There is a huge burden of diabetes-related complications, both microvascular and macrovascular, in India. With the rising prevalence of diabetes mellitus (DM), this translates to an increasing number of people with complications of DM. Diabetic peripheral neuropathy (DPN) is the most common complication among DM patients with a prevalence ranging from 18.8 to 61.9% in India. Early diagnosis of DPN can reduce associated complications. Screening services at the primary healthcare level can aid early diagnosis of complications and improve health outcomes among DM patients. This study aimed to assess the prevalence of DPN and its risk factors among the type 2 DM patients attending a rural health centre.

Methodology A cross-sectional study was conducted among 390 type 2 DM patients attending the Rural Health and Training Centre of Sri Ramachandra Medical College & Research Institute. Data was collected using a standardized questionnaire followed by general inspection and physical examination of the feet. Blood sample was taken to estimate HbA1c and urine sample was collected to detect presence of albumin.

Results Among the 390 participants, 175 (44.9%) had neuropathy of which 87 (51.5%) were symptomatic. Educational status of primary schooling and less (OR = 3.34; $p < 0.001$), duration of DM (OR = 1.73; $p = 0.038$), higher HbA1c levels (OR = 2.87; $p = 0.018$), presence of urine albumin (OR = 2.57; $p = 0.033$) and peripheral vascular disease (OR = 2.85; $p < 0.001$) were predictors for DPN.

Conclusion The present study shows that the prevalence of peripheral neuropathy is high in rural areas. Regular screening using simple clinical bedside methods and affordable tools can help early identification of DPN and prevent complications like foot ulcer which ultimately leads to amputation.

Keywords Diabetic peripheral neuropathy · Type 2 diabetes mellitus · Rural · Foot examination · HbA1c · Monofilament · VibraTip

Background

According to the International Diabetes Federation 2017 estimates, 425 million people are living with diabetes mellitus (DM) in the world. By 2045, the number is predicted to rise to 629 million people. India, in 2017, had 72,946,400 patients, the second largest number of people living with diabetes. The current prevalence in India is 8.8% [1]. According to ICMR-INDIAB study, the prevalence of DM in Tamil Nadu is 13.7% in urban areas and 7.8% in rural areas with a higher proportion of undiagnosed persons living with diabetes in rural areas when compared with urban areas [2, 3].

There is a huge burden of DM-related complications, both microvascular and macrovascular, in India [4, 5]. The rising prevalence of DM translates to an increasing number of people with complications [6, 7]. Diabetic peripheral neuropathy (DPN) is the most common complication among type 2 DM patients [8].

The prevalence of DPN in the literature ranged from 18.8 to 61.9% [9–12]. DPN may be either asymptomatic or symptomatic. When symptomatic, it presents most

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frequently with burning pain, tingling sensation and hyperaesthesia which is distressing for the patient. About half of them will have no symptoms and are less likely to seek medical care. Furthermore, primary care physicians may also overlook the need to do a foot examination among them. These asymptomatic DPN patients can only be diagnosed on examination or when they present with a painless foot ulcer [13]. Foot ulcers and recurrent infections are is common among patients with DPN, and if not managed properly, it eventually leads to amputation. This increases disability and further reduces the already impaired quality of life among them [14]. Early diagnosis of DPN can help reduce the high incidence of diabetic foot. Most of the amputations among DM patients begin with ulcers. This can be prevented with appropriate foot care practices and regular screening to assess the risk for foot complications. Hence, all DM patients should be screened for DPN at diagnosis and regularly thereafter. Besides, several studies have shown that neuropathic symptoms can improve with optimization of blood sugar control and avoidance of extreme blood glucose fluctuations before any severe morbidity sets in [8].

Patients visiting this rural centre were from villages with limited access to transportation for travel to a higher care centre. In addition to this, most of the population are daily wage labourers. Hence, travel was a costly and burdensome affair for several families. The first point of contact with the healthcare system for such a population in rural areas is a primary health centre. Therefore, screening services at this level for early diagnosis can prevent complications and improve health outcomes. We focused on identifying patients with DPN using simple clinical bedside methods and affordable tools to aid diagnosis at a primary healthcare level.

The objective of this study was to assess the prevalence of DPN among type 2 DM patients attending a rural health centre and to identify its risk factors.

Materials and methods

Study setting

The study was conducted among type 2 DM patients attending the Rural Health and Training Centre (RHTC) at Vayalanallur in Poonamallee block. The centre is owned by Sri Ramachandra Medical College & Research Institute and administered by the Department of Community Medicine.

All patients diagnosed with DM are registered at the centre, and a treatment card is issued for each registered patient to record details of all the visits such as clinical examination findings, blood sugar values and treatment advised at each visit. The patients visit the centre once in a fortnight when the medical officer does a complete physical examination. She then provides them with medications for 2 weeks. In case of complications or uncontrolled blood glucose, the patients are referred to the tertiary care centre for further evaluation and management.

Study design and population

This was a cross-sectional study conducted from January 2017 to March 2017 to estimate the prevalence of DPN among type 2 DM patients. This study was a part of a larger study which enrolled all DM patients registered at the centre with regular follow-up for the last 6 months. Gestational diabetes mellitus and type 1 diabetes mellitus patients were excluded. Newly diagnosed type 2 DM patients were also excluded since regular follow-up could not be ensured. The total number of DM patients registered at the centre is 500. Of these, 100 were not visiting the centre for follow-up visits regularly and 10 were newly diagnosed, hence were excluded and the remaining 390 were enrolled for the study. Of these 390, 104 were males and 286 were females.

Study variables and data collection

Each patient was interviewed for approximately 30 min to obtain complete information. We used a pre-tested structured questionnaire to collect demographic information and to elicit symptoms of DPN. This was followed by physical examination. Anthropometric measures such as weight and height were measured according to the World Health Organization guidelines. Body mass index (BMI) was calculated as a person's weight in kilograms divided by the square of his height in meters (kg/m^2). The cut-off for overweight was greater than or equal to 25 and for obesity was greater than or equal to 30 [15, 16].

Blood pressure was measured, and patients with either systolic blood pressure of > 140 mmHg or diastolic blood pressure of > 90 mmHg were diagnosed with hypertension [17, 18].

A careful examination of the feet was then carried out in a well-lit room. The assessment was done under 4 categories: (a) dermatological, (b) musculoskeletal, (c) neurological and (d) vascular.

We started with an inspection of the feet which included dermatological assessment and musculoskeletal assessment. For dermatological assessment, the feet were inspected for absent hair, deformed nails, dry skin, fissures, ulceration, areas of erythema, old healed scars and gangrene. For musculoskeletal assessment, presence of wasting and deformities such as claw toes, Charcot joint and prominent metatarsal heads were recorded [19].

Neurological assessment was done using 3 simple clinical tests: (1)10-g monofilament, (2)128 Hz VibraTip and (3) ankle reflexes.

Loss of protective sensation was determined using monofilaments (10 g/5.07) [20, 21]. The sensation of pressure using the buckling 10-g monofilament was first demonstrated to the patient on the upper arm. The sites of the foot were then examined by asking the patient to respond "yes" or "no" when asked whether the monofilament is being applied to the particular site; the patient was expected to recognize the perception of pressure as well as identify the correct site. Areas of callus were avoided for testing.

VibraTip, which gives a vibratory stimulus of 128-Hz tuning fork, was used to test vibration perception [22]. It was first demonstrated on the patient's head and then tested on the feet.

Vibration and pressure, both, were tested on 5 areas of both feet: plantar surface of the distal hallux, 1st metatarsal, 5th metatarsal, heel and dorsal surface of the foot. Inability to perceive pressure sensation or/and vibration sensation on at least 3 of the 5 areas tested was labelled as an abnormal test result. This was followed by testing ankle reflex using a reflex hammer with the patient resting on a couch. If a response was initially absent, the patient was asked to hook fingers together and pull, while the ankle reflex was tested again with reinforcement. A total absence of ankle reflex either at rest or upon reinforcement was regarded as an abnormal result. Vascular examination included palpation of the posterior tibial and dorsalis pedis pulses which was characterized as either "present" or "absent" [23, 24].

Blood investigations: the most recent fasting blood sugar (FBS) and postprandial blood sugar (PPBS) values were noted from the treatment card. Glycosylated hemoglobin (HbA1c) was measured for each patient using the Aina HbA1c Monitoring System, which is a smartphone-based device. This is a point-of-care testing device which measures glycosylated hemoglobin (HbA1c) levels using capillary fingerstick. It has been validated at various clinical centres across the world with comparable results to the gold standard analysers [25]. It takes about 3 min to test and obtain the result for each patient. The investigators performed the test themselves after they were trained in operating the device. HbA1c levels of > 9.5 were considered high uncontrolled sugars which implicate rapid progression of microvascular complications. [26, 27]

A single spot urine specimen was collected from participants and presence of albumin was assessed by the dipstick test.

Operational definition

Diabetic peripheral neuropathy (DPN) was diagnosed in the presence of the following in any one foot [19–24]:

1. Absence of ankle reflex
2. Diminished pressure sensation in at least 3 out of the 5 areas tested
3. Diminished vibration perception in at least 3 out of the 5 areas tested

Peripheral vascular disease (PVD) was diagnosed when the patient reported definitive history of intermittent claudication or if one or more peripheral pulses absent in any one foot [25].

Data analysis

Data entry and analysis were done using Statistical Package for Social Sciences (SPSS) version 16 software after checking for completeness. Descriptive statistical analysis was used to analyse the background variables. Median and range have been reported for quantitative variables. Frequency and percentage are reported for qualitative variables. Using chi-square, the associations of risk factors were analysed. The odds ratios (ORs) and their 95% confidence intervals (CIs) were computed. A p value of < 0.05 was considered to be statistically significant. Binary logistic regression was performed using Backward-Wald method to find the predictors for occurrence of DPN. Variables and the main outcome were entered in the logistic regression model. Adjusted odds ratio (AOR) was used to estimate the strength of the relationship between DPN and the risk factors and a p value of < 0.05 was considered statistically significant.

Results

The study included a total of 390 type 2 DM patients, of which 104 were males and 286 were females. The median age of the study participant was 56 years (IQR 50–64). Median BMI of the study participants was 25.88 kg/m^2 (IQR 23.27–29.04). A positive family history of DM was present among 179 (45.9%) participants. Median duration since diagnosis of DM was 4 years (IQR 2–10). Majority of the participants were on metformin, either alone or along with another oral hypoglycemic agent (OHA), and only 4.6% of the participants were on insulin along with another OHA. Details of the demographic characteristics are given in Table 1.

The prevalence of DPN was 44.9% with almost equal prevalence among males (46.2%) and females (44.4%). Among the study participants, pressure sensation was diminished/absent in 117 (30%) subjects, ankle reflex was absent in 90 (23.1%) subjects and vibration perception was diminished/absent in 66 (16.9%) subjects (Fig. 1).

Among the study participants, 169 (43.3%) were reported to have symptoms suggestive of DPN. Among those diagnosed with DPN, 87 (51.5%) were symptomatic. The most frequently reported symptoms in this study were burning,

Table 1 Characteristics of the study participants

Variables	N	%
Age (n = 390)		
≤ 50	119	30.5
51–65	203	52.1
≥ 66	68	17.4
Sex (n = 390)		
Males	104	26.7
Females	286	73.3
Education (n = 389)		
Primary and less	252	64.8
High school and above	137	35.2
Working status (n = 386)		
Unemployed	260	67.4
Employed	126	32.6
Duration of DM (n = 379)		
< 5 years	224	59.1
5–10 years	100	26.4
> 10 years	55	14.5
Body mass index (n = 386)		
Normal (18.5–24.99)	159	41.2
Overweight (25.00–29.99)	147	38.1
Obese (≥ 30)	80	20.7
Treatment[a]		
OHA and insulin	18	4.6
Metformin	373	95.6
Glynase	256	65.5
Glibenclamide	28	7.2
Biochemical		
HbA1c		
< 7.0	216	55.4
7.0–9.5	131	33.6
> 9.5	43	11
FBS > 126 mg/dl (n = 384)	189	49.2
PPBS > 200 mg/dl (n = 384)	230	59

[a] Total will not tally due to multiple responses

pricking and pain. The details of dermatological, musculoskeletal, neurological and vascular assessment are given in Table 2.

The prevalence of DPN among the study participants according to the relevant socio-demographic, clinical and laboratory characteristics is given in Table 3. Prevalence was almost equal among males (46.2%) and females (44.4%) with no significant difference according to sex. There was a significant increase in the prevalence of DPN with increasing age (p = 0.009) and subjects > 70 years had an increased chance to have DPN (OR = 3.17). Prevalence of DPN also increased with duration of DM, and this difference in proportion was statistically significant (p = 0.009). There was a significant

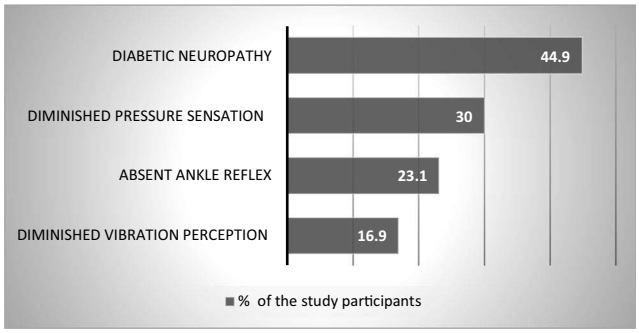

Fig. 1 Prevalence of diabetic peripheral neuropathy

association between DPN and glycemic parameters such as fasting blood sugar > 126 mg/dl (OR = 1.95, p = 0.001), postprandial blood sugar > 200 mg/dl (OR = 2.05, p < 0.001) and glycosylated hemoglobin > 9.5 (OR = 2.23, p = 0.043).

Binary logistic regression analysis of the prevalence of DPN was performed using age, duration since diagnosis, education status, HbA1c, systolic blood pressure, presence of urine albumin and PVD as predictors. This confirmed that education status of primary schooling and less (p < 0.001), duration of disease > 5 years (p = 0.038), higher HbA1C levels (p = 0.018), presence of urinary albumin (p = 0.014) and PVD (p = 0.001) had significant association with DPN. Details are given in Table 3.

Discussion

The present study was conducted among type 2 DM patients attending a rural health centre to determine the prevalence of DPN and identify its risk factors. A total of 390 DM patients were enrolled in the study. Semmes-Weinstein (SW) 10-g monofilament, VPT using VibraTip and ankle reflex were used to diagnose DPN. The prevalence of DPN in this study was 44.9%. On conducting binary logistic regression analysis, educational status of primary schooling and less (OR = 3.34; p < 0.001), duration of DM (OR = 1.73; p = 0.038) higher HbA1c levels (OR = 2.87; p = 0.018), presence of urine albumin (OR = 2.57; p = 0.033) and peripheral vascular disease (OR = 2.85; p < 0.001) were identified as predictors for DPN.

The prevalence of DPN in this study was 44.9%. Similar results were reported by George et al. They conducted a study in a secondary rural hospital, using the Michigan Neuropathy Screening Instrument (MNSI) tool to diagnose DPN. Among the 212 participants, 99 (47%) were diagnosed to have DPN [28]. Another study conducted in rural Pondicherry in a tertiary care centre, using MNSI, reported a prevalence of 52.9% which was slightly higher than the current study [14]. A study in rural Andhra Pradesh using SW 10-g monofilament, VPT test by 128-Hz tuning fork and ankle reflex tests reported a prevalence of 39.3% [29]. This was slightly lower than the

Table 2 Clinical profile of study participants

Symptoms of DPN		*N*	%
1.	Any 1 or more symptoms	169	43.3
2.	Burning	88	22.6
3.	Pricking	84	21.5
4.	Pain	72	18.5
5.	Numbness	67	17.2
6.	Tingling	35	8.9
	Physical examination	Right foot *N* (%)	Left foot *N* (%)
A	Dermatological and musculoskeletal assessment		
1.	Absent hair	89 (22.8)	89 (22.8)
2.	Deformed nails	85 (21.8)	94 (24.1)
3.	Fissured skin	78 (20)	81 (20.8)
4.	Ulceration	10 (2.6)	13 (3.3)
5.	Old healed scar	10 (2.6)	11 (2.8)
6.	Gangrene	2 (0.5)	3 (0.8)
7.	Deformities	24 (6.2)	
B	Neurological assessment		
1.	Monofilament test—pressure sensation absent/ reduced	110 (28.2)	107 (27.4)
2.	Vibration test—vibration perception absent/ reduced	55 (14.1)	64 (16.4)
3.	Ankle reflex—absent	81 (20.8)	85 (21.8)
C]	Vascular assessment		
1.	Dorsalis pedis artery—pulsations absent	20(5.1)	19 (4.9)
2.	Posterior tibial artery—pulsations absent	29 (7.4)	33 (8.5)

prevalence in the current study. A study conducted in Lucknow using Neuropathy Symptom Score (NSS) and Neuropathy Disability Score (NDS) reported a prevalence of 29.2%, which was lower than in this study. This could be because only patients diagnosed within the last 6 months were included in the study. The same study though showed abnormal VPT using a VibraTip among 43.3% with a significant correlation with NDS, which is similar to our prevalence of DPN [30]. The CURES-55 study used VibraTip for diagnosis of DPN and reported a prevalence of 26.1% [4]. This was lower than the prevalence of the current study which could be because the CURES-55 was a population-based study, whereas ours was a facility-based study. Our results confirm a high prevalence of DPN in rural areas and are similar to the results obtained with the use of the MNSI tool.

In the current study, the prevalence among males (46.2%) was slightly higher than among and females (44.4%) but this difference was not statistically significant. This was similar to findings reported by Bansal et al., J Cazebas-Cerrato and Javed et al. [31–33], although there are studies that report males to be at a higher risk of developing DPN when compared to females [34–36].

Education of primary schooling or less was identified as a risk factor for the occurrence of DPN in this study. Van der Meer and colleague reported that DM patients with a low level of education had worse outcomes in terms of complications [37]. A study conducted in India reported a higher prevalence of microvascular complications among DM patients with lower educational status when compared to those with better education [38]. These results support our study and can be attributed to the fact that individuals with higher educational status are more aware of the disease and its complications. They are more likely to adopt and adhere to lifestyle modifications, medications and appropriate dietary practices [39].

In the current study, high levels of HbA1c were also identified as a risk factor for the presence of DPN. A meta-analysis was done by Liu et al. to study the risk factors for DPN which included studies from China, India, Bangladesh and Kuwait. This study reported Hba1c as a risk factor for DPN [40]. A study by Kasper et al. reported that prolonged uncontrolled hyperglycemia has been associated with DPN and other microvascular and macrovascular complications [41]. A study by Ishibashi et al. reported tight glycemic control in newly diagnosed type 2 DM patients can delay the occurrence of microvascular complications including neuropathy and nephropathy [42]. This demonstrates that glycemic status influences the occurrence and progression of diabetes-related complications.

The current study also reported the presence of PVD to be a risk factor for DPN. A study conducted in Germany to assess risk factors of DPN reported that the presence of diabetes-related complications such as peripheral arterial

Table 3 Associated factors of diabetic peripheral neuropathy and logistic regression analysis

Variables	Neuropathy Present No. (%)	OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Sex					
Female	127 (44.4)	1			
Male	48 (46.2)	1.07 (0.68–1.68)	0.759		
Age					
≤ 50 years	41(34.5)	1	0.009		
51–70 years	119 (48.2)	1.77 (1.12–2.78)			
> 70 years	15 (62.5)	3.17 (1.28–7.87)			
Duration of diabetes mellitus					
<5 years	88 (39.3)	1		1	
>5 years	82 (52.9)	1.74 (1.15–2.63)	0.009	1.73 (1.03–2.92)	0.038
Education					
High school and above	42 (30.7)	1		1	
Primary and less	133 (52.8)	2.53 (1.63–3.92)	< 0.001	3.34 (1.91–5.82)	< 0.001
Tobacco use					
No	164 (44)	1			
Yes	11 (64.7)	2.34 (0.85–6.45)	0.093		
HbA1c					
< 7.0	93 (43.1)	1		1	
7.0–9.5	55 (42)	0.96(0.62–1.48)			
> 9.5	27 (62.8)	2.23(1.14–4.38)	0.043	2.87 (1.19–6.85)	0.018
Systolic BP					
<120	45 (36)	1			
120–139	97 (49)	1.71 (1.08–2.70)			
≥ 140	33 (54.1)	2.09 (1.13–3.90)	0.026		
Urine albumin					
Absent	117 (44.5)	1		1	
Present	21 (67.7)	2.62 (1.19–5.78)	0.014	2.57 (1.08–6.12)	0.033
Peripheral vascular disease (PVD)					
Absent	135 (40.8)	1		1	
Present	40 (67.8)	3.06 (1.69–5.51)	< 0.001	3.93 (1.77–8.75)	0.001

disease, nephropathy and retinopathy was associated with increased occurrence of DPN [43]. This is comparable to our results.

The current study has some limitations. Firstly, nerve conduction studies (NCS) which is the gold standard test to diagnose DPN could not be performed due to logistic and financial constraints. This could have led to the underestimation of DPN prevalence. Secondly, we did not assess other factors responsible for peripheral neuropathy like alcohol abuse, vitamin B12 deficiency, chronic inflammatory diseases, drugs and hereditary disorders [44].

The strength of this study is the use of simple, non-invasive, economical and quick methods to evaluate DPN. The ease to perform these bedside tests in a busy clinical setting and its availability at a low cost make them good screening tests at a primary care level. Unfortunately, neuropathy screening is underutilized in primary care practice.

In conclusion, this study reveals a high prevalence of DPN among type 2 DM patients in a rural area. Almost half of the participants with DPN had symptoms. Higher HbA1c levels and presence of urine albumin were associated with higher risk of DPN. Using point-of-care tests for detecting urine albumin and HbA1c can help in early diagnosis. Additionally, participants who had lower educational status, higher duration of disease and presence of PVD were at a higher risk for DPN. Presence of symptoms and risk factors for DPN should urge the primary care physicians to screen for DPN. Simple foot examination like inspection of feet, testing of sensation, palpation of pulses and testing of reflexes done on a periodical basis for all diabetic patients

attending primary health centres will help early diagnosis and timely management of the patients to reduce ulceration and amputation.

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Compliance with ethical standards

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

Ethics This study was performed in line with the principles of the Declaration of Helsinki. The study protocol was approved by Sri Ramachandra Institutional Ethics Committee (Ref: IEC-NI/16/Nov/56/81). Written informed consent was obtained from all study participants.

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CORRECTION

Correction to: Prevalence of peripheral neuropathy among type 2 diabetes mellitus patients in a rural health centre in South India

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The correct order of the Author names is shown in this paper.
The original article has been corrected.

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ORIGINAL ARTICLE

Relationship of HbA1c with plasma atherogenic index and non-HDL cholesterol in patients with type 2 diabetes mellitus

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Abstract

Purpose Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular diseases (CVD). The plasma atherogenic index (PAI) has been suggested as a novel marker of atherosclerosis and coronary heart disease. The present study is conducted to investigate the relationship between glycated hemoglobin (HbA1c), non-HDL (high-density lipoprotein) cholesterol, and atherogenic index within patients with T2DM.

Materials and methods A total of 4252 patients with T2DM were screened retrospectively and parameters including glucose, HbA1c, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, TSH, age, and gender were recorded. Non-HDL cholesterol and PAI were calculated as follows:

$$\mathrm{PAI} = \mathrm{TG} \div \mathrm{HDL\ cholesterol}$$

$$\mathrm{non{-}HDL} = \mathrm{total\ cholesterol{-}HDL\ cholesterol}$$

Results Mean age was 57.06 ± 11.39 years. Mean HbA1c was 8.49 ± 1.86%, PAI ratio was 4.12 ± 3.88 mg/dl, and mean non-HDL cholesterol was 156.50 ± 45.39 mg/dl. Non-HDL cholesterol ($r = 0.427$; $p < 0.001$), HbA1c ($r = 0.163$; $p < 0.001$), and glucose ($r = 0.154$; $p < 0.001$) showed a significantly positive correlation with PAI.

Conclusion Although a respectable attention is drawn to non-HDL cholesterol based on the present data, PAI may have a stronger relationship with HbA1c in patients with T2DM. PAI may be beneficial in predicting patients who have high risk for CVD in clinical practice.

Keywords Diabetes mellitus · Non-HDL cholesterol · Plasma atherogenic index

Introduction

Type 2 diabetes mellitus (T2DM) is a prevalent chronic disease that affects carbohydrate, lipid, and protein metabolisms with increasing incidence. It is accepted as a major risk factor for cardiovascular diseases (CVD). Patients with T2DM are shown to have 2–4 times increased risk of CVD mortality compared to individuals without diabetes [1, 2]. Although pathophysiology is not fully understood, the factors like hypertension and dyslipidemia are thought to contribute to progression of complications as well as hyperglycemia [3].

Based on these findings, current guidelines provide clear targets for low-density lipoprotein (LDL)/high-density lipoprotein (HDL) cholesterol, triglyceride, and non-HDL cholesterol levels in patients with T2DM [4].

The plasma atherogenic index (PAI) has recently been the focus of attention as a marker of atherosclerosis and coronary heart disease [5–7]. There are remarkable accumulating data about the relationship between PAI and different groups including diabetics with not only macrovascular complications but also microvascular complications. PAI may be considered as a strong predictive marker in the early determination of

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patients at high risk for cardiovascular diseases in clinical practice [5, 8, 9].

In the present study, it is aimed to evaluate the relationship of HbA1c with non-HDL cholesterol and atherogenic index and the difference between the gender in patients with T2DM who did not receive statin treatment.

Materials and methods

Following the approval of the ethics committee, ICD code of DM was screened retrospectively in the patient archive. In total, 11,659 patients with DM who were admitted to the Division of Endocrinology and Metabolism, Department of Internal Medicine, Bakirkoy Dr. Sadi Konuk Training and Research Hospital (Istanbul, Turkey) within year 2015–2018 were found. Patients who had type 1 DM and gestational diabetes mellitus, hypothyroidism, missing values for lipids and HbA1c, and HbA1c levels below 6.5% were excluded; 4252 patients remained. Data including age, gender, HbA1c, TSH, total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, and glucose were recorded. The reference ranges were as follows: HbA1c: 4–6%, TSH: 0.27–4.2 mIU/ml, total cholesterol: 0–200 mg/dl, triglyceride: 0–200 mg/dl, LDL cholesterol: 0–130 mg/dl, HDL cholesterol: 40–60 mg/dl, and glucose: 74–106 mg/dl.

Cholesterol, triglyceride, and LDL cholesterol levels were measured enzymatically on the Beckman Coulter AU5800 instrument by the Friedewald formula; glucose levels were measured on the Beckman Coulter AU5800 instrument by the hexokinase method; TSH levels were measured immunoenzymatically on the Beckman Coulter Dxl 800 instrument by the chemiluminescence method; and HbA1c levels were measured on the ARKRAY ADAMS A1c HA-8180V instrument by the HPLC method.

PAI was calculated with the formula: $PAI = Tri\text{-}glyceride \div HDL$, and non-HDL cholesterol was calculated with the formula: $Non - HDL\ cholesterol = Total\ Cholesterol - HDL\ cholesterol$ [6].

Statistical analysis

Statistical evaluation was performed using SPSS 25.0 package program (SPSS Inc., Chicago, IL) for Windows OS. Continuous variables were expressed as mean ± SD, while categorical variables were expressed as percentages. Differences in continuous variables between two groups were compared using the Student *t* test or Mann-Whitney *U* test based on their distribution. Differences between categorical variables were evaluated by using the chi-square test. In order to choose parametric (Pearson correlations) or non-parametric (Spearman correlations) methods, we tested the distribution of each variable with the Kolmogorov-Smirnov test. Comparisons between groups were analyzed by the chi-square test. The significance threshold was set at 0.05.

In this study, power analysis was performed with MedCalc 19.2, based on the data obtained by the power analysis plot application and the design of the relationship between HbA1c and plasma atherogenic index and non-HDL cholesterol. As a result of the plot application, it was determined that the sample size calculated based on the relationship between HbA1c and non-HDL cholesterol was 4242, while the sample size calculated from the relationship between HbA1c and the plasma atherogenic index was 381. It was decided to study 4242 cases with %80 power and 0.05 margin of error (MedCalc Statistical Software version 19.2 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2020))

Results

A total of 4252 patients—2572 (60.5%) females and 1680 (39.5%) males—with T2DM were included into the study. Mean values for age, cholesterol levels, HDL cholesterol levels, TSH levels, and non-HDL cholesterol levels were significantly higher in females compared to males ($p < 0.001$ for each). HbA1c ($p < 0.001$) and PAI ($p < 0.001$) were found to be significantly low in female patients.

Distribution of data in female and male patients is shown in Table 1. In correlation analysis, non-HDL cholesterol ($r = 0.427$, $p < 0.001$), HbA1c ($r = 0.163$, $p < 0.001$), and glucose ($r = 0.154$, $p < 0.001$) levels showed a significantly positive correlation with PAI, while a significant negative correlation was observed between PAI and age ($r = -0.090$, $p < 0.001$).

Table 1 Characteristics of the patient group according to gender

	Female ($n = 2572$)	Male ($n = 1680$)	*p* value
Age (years)	57.51 ± 1 1.31	56.35 ± 11.49	*0.0001*
HbA1c (%)	8.41 ± 1.84	8.61 ± 1.89	*0.0001*
Glucose (mg/dl)	185.34 ± 75.50	189.39 ± 78.16	0.058
Cholesterol (mg/dl)	209.31 ± 46.10	196.08 ± 44.31	*0.0001*
Triglyceride (mg/dl)	167.19 ± 92.32	171.72 ± 114.97	0.534
HDL (mg/dl)	50.66 ± 14.18	42.88 ± 11.35	*0.0001*
TSH (mIU/l)	1.96 ± 4.71	1.66 ± 0.84	*0.0001*
FT4 (ng/dl)	1.34 ± 0.23	1.31 ± 0.21	*0.018*
PAI (mg/dl)	3.81 ± 3.40	4.59 ± 4.48	*0.0001*
Non-HDL (mg/dl)	158.65 ± 45.64	153.20 ± 44.83	*0.0001*

Data are given as mean ± standard deviation

HDL high-density lipoprotein, *TSH* thyroid-stimulating hormone, *PAI* plasma atherogenic index

Significant *p* values are in italics

Mean age of the patients was 57.05 ± 11.39 years. Mean HbA1c was 8.49 ± 1.86%, PAI ratio was 4.12 ± 3.88, and mean non-HDL cholesterol level was 156.50 ± 45.39 mg/dl in all patients. Distribution of data in female and male patients is shown in Table 1.

In correlation analysis, non-HDL cholesterol ($r = 0.427$, $p < 0.001$), HbA1c ($r = 0.163$, $p < 0.001$), and glucose ($r = 0.154$, $p < 0.001$) levels showed a significantly positive correlation with PAI, while a significant negative correlation was observed between PAI and age ($r = -0.090$, $p < 0.001$).

When patients were classified into groups based on their HbA1c values (HbA1c ≤ 7.0% and HbA1c > 7%), PAI was significantly higher in the group with high HbA1c levels ($p < 0.001$) (Table 2).

Discussion

The close relationship with DM and cardiovascular disease is a well-known issue which was demonstrated by numerous studies. The patients with DM were prone to heart disease and stroke two to four times higher when compared to those without diabetes. Cardiovascular problems are leading causes of morbidity and mortality in diabetic populations with increased relative risk irrespective of gender [10–13].

HbA1c is recently described as an independent risk factor for cardiovascular disease besides pointing the degree of long-term glycemic control, and increase in HbA1c values goes with the increase in estimated risk of coronary artery disease (CAD) [14, 15].

The importance of total cholesterol as a risk factor for CAD was demonstrated by the Framingham and MRFIT (Multiple Risk Factor Intervention Trial) trials; LDL cholesterol by 4S, CARE, LIPID, WOSCOPS, AFCAPS/TEXCAPS, and HPS trials; low HDL by Framingham and VA-HIT trials; and high triglyceride by PROCAM and Baltimore COLTS trials [16–19].

Table 2 Results according to HbA1c-based classification groups

	HbA1c ≤ 7%	HbA1c > 7%	*p* value
Age (years)	58.18 ± 11.4	56.28 ± 11.33	*0.0001*
HbA1c (%)	6.92 ± 0.31	9.57 ± 1.71	*0.0001*
Glucose (mg/dl)	138.74 ± 34.04	220.29 ± 7 9.99	*0.0001*
Cholesterol (mg/dl)	201.79 ± 43.41	205.63 ± 47.4	0.0170
Triglyceride (mg/dl)	154.45 ± 76.6	178.95 ± 115.14	*0.0001*
HDL (mg/dl)	49.27 ± 13.63	46.42 ± 1 3.58	*0.0001*
TSH (mIU/l)	1.81 ± 0.94	1.74 ± 0.91	*0.0090*
FT4 (IU/ml)	1.32 ± 0.22	1.34 ± 0.22	*0.0020*
PAI (mg/dl)	3.54 ± 2.55	4.51 ± 4.54	*0.0001*
Non-HDL (mg/dl)	152.51 ± 42.78	159.21 ± 46.9	*0.0001*

TSH thyroid-stimulating hormone, *PAI* plasma atherogenic index

Besides the proven relationship between glycemic regulation and triglyceride levels [20, 21], hypertriglyceridemia itself was also enounced to influence atherogenic plasma lipoprotein particles in T2DM [22].

Improvement of glycemic control and other cardiovascular risk factors in patients with T2DM is considered as an efficient and cost-effective strategy in order to prevent cardiovascular events [23].

Because of its possibility to predict atherosclerotic events, practicality, and prediction power, targets for non-HDL cholesterol were clearly stated for diabetic population in current guidelines such as the National Lipid Association (NLA), International Atherosclerosis Society, and European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) [24–26].

The plasma atherogenic index is a novel index suggested to have a strong predictive value in plenty of metabolic disorders such as obesity, hepatosteatosis, impaired glucose tolerance, diabetes, vascular diseases, and polycystic ovary syndrome [27–31].

The data from the present study, in which concurrent data of 4252 patients were examined, showed that the atherogenic index and non-HDL cholesterol values increase parallel to the elevation of HbA1c %. In addition, when the relationship was compared, PAI was observed to have a stronger relationship with HbA1c than non-HDL cholesterol.

Prior papers also reported a relationship between PAI and glucose control. In the study conducted by Li et al. [32] in 2523 patients with T2DM, PAI showed a positive correlation with fasting blood glucose (FBG), postprandial blood glucose (PBG), and triglyceride cholesterol, and a negative correlation with HDL cholesterol in accordance with our findings. Although the sample size is limited, Song et al. [33] also found a link between HbA1c and PAI.

The usefulness of cardiometabolic risk indices including PAI, and non-HDL cholesterol between diabetic and non-diabetic patients was evaluated in the study by Adu et al. [34] and named indices were found significantly high in diabetic patients compared to non-diabetic patients. The results interpreted as routine use of the indices may support the earlier prediction of any cardiovascular complication.

Recent studies suggested that PAI may also be a good predictor of atherosclerosis demonstrated with coronary angiography [35], and in particular it is advocated to foresee the coronary events in diabetic patients when compared with other indices such as cardiogenic risk ratio and atherogenic coefficient [36].

Female patients have lower HbA1c levels and PAI when compared to men in the present study. This result does not seem to be surprising, so women are known to be more compatible with treatment. Some other factors like anemia or menopausal status may contribute to glycosylation of hemoglobin, beyond the purpose of this study [37–39].

The present study may contribute to the efforts in order to determine a practicable, cost-effective clinical tool for earlier prediction of cardiovascular diseases. Although this is one of the largest studies by sample size to our knowledge, it was a retrospective study, and detailed information could not be obtained for duration of diabetes, cardiovascular history, history of tobacco/alcohol use, and history of drug use. Comparison with the non-diabetic patient group was not performed. Prospective studies including control groups are recommended.

Limitations of the study

As this was a retrospective study, detailed information could not be obtained for duration of diabetes, cardiovascular history, history of tobacco/alcohol use, and history of drug use. Comparison with the non-diabetic patient group was not performed.

Authors' contributions EB has made substantial contributions to the conception and design. AE, OP, YSA, HP, SD, and IC have made contributions to the acquisition of data. YO has made contributions to analysis and interpretation of data. EB, MM, and IC have given final approval of the version to be published.

Compliance with ethical standards

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

Ethical approval This study was approved by the İstanbul SBU, Bakirkoy, Dr. Sadi Konuk SUAM Ethical Committee.

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The sample sizes are very limited in the previous studies that investigate the correlation between PAI and glucose and HbA1c levels. The data gained with this study show that the atherogenic index and non-HDL cholesterol values increase with the elevated levels of HbA1c. Although non-HDL cholesterol is paid more attention in clinical practice, PAI may have a stronger relationship with HbA1c in diabetic patients. Paying enough attention to PAI may be beneficial for long-term cardiovascular risk management in diabetic patients.

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ORIGINAL ARTICLE

Investigating the relationship between myocardial infarction and the ratio of glycated albumin to glycated hemoglobin in patients admitted to cardiac ward

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Abstract

Introduction Diabetes mellitus is an associated risk factor for coronary artery disease (CAD). There is a growing interest in myocardial infarction (MI) to better understand the relationship between hyperglycemia and CVD. Glycated hemoglobin (HbA1c) is the standard measure for assessing glucose regulation in diabetes mellitus and an indicator of potential cardiovascular risk and exposure to glucose concentrations over a duration of approximately 3 months. Glycated albumin (GA) may be useful for evaluating hyperglycemia in settings in which HbA1c screening is problematic or inaccessible. Another indicator that has been considered recently is the GA/HbA1c ratio. The goal of this study was to investigate the relationship between GA/HbA1c and the presence of MI and identify the sugar fluctuations as a suitable indicator for early screening and prevention of MI.

Methods This was a case-control study of diabetic patients with MI and patients with type 2 diabetes with no history of heart problems. Each group consisted of 117 participants (117 cases and 117 controls), and the total number of participants was 234. The data collection tools included laboratory tests and a demographic questionnaire. Each patient was assigned to either the case or the control group in a simple and convenient way and the relationship between MI and the GA/HbA1c ratio was investigated.

Results The findings of this study indicated that the ratio of glycated albumin to glycated hemoglobin was higher in the case group with MI than the control group ($p = 0.001$). To achieve the objectives of the study, descriptive statistics and the Mann-Whitney test were used to analyze the data.

Conclusion This study revealed the relationship between MI and the GA/HbA1c ratio. It can be said that prior to the occurrence of MI, blood glucose levels are a good indicator of recent glucose fluctuations, as well as the prediction and occurrence of MI. Therefore, the improved control of blood sugar and avoidance of high fluctuation may prevent MI from occurring.

Keywords Myocardial infarction · MI · Coronary artery disease · CAD · Glycated albumin GA · Glycated hemoglobin · HbA1c · GA/HbA1c ratio · Diabetes mellitus · Iran

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Introduction

Diabetes mellitus (DM) is a chronic and metabolic disease characterized by hyperglycemia which occurs as a consequence of severe insulin insufficiency or conditions that may contribute to increased mortality and morbidity by affecting multiple processes [1]. The International Diabetes Federation (IDF) reports that one in eleven adults has DM, totaling about 415 million individuals, 193 million of which have not yet been diagnosed [2].

The main goal of diabetes treatment is to avoid the development and progression of chronic diabetic complications [3]. Coronary artery disease (CAD) is one of the important complications associated with diabetes. Glucose metabolism abnormalities and blood glucose levels are considered a continuous risk factor for cardiovascular diseases (CVDs) [4]. Clinical studies have revealed that atherosclerosis, a chronic inflammatory process, is activated at the early stage of hyperglycemia—when the level of glycemia is not sufficiently high to indicate diabetes—rather than the next stages in which the diagnosis of diabetes is confirmed [3].

One of the most important factors in the pathophysiology of diabetes is the role of non-enzymatic glycosylation of proteins, which has been shown by several reports [5]. Glycosylated proteins also affect metabolic control and pathogenesis of the complications of diabetes. In diabetes, the concentration of glycosylated albumin (GA) and advanced glycation end-products (AGE) increases. Serum albumin is one of the important proteins which undergoes the non-enzymatic glycosylated process [6]. According to recent studies, the lack of blood glucose control and glucose fluctuations increase the risk of CVD and cause most of the deaths in patients with type 2 diabetes [7].

There is a growing interest in acute myocardial infarction (AMI) as an acute coronary syndrome (ACS) to better understand the relationship between hyperglycemia and CVD. One of the ways to reduce the risk of MI in diabetic patients is by preventing glucose fluctuations [8]. There are some standard glycemic markers such as glycated hemoglobin A1c (HbA1c) and non-traditional glycemic markers including glycated albumin (GA); the ratio of GA to HbA1c (GA/HbA1c) can determine the blood glucose levels in CAD patients at different times [9]. HbA1c, as a standard glycemic marker, represents exposure to glucose concentrations over a duration of approximately 3 months, has long been used to monitor glycemic control in patients with DM [10], and is recommended as a guide for the treatment of DM [11].

Moreover, HbA1c was recognized as a marker to evaluate the secondary vascular complications such as MI, resulting from metabolic incidents in diabetic patients [12]. A meta-analysis study has shown the relationship between CVD and the increase of HbA1c in type 2 diabetes [13]. However, HbA1c has significant limitations; for instance, it does not change rapidly in response to the treatment changes, so it has been known as a long-term glycemic marker. There is a variety of conditions that affect the reliability of the test result and its accuracy, such as anemia, kidney disease, liver disease, and irregular hemoglobin types [14].

In addition, glycemic variability is not identified by the HbA1c test. Moreover, analysis of the data on the diabetes prevention program revealed the existence of ethnic heterogeneity in HbA1c tests in patients with diabetes [6]. In several countries, including India, HbA1c has shown insufficient predictive accuracy in diagnosing diabetes, and there is no opinion on the acceptable reference line of HbA1c for the diagnosis of diabetes in this high-risk population [12]. All these limitations increase the probability that HbA1c might not be the only glycemic control marker to reveal the cardiovascular complications of diabetes [15].

GA is the second glycemic biomarker, and is one of the fructosamines that is used less often than HbA1c, but can be measured in serum or plasma; it is useful for evaluating hyperglycemia in settings in which HbA1c screening is inaccessible or unreliable [10], or for monitoring the short-term glucose control changes in patients [6], because GA (glucose which is specifically bound to albumin) reflects the glycemic control over the past 10–14 days [6] which is due to the shorter half-life of serum albumin circulation (17 days) [16]. The results of some studies have shown that following the addition of recognized and equivalent glucose concentrations, GA production was approximately 4.5 times higher than HbA1c, so GA is produced quicker than HbA1c [17]. This increases GA sensitivity to rapid fluctuations in glucose levels which may not be detected efficiently with an independent plasma glucose measurement [18]. In contrast, HbA1c does not show rapid changes [14]. Hyperglycemia results in the production of GA through the non-enzymatic attachment of glucose molecules to the free primary amine residues which eventually leads to the production of AGE compounds [19]. GA also has a significant role in the diagnosis of acute cardiac complications of diabetes. Regarding the prediction of CAD severity, several studies have shown that GA is preferable to HbA1c in patients with type 2 diabetes for assessing the degree of CAD progression [20].

GA levels are not altered by anemia, chronic kidney disease, pregnancy, or variant hemoglobin; however, in certain cases including infancy, hyperthyroidism, and nephrotic syndrome, abnormally low GA levels can occur [21]. Abnormally elevated concentrations of GA can result in liver and hypothyroid cirrhosis [22]. Furthermore, there is a similar relationship between GA and BMI, such that the GA levels are low in obese individuals and elevated in thin individuals [23].

Total glycated proteins are an indicator of glycemic control and have been suggested as a valuable method for diagnosing diabetes, assessing the appropriate diabetes treatment, and even predicting the risk of comorbidities including CADs

such as ACS. Though HbA1c indicates the glycemic control over a long period of time, it does not accurately reflect glycemic control in situations with rapid changes in the lifetime of red cells. In addition, in hematologic disorders such as anemia and hemoglobin variants, HbA1c becomes abnormal. The Diabetes Management and Complication Trial (DCCT) suggested that HbA1c alone did not sufficiently describe the occurrence of CVD.

HbA1c may not be a sensitive marker of glycemic fluctuation [16]; however, GA is not affected by the changes in erythrocytes' lifetime and can be a good marker of rapid glucose fluctuations [21]. Despite all the advantages of GA, it does not replace the use of HbA1c, since every test has its benefits and limitations. Therefore, to predict the complication of diabetes, both glycated protein markers can be good glycemic controls, when used together [24].

Another indicator that has recently been considered is the GA/HbA1c ratio. This ratio increases with the decrease of the base function of B cells. A relationship has also been found between this ratio and the ratio of fasting C-peptide immunoreactivity (FCPR) to fasting plasma glucose (FPG) (FCPR index) in type 2 diabetes. On this basis, it can be assumed that the GA/HbA1c ratio can perform better as a clinical marker of blood glucose changes [25]. Since postprandial hyperglycemia is shown to be associated with cardiovascular mortality, the factors causing postprandial glucose excursions need to be investigated [26]. Recently, there has been much interest in using an indicator of glycemic status to assess the extent of acute CAD [21]. Serum GA in glucose excursions is a more sensitive marker than HbA1c. According to this mechanism, which includes marked fluctuations in plasma glucose levels, the GA/HbA1c ratio can be a good marker to show recent fluctuations in diabetic patients [26]. ACS, such as MI, is one of the common cardiovascular complications of diabetes, which increases treatment costs and mortality [15], so it is better to find a prevention method for more accurate and earlier recognition. Between these glycated indicators, the GA/HbA1c ratio can be a suitable indicator to identify glucose fluctuations of the past 2 weeks, which is equivalent to the half-life of albumin [24], for the screening and prevention of MI. Nonetheless, few studies have compared the relationship between MI and the ratio of GA to HbA1c in patients, at the same time.

The aim of this study was to investigate the relationship between the GA/HbA1c ratio and MI. In addition, recent fluctuations in blood glucose before the onset of MI were evaluated to investigate whether these fluctuations were associated with MI.

Methods

This was a case-control study conducted during 2017–2018 in Shafa and Afzalipour Educational Hospitals affiliated with Kerman University of Medical Sciences. The research sample was selected from the patients with MI and the diabetic patients admitted to the cardiac ward and endocrine clinic of these hospitals.

In this study, the inclusion criteria of the case group were as follows: patients who had diabetes for more than 5 years, had myocardial infarction, were admitted to the cardiac ward, and their disease was confirmed by the symptoms, physical examination, ECG, cardiac enzymes, and other parameters that a cardiologist considers. The age of the case group was 33–84 years.

The control group consisted of patients who had type 2 diabetes for more than 5 years and had visited the endocrine clinic for their usual follow-up. These diabetic patients did not have ACS according to their history, physical examination, and ECG.

Diagnosis of diabetic patients was based on the fasting blood glucose levels of more than 7 mmol/L or glucose of more than 11 mmol/L after a meal, or using hypoglycemic medication. Approximately 20% of the diabetic patients in this research used a combination of oral agents and insulin, and the rest used only oral agents. The control group's age was 27–88 years.

The exclusion criteria, on the other hand, included blood transfusion over the past 3 months, history of hypoglycemia leading to hospitalization within 3 weeks, hemoglobinopathy anemia, kidney or digestive diseases associated with protein excretion, liver disease, and medications that are related to albumin (steroids).

The data collection tools included laboratory tests and a demographic questionnaire.

Laboratory tests were GA and HbA1c and the other tests that were conducted at the same time included hemoglobin test to rule out anemia, fasting blood sugar (FBS) to control diabetes, blood urea nitrogen (BUN) and creatinine (Cr) to rule out kidney disease, liver functional tests including aspartate transaminase (AST) and alanine aminotransferase (ALT) to rule out liver disease, and low-density lipoprotein (LDL) and high-density lipoprotein (HDL) to identify hyperlipidemia, which is a risk factor for MI. The demographic questionnaire consisted of age, sex, cigarette smoking, hypertension, and duration of diabetes. To determine the sample size, using the study by Pu et al (2007) and by selecting the alpha and power of 5% and 80%, respectively, the number of samples for each group was obtained as 117 (117 cases and 117 controls), and the total number of samples was 234 [27].

For the case group, any patient who was diagnosed with MI by a physician, based on cardiac enzymes, ECG, and symptoms of the disease and was admitted to the cardiac ward, and for the control group, any patient who was admitted to the endocrine clinic for the usual follow-up, had no symptoms of acute heart syndrome, and met the inclusion criteria, was included in our study list. The researchers selected the eligible

subjects for the case and control groups from the list of the patients in the cardiac ward and endocrine clinic using a convenient and simple method. After explaining the research method, if the subjects were willing, the consent form was filled. In the case group, on the first day, a blood sample was taken from the patients after 12 h of fasting, with a sterile method to perform tests such as hemoglobin, FBS, BUN, Cr, LFT, HDL, and LDL and then poured into special and standard laboratory tubes. At the same time, 4 cc of blood was poured into a separate tube to measure GA and HbA1c. Moreover, in the control group, patients had fasted for 12 h before the daily blood sugar test because routine follow-up was recommended to them, and therefore participating in our first day test was not a concern for them. As the blood sample was taken, the patient's demographic questionnaire was being completed. It is notable that HbA1c shows the blood glucose fluctuations in the patient over the past 3 months; however, GA shows the patient's blood glucose fluctuations over the past 2 weeks. In this study, sampling was performed on the first day, so stress due to MI did not significantly affect HbA1c and GA levels.

Each patient's test tubes were sent to the laboratory with the collaboration of the laboratory staff. The results of the hemoglobin, FBS, BUN, Cr, LFT, HDL, LDL, HbA1c, and GA tests were reported to the researchers and recorded in a unique sheet for each patient. The GA test sample was centrifuged and its plasma was measured by the appropriate method.

Laboratory measurements

Biochemical parameters including FBS, BUN, Cr, AST, ALT, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were quantified using commercial kits (Pars Azmoon, Iran). HbA1c was measured by the cation exchange chromatography method using the HbA1c Nycocard kits (Oslo, Norway).

Determination of GA serum levels

Serum levels of GA were measured using ELISA kits (Shanghai Crystal Day Biotech Co., LTD, China) according to the manufacturer's instructions. Briefly, 50 μL of standard solution (including secondary antibodies labeled with biotin) and 50 μL of streptavidin-HRP were added to the wells that were pre-coated with the GA monoclonal antibody. Moreover, 40 μL of the sample, 10 μL of secondary antibodies labeled with biotin, and 50 μL of streptavidin-HRP were loaded into the wells. The plate was incubated at 37 °C for 60 min. After the wells were rinsed 5 times with washing solution, 50 μL of the chromogen solutions A and B was added to each well. After 10 min of incubation at 37 °C, the reaction was stopped with the help of a stop solution. The optical density (OD) of each well was measured at the wavelength of 450 nm with an ELISA reader. The intra-assay coefficients of variation (CV) and the inter-assay CV for GA were < 10% and < 12%, respectively.

To achieve the objectives of the study, descriptive statistics and the Mann-Whitney test were used to analyze the data and describe the numerical results. SPSS 23 software was utilized for statistical analysis.

Results

Descriptive statistics for the demographic data was calculated. The homogeneity of the distributions between the two groups was examined using the chi-square test (Table 1). As can be seen, the demographic data such as age, gender, hypertension (HTN) history, and cigarette smoking are demonstrated in Table 1. The difference between the two groups in terms of these characteristics was analyzed using the chi-square test, and no statistically significant difference was observed between the control and case groups.

According to the Kolmogorov-Smirnov test, the data was not normally distributed, so a non-parametric test was used for analysis. The association between HbA1c levels, GA, and GA/HbA1c ratio was estimated using the Mann-Whitney test. The findings of this study indicated that the two groups had statistically significant differences in HbA1c levels and the GA/HbA1c ratio, but had no significant differences in GA according to the Mann-Whitney test (Table 2). The findings showed that GA was higher in the case group than the control group, although the difference between the two groups was not statistically significant. HbA1c was higher in the control group than the case group. The ratio of GA/HbA1c in the case group was higher than the control group.

Discussion

In this study, the relationship between MI, which is a diabetes complication, and the ratio of GA to glycated hemoglobin was investigated. The findings of the current study showed that the ratio of GA/HbA1c in the case group was higher than in the control group ($p = 0.000$). This indicates that prior to the occurrence of MI, the changes in the blood glucose levels and the fluctuations can be a good indicator for the prediction and occurrence of MI. Scientific studies have screened different approaches to evaluate GA and the GA/HbA1c ratio for the diagnosis of long-term diabetes complications. The benefits and disadvantages of each of them are mentioned in the studies.

The findings of the current study indicated that the two groups had no statistically significant differences in GA levels ($p = 0.09$), but the mean of GA in the case group was higher than the control group. In a research conducted by

Table 1 Comparison of demographic variables in the case and control groups

Case $N = 117$			Control $N = 117$			Chi-square result
Variable		N (%)	Variable		N (%)	$p = 0.6$
Age	Under55	49 (41.9)	Age	Under55	46 (39.3)	$\chi^2 = 0.159$
	Upper55	68 (58.1)		Upper55	71 (60.7)	
	Max-min	33–84		Max-min	27–88	
	Range	51		Range	61	
	Total	117 (100)		Total	117	
Gender	Male	84 (71.8)	Gender	Male	78 (66.7)	$p = 0.39$
	Female	33 (28.2)		Female	39 (33.3)	$\chi^2 = 0.722$
	Total	117 (100)		Total	117	
Smoking	Yes	43 (36.8)	Smoking	Yes	48 (41)	$p = 0.35$
	No	74 (63.2)		No	69 (59)	$\chi^2 = 0.847$
	Total	117 (100)		Total	117 (100)	
HTN	Yes	68 (58.1)	HTN	Yes	61 (52.1)	$p = 0.5$
	No	49 (41.9)		No	56 (47.9)	$\chi^2 = 0.450$
	Total	117		Total	117 (100)	

Yazdanpanah et al., the long-term complications of diabetes were mentioned, one of which was CVD. Blood glycated proteins such as HbA1c and GA were also analyzed in that study. Yazdanpanah showed the benefits of GA as an accurate indicator of glycemic control in the diagnosis of diabetes and the assessment of this disease's complications [21].

High GA levels better represented the fluctuations in the concentrations of blood glucose over a month's time. In comparison with HbA1c levels, GA provided additional and valuable information on glycemic control. The results of the study by Yazdanpanah on the fluctuations in GA levels as a good indicator of the prediction and occurrence of CVD were congruent with the results of the current research [21].

In a study by Jin et al., the increased levels of GA in the patients with type 2 diabetes with diffuse CAD were addressed, which was similar to the results of the current study on the association of CVD with GA levels [28]. The results of the study conducted by Lu et al. showed that such biochemical tests were significantly associated with the number of coronary vessels disease ($p < 0.01$), which was consistent with the results of the current study. However, in the study by Lu, no difference was observed in HbA1c levels between the two groups, whereas in the present study, despite the significant statistical difference in HbA1c levels between the two groups ($p = 0.000$), the mean of GA levels in the case group was lower than the control group [29].

Previous studies have reported that low normal HbA1c values may be associated with the increased risk of CVD or death via subclinical disease; this was observed in the case group of the present study. Therefore, HbA1c values can be used to assess the complications of diabetes even in low normal HbA1c levels [30], but these values are related to these complications in the long term and cannot show the early fluctuation of glucose levels in order to predict the acute coronary attack and prevent its occurrence.

Nevertheless, the general consistency of the major association of DM risk factors and elevated fructosamine and GA is encouraging and indicates that, generally, elevations in HbA1c and GA are largely driven by the same pathophysiological mechanisms that increase blood glucose levels over time [10]. Accordingly, we can say that both glycated protein indicators are useful for estimating the blood glucose levels and a change in the level of each indicator can determine the diabetic complications. Therefore, for predicting and preventing complications such as MI, it is better to assess both glycated proteins together; so the ratio of GA to HbA1c can be a more accurate indicator.

In the study by Shafi et al., it was shown that GA is a highly stable indicator and researchers have been able to perform this

Table 2 Mann-Whitney U test for comparison of HbA1c levels, GA, and the GA/HbA1c ratio between the case and control groups

Variables	Cases ($n = 117$) median	Controls ($n = 117$) median	p value
HbA1c levels	5.4	10.9	$p = 0.000$
Glycosylated albumin	16.9	14.8	$p = 0.09$
GA/HbA1c ratio	3.1	1.4	$p = 0.000$

test in multiple studies with high reliability and validity in the long-term stored samples [31]. This study demonstrated the high ability of GA to estimate the glucose levels even in stored samples. Therefore, it was concluded that to estimate the GA/HbA1c ratio, GA is a suitable factor, which is measured in our study using the appropriate laboratory method and kits.

The findings of the present study indicated that the two groups had statistically significant differences in HbA1c levels ($p = 0.000$). Measurement of HbA1c is internationally recognized as the gold standard indicator of glycemic control and is widely used to monitor the level of glucose in patients with diabetes [32]. HbA1c has also been shown to be an independent risk factor for CVD [33]. So it has an important role in the assessment of diabetic patients and their CVD, which should not be eliminated. To estimate the GA/HbA1c ratio, we need to determine the HbA1c concentration; however, it has some limitations such as delayed effects when applied in the glucose reduction treatments. Moreover, it can only indicate the mean level of blood glucose over the past 3 months and is incapable of accurately reflecting short-term glycemic variability [3]. Due to these limitations, this indicator should not be used alone when analyzing recent blood glucose fluctuations.

Considering that in the present study, the HbA1c levels were higher in the control group than the case group, it can be concluded that HbA1c alone is not a good indicator for predicting MI. However, GA was higher in the case group and since GA determines the early glucose fluctuations, the GA/HbA1c ratio was also higher in the case group of our study.

Shen et al. studied type 2 diabetes and compared the serum GA value with HbA1c to determine the existence and extent of CAD. Among 829 patients with type 2 diabetes, 664 patients had significant CAD. GA and HbA1c levels were measured in the participants. Diabetic patients with pronounced CAD had higher serum GA, but not higher HbA1c levels. GA also correlated better than HbA1c with a number of indicators of CAD severity. Thus, GA was superior to HbA1c in determining the degree of CAD progression in patients with type 2 diabetes [20]. This result is in line with the results of our study on the role of GA in the prediction of MI in the case group. Ma et al. also assessed GA, HbA1c, and the degree of CAD severity in 272 Chinese patients with CAD [34].

Some articles have discussed the advantages and disadvantages of HbA1c in the prediction of CVD, while others have addressed the GA approach to the prediction of CVD. The GA/HbA1c ratio can be a more accurate glycemic indicator in diabetic patients for revealing recent glucose fluctuations before the occurrence of MI, which is a CVD. In our study, this has been shown in patients with type 2 diabetes. In several studies, there are some methods to determine the GA/HbA1c ratio in type 1 diabetes or to compare it between the two types of diabetes.

Matsumoto et al. investigated the efficacy of the GA/HbA1c ratio versus HbA1c alone in determining glycemic control in type 1 diabetes. HbA1c, GA, and postprandial serum C-peptide immunoreactivity (CPR) were evaluated in 56 patients. The GA/HbA1c ratio was substantially higher and correlated with the mean amplitude of glucose excursion. Thus, the GA/HbA1c ratio is a sensitive indicator of glycemic control in diabetic patients [16].

In the study by Saisho et al. [15] a comparable relationship was demonstrated between GA/HbA1c and the beta cell function in the patients with type 1 and type 2 diabetes, whereas Koga et al. showed a strong negative association between the GA/HbA1c ratio and beta cell activity in the patients with type 2 diabetes [26]. According to the present research, there is a relationship between the GA/HbA1c ratio and MI in type 2 diabetes patients.

Conclusion

Blood glycated proteins represent glycemic control and have been proposed as a useful tool for diagnosing diabetes, determining the appropriate diabetes care, and even determining the risk of comorbidities, including CAD. Although HbA1c shows glycemic control over a reasonably long period of time, it does not accurately reflect glycemic control under conditions with rapid changes in the lifespan of red blood cells. GA is considered as an alternative indicator of glycemic control in diabetic patients, but in some situations, GA levels are abnormal and therefore HbA1c may be a better tool in these situations. The findings of the present study showed that the ratio of GA/HbA1c can be a good indicator to determine the risk of acute coronary diseases such as MI. The results of the current study suggested that the ratio of AG/A1c was higher in the case group with MI, which is one of diabetes long-term complications, than in the control group. Before the occurrence of MI, the GA/HbA1c ratio can be a good indicator for its prediction and occurrence because the AG/A1c ratio can show the recent fluctuations more accurately than HbA1c and GA alone. As a result, the improved control of blood sugar and the avoidance of high fluctuation may prevent MI from occurring.

Compliance with ethical standards

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

Ethical approval The researchers began the work after acquiring the code of ethics no. IR.KMU.REC.1396.1748 from the Ethics Committee.

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ORIGINAL ARTICLE

Predictive factors for reduced functional mobility in elderly diabetics and non-diabetics

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Abstract

Objective The aim of this study was to evaluate the mobility of older adults treated in primary health care units in Brazil, as well as to investigate the association between reduced mobility, sociodemographic characteristics, and health conditions in the diabetic and non-diabetic elderly.

Methods This is a cross-sectional study carried out in two primary health care units with 205 elderly individuals. The "Timed-Up-and-Go" test was used to evaluate the mobility. The variables related to reduced mobility were verified by multivariate logistic regression.

Results A total of 80% were women, 52.2% had diabetes mellitus, and the prevalence of reduced mobility was 81.0%. The following factors were significantly associated with reduced mobility in diabetics: occupation ($p = 0.040$), alcoholism ($p = 0.019$), smoking ($p = 0.039$), sedentary lifestyle ($p = 0.033$), high blood pressure ($p = 0.018$), and the percentage of body fat ($p = 0.001$). The variables that were found to be predictive factors for diabetes were as follows: triglyceride ((odds ratio [OR], 1.61; 95% confidence interval [95% CI], 1.05–2.34; $p = 0.038$)), sedentary lifestyle (OR, 2.50; 95% CI, 1.06–5.57; $p = 0.018$), and high blood pressure (OR, 2.03; 95% CI, 1.09–4.02; $p = 0.040$).

Conclusion The prevalence of reduced mobility among the diabetic older adults in the study is extremely high when compared with results from other studies conducted in Brazil and worldwide. Moreover, a decrease in mobility is one of the main risk factors for falls in older people. Therefore, intervention and health promotion actions should be proposed to maintain and improve the mobility and autonomy of the elderly.

Keywords Diabetes mellitus · Elderly · Mobility

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Introduction

Aging is a natural and inevitable process. Over the years, changes in lifestyle and improvements in the health conditions of the population have been observed, resulting in an increase in life expectancy. In this sense, it is observed that the elderly population is the fastest growing segment today, with an estimated 605 million people over the age of 65 in the world. In addition, it is estimated that in the next 30 years, the elderly population will increase by up to 300% in Asia and Latin America [1].

Population aging is characterized by a decline in physical and mental capacities, followed by limitations and increased risk for chronic-degenerative diseases. It is known that diseases can affect the functional capacity of the elderly, including mobility, which can result in functional limitations. Moreover, there are also other factors such as physical, environmental, socioeconomic, genetic, and lifestyle habits that can affect the body functions of the elderly, compromising their mobility and making them more dependent [2].

Mobility is an extremely important component of physical functioning [3]. It was broadly defined as the ability to move independently or using assistive devices from one place to another, and is most often measured in adult individuals by the Timed-Up-and-Go (TUG) and walking speed tests [4]. Some studies have shown that reduced physical function and reduced gait speed were highly predictive of falls [5] and dependence on basic activities of daily living [6], factors that are linked to the reduction of independence and autonomy of the elderly [7].

The aging process can cause some changes in the body, such as reduced muscle mass and decreased in muscle strength and power. These factors have a negative impact on the balance and functional mobility of the elderly by reducing the effectiveness of postural adjustment mechanisms and motor control, contributing to an increase in the risk of falls and fractures [8].

In this sense, the assessment of functional mobility has become a useful and important tool to evaluate the health status of the elderly, since when identified in its initial stages, impairments in physical capacity can be contained or even reversed by specific interventions, such as physical exercise programs [9]. In addition, a reduced mobility may reduce social interaction and interfere with the well-being of the elderly [10].

Also, there is evidence that an important consequence of the aging of people with diabetes mellitus (DM) is the physical disability, especially the loss of mobility. In addition, DM is associated with other comorbidities that further compromise the functionality of the elderly [11]. A study carried out in Brazil suggested that the diabetic elderly present higher risk of falls, since worse performance in the functional mobility test was found in this population when compared with the elderly without the disease [12].

Faced with these evidences, it is important to compare the mobility of diabetic and non-diabetic elderly patients through tests that evaluate the physical function and which can also be a general indicator of mobility. The TUG test is an easy-to-use, inexpensive, and efficient test for assessing mobility and has been frequently used in research [13–15].

Thus, this study aimed to evaluate the mobility of older adults treated in primary health care units in Brazil, as well as to investigate the association between reduced mobility, sociodemographic characteristics, and health conditions in the diabetic and non-diabetic elderly.

Materials and methods

This was a descriptive cross-sectional study carried out in two primary health care units (PHCUs) and in the University of Brasilia (UnB), located in Brasilia, the capital of Brazil. The data collection period was from January to July 2017. These two PHCUs are part of the Family Health Strategy, a Brazilian government program in which community health workers provide basic primary care to families in their area. In these units, the health professionals are able to resolve low-level problems, as well as forwarding complex issues to the appropriate units. Moreover, the health workers also make consultations and conduct health education sessions.

The selection of the sample occurs randomly in a conventional manner, and the medical record number of each elderly patient registered in the units was used for the sample draw. Then, the selected individuals were invited to participate in the study.

The study population consisted of 1000 elderly people who had registered in those PHCU units. A 6% error, sample distribution of 50%, and a 95% confidence interval were used to calculate the sample size, totaling 205 elderly patients. The sample was randomized and the patients having the following criteria were included age over 60 years (considered elderly in Brazil), enrolled in the PHCU, with preserved levels of consciousness to answer the research questionnaires. Also, only patients who had metal implants were excluded, because it is an impediment factor to perform the dual-energy X-ray absorptiometry (DEXA).

The first phase of the procedures took place in the PHCUs, where sociodemographic data was collected, the blood pressure was measured, and the blood collection was scheduled. A structured and previously tested instrument was applied to determine sociodemographic variables (sex, age, marital status, schooling, and occupation), behaviors (smoking, alcoholism, and sedentary lifestyle), and comorbidities. Blood pressure was measured by the auscultatory technique, with a calibrated sphygmomanometer, with an adapted cuff on the patient's left arm and a stethoscope positioned over the brachial artery line.

The anthropometric variables weight and height were obtained from the application of Lohman's techniques [16], and the weight and height measurements were used to calculate the body mass index (BMI). The following BMI reference values were considered for participants' classification: normal (22.0 to 27.0 kg/m^2), overweight (> 27 kg/m^2), and obese (≥ 30 kg/m^2) [17].

In the second phase, blood was collected through venipuncture, preferably in the antecubital fossa, with a 12-h fast. Concentrations of triglycerides, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL), total cholesterol, fasting blood glucose, and glycated hemoglobin (HbA1c) were measured in the clinical laboratory of Hospital São Francisco. Following, the TUG test was applied to assess functional mobility [18, 19]. It allows quantifying functional mobility of an individual by the time, in seconds, the task of getting up from a chair of 46 cm of height with support for the arms, to walk 3 m, to turn, and to lean back on the chair is completed. A colored mark was set on the floor to demarcate a walk of 3 m. Participants performed the TUG once before for familiarization and then again for data collection [18]. Participants who performed the test in more than 12.47 s were classified as having reduced mobility (RM) [19].

In the third phase, the percentage of body fat (BF) was evaluated by DEXA. The equipment was calibrated daily and was operated by a technically trained professional. The examination was performed in the Biophysics' Laboratory of the UnB and comprised a complete scan of the patient's body in a position of dorsal decubitus. BF was classified as normal from 25 to 37.9% and 13 to 24.9%, overweight from 38 to 42.9% and 25 to 30.9%, and obese when ≥ 43% and ≥ 31%, for women and men, respectively [20].

Statistical analysis

Data is disposed as mean ± standard deviation. The software Statistical Package for the Social Sciences (SPSS) version 20.0 was used for data analysis. The Kolmogorov-Smirnov test was applied to analyze the normality of the variables. ANOVA followed by Bonferroni's post hoc test was used to compare the means of the patients between the groups. For the final model, stepwise multiple logistic regression analysis was performed to determine the predictor variables of impaired functional capacity in the diabetic elderly and to calculate the adjusted OR. For all analysis, statistical significance level was considered $p < 0.05$.

Results

A total of 205 elderly individuals were interviewed, of whom 80.0% were female, 42.0% aged between 60 and 65 years, 45.8% were married, 34.6% presented low schooling, and 48.8% were retired (Table 1). In addition, 5.7% presented high alcoholic intake level, 8.8% smokers, and 69.3% were sedentary (Table 2). The mean age of the elderly was 68.0 ± 6.0 years.

Of the 205 elderly people evaluated, 107 (52.2%) had DM, with an average diagnosis time of 5.56 ± 7.42 years. The prevalence of reduced mobility (RM) was 81.0%. Age was not associated with RM ($p = 0.157$), but a higher rate of RM was observed in the elderly over 80 years (92.3%), followed by those aged 66–69 years (89.1%).

After the analysis of functional mobility, the sample of this study was stratified into the following groups: RM^+DM^+ (diabetic elderly with reduced mobility—47.3%), RM^+DM^- (elderly without diabetes with reduced mobility—33.6%), RM^-DM^+ (diabetic elderly without reduced mobility—9.7%), and RM^-DM^- (elderly without diabetes and without reduced mobility—9.4%) (Table 2).

Occupation, alcoholism, smoking, and sedentary lifestyle were associated with RM in diabetics. Higher prevalence of retirees was observed in the RM^+DM^+ group (54.8%) when compared with those in the RM^-DM^- group (35.3%) ($p = 0.040$). In relation to inadequate lifestyle, alcoholism was associated with impaired functional

Table 1 Sociodemographic characteristics of the study subjects (n = 205). Brasília, 2020

	n	%
Sex		
Female	164	80.0
Male	41	20.0
Age (years)		
60–65	86	42.0
66–69	46	22.4
70–75	43	21.0
76–79	17	8.3
≥ 80	13	6.3
Marital status		
Single	36	17.6
Married	94	45.8
Divorced	18	8.8
Widower	57	27.8
Schooling		
Unschooled	21	10.2
1–4 years	71	34.6
5–8 years	66	32.2
> 9 years	47	23.0
Occupation		
Active	39	19.0
Retired	100	48.8
Inactive	66	32.2

Table 2 Demographic variables, life habits, comorbidity, body composition, muscular strength, and biochemical tests of the elderly according to reduced mobility (RM^+/RM^-) and diabetes mellitus (DM^+/DM^-), Brasília, 2020

	RM^+DM^+ ($n = 97$)	RM^+DM^- ($n = 69$)	RM^-DM^+ ($n = 20$)	RM^-DM^- ($n = 19$)	Total ($N = 205$)	p
Age ($M \pm$ SD)	68.4 ± 6.1	67.3 ± 5.4	69.2 ± 4.7	65.8 ± 6.1	67.9 ± 5.7	0.868
Sex (F/M) (%)	76.3/23.7	84.6/15.4	72.2/27.8	82.4/17.6	79.3/20.7	0.514
Occupation (%(						
Active	20.5	20.0	11.1	29.4	20.2	*0.040*
Retired	54.8*	32.3	61.1	35.3	46.1	
Inactive	24.7	47.7	27.8	35.3	33.7	
Alcoholism (%)	9.7***	0.0	5.6	5.9	5.7	*0.019*
Smoking (%)	12.4**	1.4	10.0	10.5	8.3	*0.039*
Sedentary lifestyle (%)	67.0*	76.8	65.0	57.9	69.3	*0.033*
HBP (%)	83.9*	78.5	72.2	58.8	78.8	*0.018*
BMI ($M \pm$ SD)	30.5 ± 5.0	28.8 ± 5.4	30.1 ± 5.5	27.9 ± 3.6	29.8 ± 5.1	0.924
BF ($M \pm$ SD)	41.3 ± 7.0*	41.3 ± 7.8	39.0 ± 9.2	39.5 ± 5.4	40.9 ± 7.4	*0.001*
Triglycerides ($M \pm$ SD)	170.5 ± 86.3*	139.0 ± 55.2	129.1 ± 50.7	110.4 ± 53.6	154.1 ± 75.0	*0.034*
Cholesterol ($M \pm$ SD)	190.3 ± 42.7	202.6 ± 50.0*****	192.3 ± 34.5	186.1 ± 39.6	194.7 ± 44.8	*0.038*
LDL (< 100) ($M \pm$ SD)	108.0 ± 38.1**	126.3 ± 44.4	114.4 ± 30.4	110.4 ± 47.1	115.0 ± 40.8	*0.011*
HDL (> 60) ($M \pm$ SD)	45.9 ± 10.3	48.6 ± 9.6	51.9 ± 10.9	53.6 ± 21.9	47.5 ± 10.8	0.131
Blood glucose ($M \pm$ SD)	145.0 ± 58.5****	90.2 ± 13.1	125.7 ± 73.7	83.2 ± 10.9	121.9 ± 54.1	*0.001*
HbA1c ($M \pm$ SD)	7.0 ± 1.8****	5.6 ± 0.47	6.4 ± 1.8	5.3 ± 0.42	6.4 ± 1.5	*0.001*
TUG ($M \pm$ SD)	16.8 ± 4.0 ****	16.2 ± 4.0	7.5 ± 2.0	8.3 ± 1.0	14.9 ± 5.0	*0.001*

The italicized values mean p<0.05

M, mean; *SD*, standard deviation; *HBP*, high blood pressure; *BMI*, body mass index; *BF*, body fat; *LDL*, low-density lipoprotein; *HDL*, high-density lipoprotein; *HbA1c*, glycated hemoglobin

*RM^+DM^+ versus RM^-DM^-

**RM^+DM^+ versus RM^+DM^-

***RM^-DM^+ versus RM^+DM^+

****RM^+DM^+ versus all groups

*****RM^+DM^- versus RM^-DM^-

capacity, since this behavior was more prevalent in the RM^+DM^+ group (9.7%) compared with that in the RM^-DM^+ group (5.6%) ($p = 0.019$).

On the other hand, smoking was only related to DM, since the elderly of the RM^+DM^+ group (12.4%) had a higher prevalence than those of the RM^+DM^- group (1.4%) ($p = 0.039$). Higher sedentary indexes were observed in the elderly RM^+DM^+ (67.0%) compared with those in the RM^-DM^- (57.9%) ($p = 0.033$).

It was observed that 78.8% of the elderly had high blood pressure (HBP). In addition, a significant association was observed between HBP, reduced mobility, and DM, since the RM^+ DM^+ group had a higher prevalence of HBP (83.9%) when compared with the RM^-DM^- group (58.8%) ($p = 0.018$).

Regarding body composition, it was observed that the percentage of body fat was significantly associated with the reduced mobility in diabetics, since the elderly RM^+DM^+ had higher body fat mean (41.3%) when compared with those of RM^-DM^- (39.5%) ($p = 0.001$).

Considering the biochemical profile of the elderly indicated in Table 2, it was shown that triglycerides, blood glucose, and glycated hemoglobin (Hb1Ag) were associated with reduced mobility and DM. Total cholesterol and LDL were related only to reduced mobility. In relation to the lipidogram test, the triglycerides were significantly elevated in the elderly RM^+DM^+ ($M = 170.5 \pm 86.3$ mg/dL) when compared with those in RM^-DM^- ($M = 110.4 \pm 53.6$ mg/dL) ($p = 0.034$). The total cholesterol levels were higher in the elderly RM^+DM^- group (202.6 ± 50.0 mg/dL) than in RM^-DM^- ($M = 186.1 \pm 39.6$ mg/dL) ($p = 0.038$). Finally, the LDL was only associated with DM, since the RM^+DM^+ group had lower means ($M = 108.0 \pm 38.1$ mg/dL) than the RM^-DM^- group ($M = 126.3 \pm 44.4$ mg/dL) ($p = 0.011$).

Table 2 shows that the variables related to glycemic control, such as blood glucose and HbA1c, were significantly higher in the RM^+DM^- group ($M = 145 \pm 58.7$; 7.0 ± 1.8 mg/dL, respectively) when compared with those in the other three groups in the study, thus demonstrating an association

between blood glucose and HbA1c with RM and DM in the elderly ($p = 0.001$).

Regarding TUG performance, a longer test time was observed in the group of patients with DM (16.8 ± 4.0) when compared with the other group ($p < 0.001$). Sex, age, muscle strength, BMI, and HDL were not associated with RM and DM in the elderly (Table 2).

Regarding the logistic regression analysis, the variables that showed an association with reduced mobility in diabetic elderly were as follows: smoking, alcoholism, sedentary lifestyle, occupation, high blood pressure, cholesterol, triglycerides, LDL, blood glucose, HbA1c, and percentage of body fat.

After the models were tested, triglycerides, sedentary lifestyle, and HBP remained as predictor factors of reduced mobility in diabetic patients. Table 3 shows that elevated triglyceride was a predictor of low mobility in DM, increasing the risk by 1.61 times. Sedentary diabetic patients are 2.5 times more likely to have reduced mobility. Finally, elderly diabetics with hypertension have a twofold risk for reduced mobility.

Discussion

The results found in the present study indicated a high prevalence of elderly patients with reduced mobility, while other studies have found a lower prevalence such as 67.9% [21]. Some international studies also observed lower prevalence, as in the USA (36.6%) [22] and Italy (23%) [23], while similar prevalence has been observed in others, such as in the English Longitudinal Study of Ageing (ELSA) (93%) [24] and in a study conducted in South Korea (90%) [25]. The loss of mobility leads to a disability that represents an important risk factor for falls and that can affect the quality of life of the elderly, as evidenced by a study carried out in Chile with 1334 participants over 60 years old, in which older adults with functional changes presented an increased risk of falling [26].

Table 3 Predictive variables for reduced mobility in the diabetic elderly after regression tests. Brasília, 2020

Variables	OR	95% CI	*p*
High triglycerides	1.61	1.05–2.34	*0.038*
Sedentary lifestyle	2.50	1.06–5.57	*0.018*
HBP	2.03	1.09–4.02	*0.040*
Smoking	0.40	0.28–0.84	0.503
Alcoholism	1.08	0.98–1.21	0.089
Occupation	0.47	0.06–0.74	0.462
High blood glucose	0.99	0.97–1.02	0.829
High cholesterol	1.01	0.99–1.03	0.299
High HbA1c	1.12	0.70–1.79	0.697
High LDL	0.95	0.89–1.02	0.194
High BF	0.99	0.88–1.10	0.879

The italicized values mean p<0.05

HBP, high blood pressure; *HbA1c*, glycated hemoglobin; *LDL*, low-density lipoprotein; *BF*, body fat; *OR*, odds ratio; *CI*, confidence interval

The majority of the elderly in this study performed the TUG in a greater time than the proposed one, and a poor test performance was related to DM. A study in Japan with 211 elderly subjects also observed a lower TUG performance in the elderly with DM, corroborating the results of this study [27]. Also, a study conducted in the south of Brazil with diabetic adults between 50 and 65 years of age showed that those with DM had worse functional mobility and cognitive performance, favoring the hypothesis that this disease influences functional mobility and cognitive capacity [11].

It is important to highlight the evidence that suggests that the mean values of plantar pressure of the forefoot and the hind foot of patients with DM may increase, considering that the higher the percentage of load distribution in the hind foot, the longer the execution time of the TUG and, therefore, functional mobility will be diminished [28]. This can also be explained by the complications of DM, such as vascular alterations, peripheral neuropathy, and loss of vision that directly threaten the independence of this population [29].

The high prevalence of reduced mobility has a negative impact on the lives of these elderly people and those who assist them in regular activities, since it is one of the components of functional capacity that is a public health problem, as it increases the risk of hospitalization, the risk of falls, and death [30].

In this context, it was observed that the inadequate glycemic control, expressed by higher glycemia and HbA1c levels, was shown to be associated with RM. Elderly people with inadequate glycemic control have a higher risk of functional alterations with declines in physical function, resulting in incapacity and death. Older adults with higher levels of glucose are at a higher risk of functional decline [31]. A study conducted in the USA with women in the community aged 70–79 years found that HbA1c ≥ 8.0% (compared with < 5.5%) was associated with an increased risk of developing walking difficulty, low speed of walking, and low physical performance during an average follow-up of 8 years [32]. Significant association was also found between elevated levels of HbA1c and lower lean body mass, as well as with lower muscle strength [33]. In addition, it is known that the elderly with DM and poor glycemic control may present a higher risk of fractures, since higher blood glucose concentrations were associated with the accumulation of advanced glycation end products (AGES), which can lead to an increase in bone fragility [11].

For behavioral habits, alcoholism and sedentary lifestyle were significantly associated with DM and RM. It is known that alcohol may cause brain damage and cognitive

dysfunction, which impairs brain activity and affects body functions, such as coordination and cognition. This may trigger a change in overall health status, resulting in reduced mobility [34]. Regarding inactivity, a Canadian study showed that sedentary individuals had a 33% higher chance of functional disability than active individuals [35]. In addition, more active elderly people live better, since regular physical activity practice tends to minimize the natural body debilitation process related to aging [35]. In this sense, the TUG test has been considered an important tool for fragility and sarcopenia prediction, both conditions related to muscular weakness, which may cause restriction of mobility [36].

Smoking showed association only with DM. Available evidence shows that smoking increases insulin resistance, but the exact mechanism by which this habit increases the risk of DM and impairs glucose homeostasis has not yet been fully elucidated [37]. In addition, some studies [37, 38] have demonstrated that the adverse effects of smoking on DM are not only macrovascular complications, but also the progression of microvascular complications.

The majority of the elderly had HBP, which is significantly associated with reduced mobility and DM. DM and HBP are the most common risk factors for cardiovascular disease and often appear concomitantly. Therefore, the Brazilian National Household Sample Survey (PNAD) of 1998, 2003, and 2008 found a similar result, which showed a significant association between physical mobility and HBP and DM in older adults in three representative moments in which they were evaluated [39].

Another interesting fact was the positive association of BF only with RM. Individuals with obesity or overweight have a limitation in mobility since high-fat percentages increase joint and muscle stress [40]. Excess weight causes greater pressure on the plantar surface, while the accumulation of adipose tissue in the abdominal region displaces the center of gravity to the anterior region in relation to the ankle joints, generating greater body instability. Added to these factors, the aging process associated with excess adiposity leads to a decrease in muscle strength which affects the mobility in this population [41, 42].

Regarding the dyslipidemic indices, we evidenced that the elderly diabetics with higher levels of triglycerides, total cholesterol, and LDL tended to present reduced mobility. In this sense, as predictive variables of RM in the diabetic elderly, we observed elevated triglyceride, sedentary lifestyle, and HBP. Triglyceride levels were positively correlated to TUG performance time, demonstrating that the higher the triglyceride in the elderly, the longer the test run time. A study with 1622 elderly people in London showed a 2.18 times higher risk of falls in elderly patients with increased triglyceride [43]. It is also known that triglyceride is considered a component for the diagnosis of metabolic syndrome (MS). MS has been related to the physical decline in the elderly, revealing a greater probability of developing mobility limitations, since older women with MS had higher metabolic risk factors and lower capacity, lower limb strength, muscle strength, and lean leg mass [44].

Therefore, it is important to include physical exercises aimed at increasing strength and muscle mass of the elderly, especially those with DM. A study also conducted in Brasilia with 88 older women demonstrated that an increase in relative handgrip strength of 1 kg/body mass index was associated with a decrease in the TUG test of 0.7 s, showing a possible positive effect of muscle strength on the mobility of elderly women [45]. We believe that the sedentary lifestyle associated with the high level of triglycerides in the diabetic elderly contributes significantly to the increase of reduced mobility, considering the profile of the elderly observed in the present study and results of other researches already performed on this subject.

The American Diabetes Association (ADA) together with the American Society of Geriatrics (ASG) emphasized in a consensus the need for studies to determine the functional decline in the elderly with DM in order to elucidate the contributing factors. In addition to changes in body composition due to aging, such as progressive loss of muscle mass, increase in fat mass, and consequent decline in muscle strength, this study points to additional indicators that should be considered in the evaluation of the elderly, especially in the context of primary care.

As limitations of this study, we can refer to the non-evaluation of eating habits, which made it difficult to discuss some predictive factors that are related to diet, such as the higher levels of triglycerides. Another limitation refers to the fact that the evaluation of the level of physical activity was done through self-report of the participants, and not through an instrument. In addition, muscle strength could also have been assessed since it is related to functional capacity.

Conclusion

The prevalence of reduced mobility among the elderly in the study was higher than results from other studies conducted in Brazil and worldwide. Triglycerides, sedentary lifestyle, and hypertension showed to be predictive factors for reduced mobility in elderly diabetics. All these factors are modifiable factors and are directly or indirectly related to lifestyle. Therefore, these results can be used for intervention and health promotion actions aimed at maintaining and improving the functional mobility and autonomy of elderly.

It is considered that new studies should be performed, and the intensity of the influence of these factors in the mobility of this population should be further explored. Still, it would be interesting to look for variables that can be used as predictive factors for good functional capacity in the elderly.

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Authors' contribution FTFP, MMS, LRL, and SSF worked on study design, data collection and analysis, interpretation, drafting, and editing of the manuscript. YGSB and MVGC, also, worked on data collection. FTFP, MMS, AOS, and SSF collaborated on interpretation, data analysis, editing, and review of the manuscript data. ICRS collaborated on blood collection and biochemical exams. All authors read and approved the final manuscript.

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Compliance with ethical standards

The data collection occurred after the approval of the ethics committee and the participants' signature in the free and informed consent term. All the participants received a description of the study and were informed about the purpose, risks, and benefits. This research was approved by the Ethics Committee of the Secretaria de Saude do Distrito Federal (SES/DF).

Competing interests The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Effects of telemedicine intervention on the management of diabetic complications in type 2 diabetes

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Abstract

Background Some studies have shown that telemedicine is effective for managing serum glucose levels in patients with type 2 diabetes (T2DM), but few studies have examined the effect of telemedicine on the management of complications in T2DM. The aim of this study was to compare the effects of telemedicine with those of outpatient care on the following parameters in T2DM patients: hemoglobin Alc (HbA1c), urinary albumin to creatinine ratio (UACR), carotid plaque, and incidence of hypoglycemia.

Methods In total, 148 adult patients with T2DM were randomized into a telemedicine group ($n = 74$) and a control group ($n = 74$). In the telemedicine group, a wireless intelligent blood-glucose meter was used to monitor blood-glucose levels, transmit data, and upload information on diet, exercise frequency, and oral medications, while the control group underwent routine outpatient follow-up. HbA1c, UACR, incidence of hypoglycemia, and carotid plaque were measured at baseline and at 3 and 6 months in the telemedicine group and the control group.

Results There were no statistically significant differences in baselines data ($p > 0.05$) between the telemedicine group and the control group such as age (50.04 ± 5.76 vs. 52.21 ± 8.38, $p = 0.750$), diabetes course (6.24 ± 1.95 vs. 6.09 ± 1.66, $p = 0.622$), and gender (51/21 vs. 43/27, $p = 0.236$). After 6 months of follow-up, the telemedicine group, compared with the control group, showed significant decreases in incidence of hypoglycemia (25% vs. 41.4%, $p = 0.038$) and HbA1c ($7.38 \pm 1.67\%$ vs. $8.22 \pm 2.04\%$, $p < 0.01$). However, there were no significant differences in UACRs or carotid plaque ($p > 0.05$) between the telemedicine group and the control group.

Conclusions The telemedicine system reduced rate of hypoglycemia and indexes of HbA1c in patients with T2DM, whereas no significant differences in UACRs or carotid plaque were found.

Keywords Telemedicine · Glucose · Complications · Type 2 diabetes

Yuli Hu and Xiaohong Wen contributed equally to this work.

Highlights
- Telemedicine has been widely applied to the management of diabetes.
- Diabetes is an important risk factor for kidney disease, cardiovascular disease, severe hypoglycemia, and other diseases. Few studies have evaluated the effects of telemedicine on T2DM complications.
- After 6 months of follow-up, the telemedicine system reduced 18.1% rate of hypoglycemia in the telemedicine group.

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Introduction

According to estimates of the International Diabetes Federation, the number of people with diabetes worldwide was close to 425 million in 2017. By 2045, there are expected to be almost 629 million cases, with an increase in the prevalence of diabetes to 10.4% [1]. More than 90% of all diabetes cases are type 2 diabetes mellitus (T2DM) [2], which was the focus of this study. Diabetes is an important risk factor for kidney disease, cardiovascular disease, severe hypoglycemia, and other diseases [3]. Approximately 20–40% of diabetics have chronic kidney disease (CKD) or end-stage renal disease, and these renal pathologies also increase the risks of cardiovascular disease and mortality [4]. CKD affects 13.4% of the global population, with a prevalence of 14.3% in low- and middle-income countries [5–7]. The World Health Organization predicts that the CKD-related mortality rate will continue to increase, reaching 14 deaths per 100,000 population by 2030 [5]. One marker for kidney disease is the urine albumin to creatinine ratio (UACR), which was used in this study. A common complication of diabetes is hypoglycemia, which at the very least negatively affects the quality of life of diabetic patients and can be fatal [8]. Therefore, consistent control of diabetes is important to prevent acute pathologies such as hypoglycemia as well as the longer-term risks of kidney and cardiovascular events. Diabetes and its complications also impose a heavy economic burden on patients and society. The World Health Organization estimates that T2DM and its complications will account for 15% of total health costs by 2021. By 2030, the economic loss associated with T2DM will reach $1.7 trillion worldwide [9]. One approach to diabetes management is telemedicine, which is defined as the remote distribution of healthcare via information and communication technologies to people in different cities and suburban areas [10].

Telemedicine has been widely applied to the management of chronic diseases such as chronic viral hepatitis, chronic obstructive pulmonary disease patients, and hypertension [11–13]. The field of diabetes already benefits from telemedicine approaches, which allow patients and physicians to communicate electronically [14] as well as provide online diabetes education and regular physical activity management [15, 16], and programs to improve depression and self-efficacy in diabetics [17, 18]. Telemedicine can result in decreased hemoglobin Alc (HbA1c) levels, improved quality of life, and reduced economic costs for diabetics [19–21]. However, few studies have evaluated the effects of telemedicine on T2DM complications including cardiovascular disease, kidney disease, and hypoglycemia. Therefore, the aim of this study was to determine the efficacy of telemedicine in the management of T2DM complications by measuring participants' carotid plaque levels, UACRs, and the incidence of hypoglycemia.

Methods

Study design

In this randomized controlled trial, 148 T2DM patients were randomized 1:1 using a random number table into a telemedicine group ($n = 74$) and a control group ($n = 74$). Doctors who were not part of the study prepared 148 sealed opaque envelopes containing odd and even numbers, and patients randomly drew the envelopes for their group assignment (Fig. 1).

Definitions

Type 2 diabetes mellitus (T2DM) is an endocrine disease characterized by insulin resistance; pancreatic β cell function is abnormal and accompanied by relative insulin deficiency [22].

The American Diabetes Society Working Group defines hypoglycemia as a (fasting or non-fasting) blood-glucose level ≤ 3.9 mmol/L and divides it into five categories. In our study, we encountered all types of hypoglycemia, except for severe hypoglycemia events [23].

One study identified carotid plaques as carotid intima-media thickness (CIMT) ≥ 1.5 mm and as a site of focal thickening (50% thicker than the surrounding segments) [24].

Study participants

The study enrolled 168 patients who visited the Department of Endocrinology of the First People's Hospital of Huzhou between October 2017 and March 2019; 20 declined participation after consent. The inclusion criteria were a diagnosis of T2DM more than 3 months prior, age 18–70 years, ability to use a smartphone and blood-glucose meter, and voluntary participation. The exclusion criteria were severe heart, liver, or renal insufficiency; a history of cancer, coronary heart disease, or cerebral infarction; hyperthyroidism or hypothyroidism; severe infection; current treatment with adrenocortical hormones or other drugs that affect blood-glucose levels; mental illness, communication disorder, or blindness; and major trauma, major surgery, or any severe illness.

Intervention

Each month, both groups of patients received diabetes education from a diabetes specialist nurse pertaining to self-monitoring of blood-glucose levels, dietary habits, importance of medication timing, and physical activity. Participants with carotid plaque received atorvastatin 20 mg/day or aspirin 100 mg/day. The study duration was 6 months. The

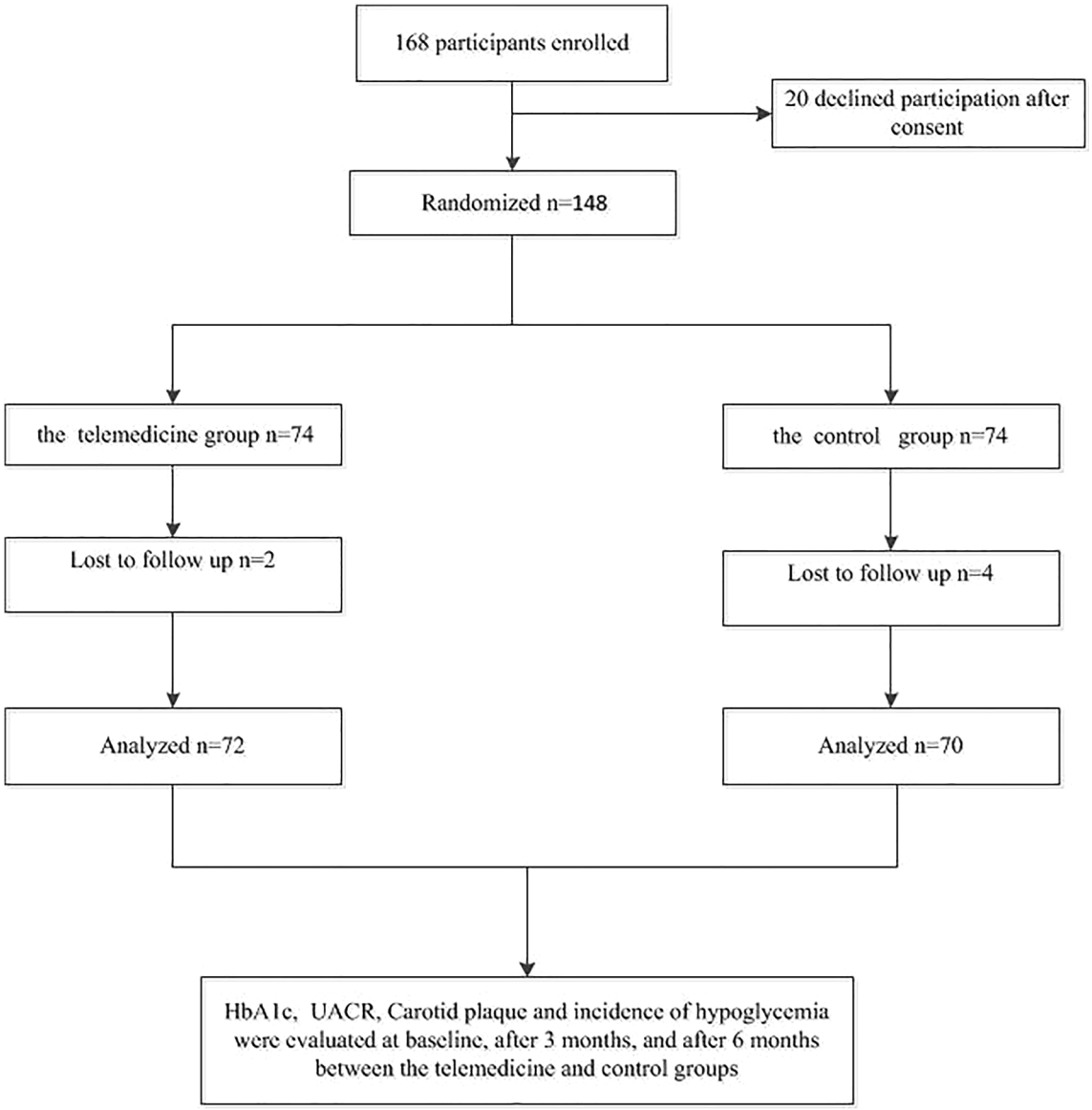

Fig. 1 A flowchart of the study design for the 168 participants enrolled

telemedicine group used an out-of-hospital blood-glucose management platform with an EZ-6 smart blood-glucose meter (Sinomedisite). The patients were taught how to use the EZ-6 glucometer, the downloaded Huayi Sugar housekeeper application, and the intelligent network software on their smartphones, with specific logins and passwords. This allowed communication between the patient and the hospital via smartphone. Blood-glucose, exercise frequency, and dietary were uploaded to the telemedicine platform each week. The blood-glucose levels measured by the glucometer were processed into a report and graph, and the data were automatically transmitted via the Internet to the telemedicine system. This allowed the researchers to view the patients' blood-glucose levels, insulin dosage, physical activity frequency, and meal data. The researchers contacted the patients, if necessary, via WeChat (Tencent), telephone, or other online connections. The patients in the control group used an intelligent blood-glucose meter that did not upload blood-glucose data via the network. These patients received conventional outpatient treatment once a month from department endocrinologists and nurses. Blood-glucose levels were uploaded once a month by the doctors and nurses.

Measurement of HbA1C, UACR, carotid plaque

Laboratory examination Overnight fasting venous blood samples were drawn from the antecubital vein of patients with T2DM, using 4-mL coagulation-promoting vacuum tubes, to determine HbA1c levels using high-performance liquid chromatography [25, 26]. We measured UACRs using a radioimmunoassay method, different 1 day morning that uses the morning's first urine sample (Siemens urine microalbumin analyzer and original reagents). Before measuring UACRs, the patients

were on a low-protein diet and avoided strenuous activities; we took the average of two UACR measurements [27].

Carotid plaque ultrasound examination Patients with T2DM underwent a carotid artery B-mode ultrasound examination using the Siemens S2000 color Doppler ultrasound diagnostic instrument, operating at a frequency of 7.5 MHz [28]. We took readings with the probe in a lateral orientation and the patients in a supine position with their head rotated in the opposite direction to the probe. The carotid artery intima-media thickness (IMT) was measured at the posterior wall 1 cm proximal to the bifurcation of the common carotid artery or at its thickest point. We measured the carotid artery on both sides three times and determined the average value. We diagnosed a carotid plaque if the carotid intima-media thickness (CIMT) was ≥ 1.5 mm or if a focal segment was 50% thicker than the neighboring segments [24].

Outcome measures

Patients in both groups baseline data were administered a questionnaire with questions on age, gender, duration of diabetes, and hypoglycemia. Systolic blood pressure and diastolic blood pressure were measured by a nurse.

Primary outcomes

Hypoglycemia was based on blood-glucose data, not on severe hypoglycemic events. In the telemedicine group, patient monitoring of hypoglycemic events via the wireless intelligent blood-glucose meter and automatic uploads of blood-glucose data was used to monitor hypoglycemic events, while the blood-sugar data of the outpatient group was exported to a physician, who counted the hypoglycemic events.

Secondary outcomes

Secondary outcomes were UACR, carotid plaque, and levels of HbA1c. The same clinical laboratory personnel measured UACR and HbA1c, and carotid plaque in all patients, but the two groups of patients were monitored at different times.

Statistical analysis

The data were analyzed using SPSS 22.0 software, and $p < 0.05$ was defined as statistical significance. Baseline characteristics were compared between groups using the independent t test (continuous, normally distributed variables), the Mann-Whitney U test (continuous, non-normally distributed variables), and chi-square test, as appropriate. In this study, the independent t test was used to compare HbA1c levels and UACR values between the telemedicine and control groups (continuous, normally distributed variables). The incidence of carotid plaque and hypoglycemia was compared using the chi-square test between the telemedicine and control groups.

Sample size calculations methods of which the HbA1c level is one of the evaluation indexes of this study. Through the preliminary experiments, 18 patients in the telemedicine group and 18 patients in the control group were estimated for sample size, and the sample size was calculated by the method of comparison of the mean of two samples, and the unilateral test level was determined: $\alpha = 0.05$, $\beta = 0.10$, $\delta = 0.964$, $\sigma = 1.907$, $u\alpha = 1.645$, and $u\beta = 1.282$. The formula is calculated according to the sample size of two independent samples, $N = 2[(u\alpha + u\beta)/(\delta/\sigma)]$ [2], $N = 67$. Assuming that the loss of follow-up rate is 10%, the final number of cases in each group is 74, and the total sample size is 148.

Results

Baseline characteristics of the T2DM patients

At baseline, sex; mean age; duration of diabetes; employment status; BMI; systolic and diastolic blood pressure and HbA1c levels; UACRs; carotid plaque; hypoglycemic therapy; lipid-lowering therapy; anti-hypertensive therapy; and hypoglycemic indexes did not differ significantly between the control and telemedicine groups ($p > 0.05$) (Table 1). 148 participants were randomized 1:1 into the telemedicine ($n = 74$) and control ($n = 74$) groups. Two patients were excluded from the telemedicine group: one withdrew voluntarily because the glucometer failed to upload the blood-glucose data, and the other was unable to return to the hospital on time. Four patients were excluded from the control group: one developed nasopharyngeal carcinoma, one had a liver transplantation, and the other two required a different blood-glucose meter (Abbott) due to finger pain. We followed the national guidelines of China [29] and the patient's condition when using the following treatment: hypoglycemic therapy, anti-hypertensive therapy, lipid-lowering therapy, and aspirin treatment.

Effect of telemedicine intervention on incidence of carotid plaque and hypoglycemia

The incidence of carotid plaque is lower in the telemedicine group than in the control group, although this difference was not significant ($p > 0.05$) (Table 2). Both groups showed a decreased incidence of hypoglycemia after intervention, but this decrease was significantly greater in the telemedicine group than in the control group ($p < 0.05$). After 6 months of intervention, hypoglycemia

Table 1 Comparisons between the telemedicine and the control groups at baseline

Characteristic	Telemedicine ($n = 72$)	Control ($n = 70$)	p value
Gender(male/female)	51/21	43/27	0.236
Age(years)	50.04 ± 5.76	52.21 ± 8.38	0.750
Duration of diabetes (years)	6.24 ± 1.95	6.09 ± 1.66	0.622
Employment(yes/no)	49/23	45/25	0.635
BMI (kg/m2)	24.69 ± 3.39	24.05 ± 3.98	0.333
SBP (mmHg)	130.22 ± 14.50	127.74 ± 14.00	0.302
DBP (mmHg)	80.08 ± 9.77	79.44 ± 9.67	0.695
HbA1C (%)	8.96 ± 1.78	8.63 ± 1.62	0.246
UACR (mg/mmol)	4.41 ± 1.45	4.22 ± 1.31	0.398
Carotid plaque, *n* (%)	30(41.7)	22(31.4)	0.205
Hypoglycemia, *n* (%)	31(43.1)	33(47.1)	0.625
Aspirin, *n* (%)	20(27.8)	16(22.9)	0.500
Hypoglycemic therapy, *n* (%)	43(59.7)	46(65.7)	0.460
Lipid-lowering therapy, *n* (%)	21(29.2)	15(21.4)	0.289
Anti-hypertensive therapy, *n* (%)	11(15.3)	8(11.4)	0.501

Data are mean ± SD (standard deviation)

and carotid plaque are present in 18 (25%) and 29 (41.4%), 27(37.5%), and 27(38.6%) patients in the telemedicine and control groups, respectively (Table 2).

Effect of telemedicine intervention on HbA1c levels and UACR

After 3 and 6 months, the HbA1c levels are significantly lower in the telemedicine group than in the control group (all $p < 0.01$) (Table 2). However, there is no significant difference in UACRs between the two groups ($p > 0.05$) (Table 2).

Table 2 Comparisons between the telemedicine and control groups in terms of metabolic and T2DM complications measures

Measures	Telemedicine	Control	p value
Carotid plaque			
3 months, *n* (%)	29 (40.3)	25 (35.7)	0.575
6 months, *n* (%)	27 (37.5)	27 (38.6)	0.895
Hypoglycemia			
3 months, *n* (%)	26 (36.1)	30 (42.9)	0.411
6 months, *n* (%)	18 (25)	29 (41.4)	0.038
HbA1c (%)			
3 months	7.51 ± 1.82	8.42 ± 2.29	0.009
6 months	7.38 ± 1.67	8.22 ± 2.04	0.008
UACR (mg/mmol)			
3 months	4.29 ± 1.38	4.24 ± 1.33	0.830
6 months	4.36 ± 1.45	4.56 ± 1.11	0.367

Data are means ± SD (standard deviation)

Discussion

In our 6-month study, the incidence of carotid plaque tended to decrease in the telemedicine group from 30 (41.7%) to 27(37.5%), whereas it tended to increase in the control group from 22 (31.4%) to 27 (38.6), but there was no significant difference between the two groups ($p > 0.05$). It may be that more time was needed for a significant difference to become apparent or that other factors are involved. The risk factors for carotid plaque include blood-glucose level, smoking, sex, and blood fibrin level [30, 31]. Further studies with larger sample sizes and longer intervention times are needed to confirm these results.

The 2002 clinical practice guidelines of the National Kidney Foundation for CKD recommend using the UACR instead of 24-h urinary protein quantification to evaluate urinary protein excretion in patients with kidney disease [32]. The UACR is an accurate indicator of renal protein excretion and early diabetic nephropathy [33]. Therefore, we used the UACR to detect early diabetic nephropathy in patients with T2DM. After 6 months of telemedicine intervention, the UACR in the telemedicine group compared with the control group is not statistically significant ($p > 0.05$). There are many additional risk factors for diabetic nephropathy, including high blood-glucose and lipid levels, high blood pressure, smoking history, and a genetic history of diabetic nephropathy [34]. The lack of a significant difference in UACR values in this study may have been due to the small sample size or a follow-up period that was insufficient to detect changes.

Periods of hypoglycemia increase the incidence of falls and cardiovascular and cerebrovascular disease, as well as medical expenses and hospital stays [35, 36]. Consequently, it is

important to prevent hypoglycemia. Telemedicine intervention led to a lower incidence of hypoglycemia compared with the control group ($p = 0.038$). The telemedicine platform may have improved the patients' understanding of hypoglycemia, enabling them to take measures to prevent it. Furthermore, medical staff may have checked blood-glucose levels more regularly and provided timely treatment advice to prevent hypoglycemia in the telemedicine group compared with the control group. Similar to our study, a meta-analysis found that telemedicine intervention decreased the incidence of hypoglycemia [19].

The results of this randomized controlled trial imply that telemedicine improved glucose metabolism in terms of HbA1C levels, similar to other studies showing that telemedicine reduced HbA1c [37, 38].

We determined the reason for the better glycemic control in the patients of the telemedicine group than in others after the intervention. The telemedicine system was established so that patients monitored their blood-glucose levels while connected to the WI-FI network, and the data were automatically transmitted via the Internet to the telemedicine system. The research team regularly checked the patient data and contacted patients in cases of abnormality to modify the treatment. Maintaining low HbA1c levels decreases the risk of microvascular complications, death and cardiac infarction, and improves the life quality of patients.

This study has a few limitations. First, there was no blinding of the outcome measures, because one examiner (a member of the study team) measured all indicators in the T2DM patients. However, a lack of blinding has less effect on objectively assessed outcomes [39]. Second, the study duration of 6 months was too short, and/or the sample size was too small to observe differences in some indicators, such as carotid plaque and UACR. Therefore, increasing the study duration and sample size is necessary to determine the effects of telemedicine in T2DM patients. Third, all participants were from a single hospital, and thus the generalizability of our results may be limited.

Conclusions

Our study found that the telemedicine system can reduce HbA1c levels and the occurrence of hypoglycemic events. We found no significant effects of telemedicine on UACRs or carotid plaque results.

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Compliance with ethical standards The study is approved by the Ethics Committee of The First People's Hospital of Huzhou, Zhejiang Province, China (no. 2016033), and all subjects provided written informed consent prior to participating.

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ORIGINAL ARTICLE

Lipohypertrophy in insulin injecting patients with diabetes mellitus: an under-recognized barrier for glycemic control

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Abstract

Background Lipohypertrophy is the one of the commonest local complications that significantly affects glycemic control in patients of diabetes mellitus on treatment with insulin. Our study aimed at assessing the clinical and ultrasonographic characteristics and risk factors for lipohypertrophy on the abdomen in a cohort of insulin-injecting Indian diabetes patients.

Materials Eighty-eight consecutive patients with type 1 (15/88) or type 2 diabetes mellitus (73/88) were included in this cross-sectional study conducted over a period of 6 months. The prevalence of lipohypertrophy and associated risk factors was assessed by clinical examination. A novel ultrasonographic characterisation of lipohypertrophy (LH) using a predetermined grading system was performed by two sonologists who were blinded to the underlying clinical findings. Kappa statistics was used to calculate the agreement between the clinical and ultrasound methods of detection of lipohypertrophy.

Results The prevalence of lipohypertrophy was 68% on clinical examination and 90% on ultrasonography with moderate kappa agreement (60%). The commonest patterns on clinical and ultrasonographic assessment were Grade 2 (palpable and visible − 43%) and nodular hyperechoic subcutaneous dystrophy (33%), respectively. Duration of insulin use, incorrect site rotation, and repeated needle reuse ($p < 0.01$) were the most important risk factors. The total daily dose of insulin ($p = 0.01$) and mean Hba1c ($p = 0.02$) were significantly higher in those with clinically detected lipohypertrophy. The needle length, caliber, the mode of delivery, or regimen of insulin used did not significantly impact development of lipohypertrophy ($p = 0.15$).

Conclusion A thorough clinical examination of insulin injection sites is of paramount importance in detecting lipohyperyrophy. Adequate control of risk factors can significantly impact insulin requirements and glycemic control, while ultrasonography can prove to be a novel and sensitive tool to detect abdominal lipohypertrophy in the majority of patients, even when clinical examination is non-contributory.

Keywords Lipohyeprtrophy · Insulin · Injection · Rotation · Diabetes

Introduction

Intensive insulin therapy is the corner stone of treatment to achieve optimal glycemic control and reduce the long-term complications in type 1 diabetes mellitus and long-standing type 2 diabetes mellitus [1, 2]. This form of therapy is associated with cutaneous complications like erythema, pruritus, induration, lipohypertrophy, and atypical cutaneous infections. Lipohypertrophy is one of the commonest local complications associated with subcutaneous insulin therapy and one of the important under-recognized causes for poor glycemic control [1]. Insulin lipohypertrophy denotes a benign abnormal accumulation of adipose tissue at the insulin injection site, with the lipogenic effect of insulin being postulated as one of the key mechanisms [3]. However, factors like repeated microtrauma from long-term injection use, reuse of blunted needles, and improper injection technique are suggested to have an equally important contribution to the development of lipohypertrophy. The prevalence of lipohypertrophy in

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insulin injecting patients with diabetes mellitus has ranged from 30 to 65 % in various studies [3–6].

Ultrasonographic screening of insulin injecting sites for lipohypertrophy has been shown to reveal a higher detection rate of 86.5% when compared with 30.7% by clinical examination in a study by Natalia et al. [7]. Ultrasonography may also help in the characterization of insulin lipohypertrophy.

However, there is limited literature on the prevalence of lipohypertrophy in Indian subjects [8, 9]. The data on the ultrasonographic characterization of these lesions and the risk factors are also limited. Therefore, we undertook this study to look at the prevalence of lipohypertrophy in insulin injecting patients with diabetes mellitus as detected by clinical examination and ultrasonography. We also studied their characteristics on ultrasonography, the risk factors, and their association with glycemic status.

Material and methods

This was a cross-sectional study where in consecutive patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) on subcutaneous insulin injections attending the department of Endocrinology as an outpatient were recruited. Subjects using insulin pumps, pregnant women, those patients on immune-suppressive agents, and those with secondary diabetes such as acute and chronic pancreatitis, fibrocalcific pancreatic diabetes, pancreatic cancers, acromegaly, Cushing's syndrome, hyperthyroidism, primary hyperparathyroidism, primary hyperaldosteronism, drug-induced diabetes, congenital and acquired lipodystrophic diabetes, and syndromic presentations were excluded.

Data were obtained regarding the age, sex, body mass index (BMI), type of diabetes mellitus, time since diagnosis of DM, duration of insulin use, insulin regimen, insulin injecting devices, needle length, frequency of needle change, and rotation of insulin injecting site. All subjects underwent a detailed clinical examination including anthropometry. Hba1c measured by the high-performance liquid chromatography method (HPLC) within the past 3 months was taken for the analysis.

The presence of lipohypertrophy was assessed in patients by clinical examination of the abdomen by inspection and palpation and were graded from 0 to 2 as follows: grade 0: no changes, grade 1: visible hypertrophy of the fat tissue but palpably normal consistency, grade 2: massive thickening of the fat tissue with a higher consistency [10].

Though some studies have considered lipoatrophy as grade 3, the rarity of occurrence and completely different etiopathogenetic mechanisms leading to lipoatrophy make it a distinct entity [11]. Therefore, we have not considered it in our grading system for lipohypertrophy.

All subjects underwent an ultrasound screening of the dermis and subcutaneous tissue of the abdomen for evidence of lipohypertrophy by the radiologist who was blinded to the patient's clinical findings. Ultrasonography was performed using a Philips EPIQ 5G machine, transducer L18-5 broadband linear array working on 18 to 5 MHz extended operating frequency. On the ultrasonography, the normal dermis is homogenously hyperechoic when compared with the subdermal fatty tissue and ranges between 1 and 4 mm in thickness. There is a well-defined and regular demarcation between dermis and the subcutis [12]. The subcutaneous tissue offers a hypoechoic background secondary to the fat lobules and a hyperechoic connective web with very thin septa between the lobules. The hyperechoic muscularis fasciae are seen beneath the subcutis layer [9]. Based on the thickness, echogenity, echotexture, delineation between dermis, subcutis and muscularis layers, and subcutis vasculature on ultrasound, the lipohypertrophy was further classified based on the system suggested by Kapeluto and colleagues [12, 13].

Statistical analysis

A sample size of 80 subjects was required to study the prevalence of lipohypertrophy on clinical examination with a precision of 10% and 95% confidence interval based on the 30% prevalence of lipohypertrophy reported by Natalia et al. [7]. The clinical characteristics of the study populations were expressed as mean and standard deviation and percentages. The agreement between the clinical and ultrasonographic detection of the lipohypertrophy was determined using Kappa. The factors influencing the development of lipohypertrophy were evaluated using the chi-square test, and $p < 0.05$ was considered significant. Independent variables influencing the occurrence of lipohypertrophy were evaluated using multiple logistic regression analysis.

Results

A total of $n = 116$ consecutive patients with diabetes mellitus ($n = 89$ T2DM and $n = 27$ T1DM subjects) on insulin therapy were screened for the study, of which $n = 88$ (64 male, 24 female) were studied based on predetermined inclusion criteria and willingness to give informed consent. The study duration was for a period of one year (March 2016 to February 2017). The T2DM patients constituted 83% ($n = 73$) of subjects and 17% ($n = 15$) were T1DM. The baseline characteristics of the T1DM and T2DM subjects are provided in Table 1. The mean duration of insulin usage was 77.5 ± 79.4 months. The total daily dose (TDD) of insulin was 55.3 ± 28.0 units. The mean Hba1c of the study subjects was 8.9 ± 2.1%. Sixty patients (68.2%) were found to have the clinical evidence of lipohypertrophy, of which 22 (36.7%) patients were

Table 1 Baseline characteristics in the study population (n = 88)

Characteristics (N = 88)	Type 1 (n = 15)	Type 2 (n = 73)
Age (years)	25.2 ± 7.2	56.7 ± 10.3
BMI (kg/m)2	21.2 ± 4.3	27.5 ± 4.6
Duration of DM (years)	16.2 ± 7.8	22.9 ± 9.9
Insulin use (months)	100.6 ± 84.0	73.7 ± 78.6
Total insulin dose (IU/day)	44.40 ± 16.52	57.58 ± 40.80
HbA1c (%)	7.99 ± 3.0	9.08 ± 1.85

found to have grade 1 and 38 (63.3%) patients were found to have grade 2 lipohypertrophy, based on the clinical classification of insulin lipohypertrophy [10].

On ultrasound screening of insulin injecting sites at abdomen, 79 (89.7%) patients were found to have evidence of lipohypertrophy. Based on ultrasonographic characteristics, lipohypertrophy was further classified as in Fig. 1.

On comparison of the clinical and ultrasound screening for lipohypertrophy, the ultrasonography detected an additional 19 patients with lipohypertrophy who were not detected clinically. There was a moderate agreement (kappa value 0.545) between the clinical and ultrasound detection of lipohypertrophy (Table 2).

Factors associated with development of Lipohypertrophy

The comparison of the various clinical characteristics of patients with the clinical evidence of lipohypertrophy versus those without lipohypertrophy is shown in Table 3.

Table 2 Comparison between clinical and ultrasound detection of lipohypertrophy (n = 88)

Method of detection*	Lipohypertrophy status (n = 88)	
	Present	Absent
Clinical (%)	60 (68.2%)	28 (31.8%)
Ultrasound (%)	79 (89.8%)	9 (10.2%)

*Degree of agreement between clinical and USG method: Kappa value = 0.545

Lipohypertrophy was significantly more common in the T2DM when compared with the T1DM (p = 0.05). The clinical evidence of lipohypertrophy was significantly higher in men, obese subjects, those not rotating insulin injecting sites, and frequency of needle reuse > 5 and > 60 months of insulin use (Table 4). The total daily dose of insulin was significantly higher in patients with clinical evidence of lipohypertrophy as compared with those without lipohypertrophy (61.60 ± 23.13 v 41.89 ± 17.93, p = 0.01). Similarly, the mean Hba1c was significantly higher in those with clinical evidence of lipohypertrophy (9.52 ± 2.14 vs 8.46 ± 1.99, p = 0.02), with the significance persisting after dividing the study subjects based on Hba1c values of either less than or more than 7% . On multiple logistic regression, the duration of insulin use more than 60 months and incorrect insulin site rotation technique were associated with the risk of insulin lipohypertrophy (Table 4).

A sub-group analysis was performed to compare those detected with lipohypertrophy by USG (n = 79) with those having no ultrasound evidence of lipohypertrophy (n = 9). The mean Hba1c (9.12 ± 2.53 vs 8.68 ± 1.39 %, p = 0.03) and total

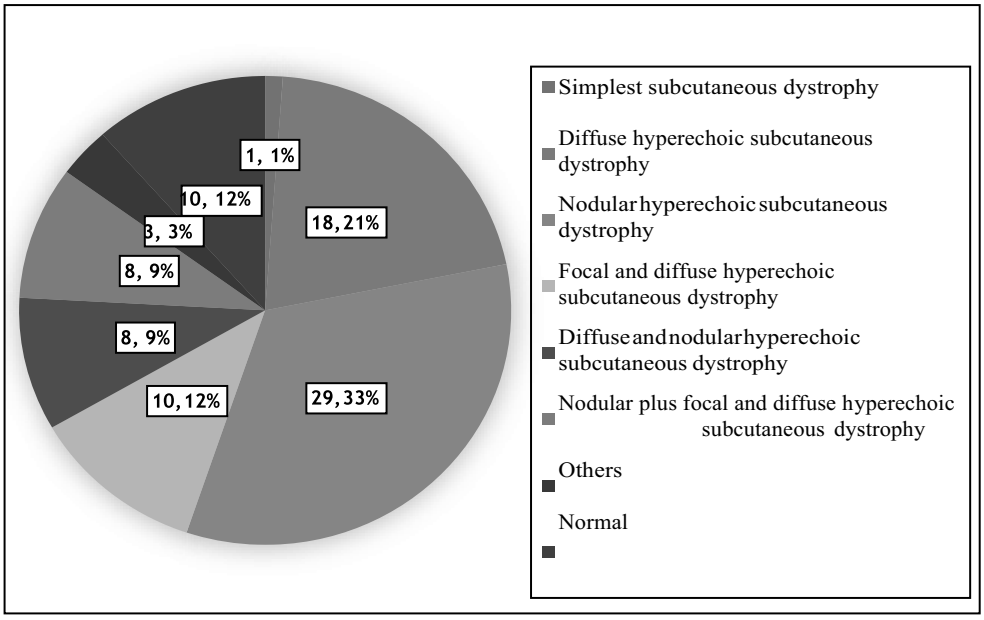

Fig. 1 Ultrasound classification of lipohypertrophy

Table 3 Comparison of characteristics of patients with lipohypertrophy ($n = 60$) and patients without lipohyperttrophy ($n = 28$) detected by the clinical method

Variable	Total subjects number (%) ($N = 88$)	Lipohypertrophy status by clinical method		*P* value (chi-square)
		Present ($N = 60$) Number (%)	Not present ($N = 28$) Number (%)	
Gender				
Men	64 (72.7%)	48 (75%)	16 (25%)	0.039
Women	24 (27.3%)	12 (50%)	12 (50%)	
BMI				
Obese	52 (60.5%)	39 (75%)	13 (25%)	0.041
Not obese	36 (39.5%)	21 (55%)	15 (45%)	
Type of diabetes				
Type 1 DM	15 (17%)	7 (46.7%)	8 (53.3%)	0.05
Type 2 DM	73 (83%)	53(72.7%)	20(27.3%)	
Change of injection site (rotation)				
Injection site not changed	77 (87.5%)	58 (75.3%)	19 (24.7%)	0.001
Injection site changed	11 (12.5%)	2 (18.2%)	9 (81.8%)	
Needle change frequency				
≤ 5 times	38 (43.7%)	22 (57.9%)	16 (42.1%)	0.042
> 5 times	49 (56.3%)	38 (77.6%)	11 (22.4%)	
Duration of insulin usage				
< 60 months	49(55.7%)	29 (59.2%)	20 (40.8%)	0.02
> 60 months	39 (44.3%)	31 (79.5%)	8 (20.5%)	
Insulin regimen				
Premix	54 (61.4%)	38 (70.4%)	16 (29.6%)	0.16
Basal bolus	21 (23.9%)	16 (76.2%)	5 (23.8%)	
Split mix	13 (14.8%)	6 (46.2%)	7 (53.8%)	
Use of device				
Syringe only	72 (81.8%)	51 (70.8%)	21 (29.2%)	0.50
Pen only	12 (13.6%)	7 (58.3%)	5 (41.7%)	
Syringe + Pen	4 (4.5%)	2 (50%)	2 (50%)	
Length of needle				
4 mm	12 (13.6%)	7 (58.3%)	5 (41.7%)	0.35
6 mm	66 (75.0%)	47(71.2%)	19(28.8%)	
8 mm	10 (11.4%)	6 (60%)	4 (40%)	
Needle calibration				
G– syringe	76 (86.4%)	53 (69.7%)	23 (30.3%)	0.33
G – pen (4mm)	11 (12.5%)	6 (54.5%)	5 (45.5 %)	
31 G – pen (6mm)	5 (5.7%)	3 (60%)	2 (40%)	
HbA1c levels				
Less than 7%	15 (19.3%)	10 (66.7%)	5 (33.3%)	0.035
More than 7%	73 (80.7%)	50 (67.6%)	23 (32.4%)	
HbA1c level (mean)	8.90 ± 2.10	9.52 ± 2.14	8.46 ± 1.99	0.020
Total Daily Dose of insulin (mean IU/day)	55.3 ± 28.0	61.60 ± 23.1	41.89 ± 17.93	0.010
Type of insulin injection				0.29
Conventional	55 (62.6%)	38 (69.1%)	17 (30.9%)	
Analogue	33 (37.4%)	22 (66.7%)	11 (33.3%)	

daily dose of insulin (58.82 ± 25.16 v 44.78 ± 23.45 IU/d, $p = 0.05$) in the former was significantly higher than the latter. Amongst the risk factors, USG evidence of lipohypertrophy was higher in those not rotating injection sites ($p = 0.07$) and using insulin for more than 60 months ($p = 0.08$), with a trend towards statistical significance. The other factors failed to show significant differences between the two sub-groups, probably owing to the small sample size.

Table 4 Multiple logistic regression analysis of factors determining the risk of insulin lipohypertrophy

Risk factors	OR	*P* value	95% CI
Duration of insulin use > 60 months	4.1	.022	1.2–14.2
Needle reuse > 5 times	1.4	.476	0.5–4.3
Incorrect insulin site rotation technique	11.8	.002	2.4–58.2

Discussion

Diabetes mellitus (DM) is a chronic disease with every patient of type 1 DM and a large number of type 2 DM patients requiring insulin for optimal glycemic control. The most common local complication seen in patients with DM on treatment with insulin is lipohypertrophy [9, 14, 15].

In our study the prevalence of lipohypertrophy at the insulin injecting site was 68.2%. This is similar to a study Blanco et al. which showed a prevalence of 64.4% [5], while being significantly higher than Frid et al. who observed self-reported lipohypertrophy in 29.0% of patients while 30.8% were detected by health care professionals (HCPs) [16, 17]. On the basis of clinical examination, we have further classified lipohypertrophy according to grade 0 through grade 2. Majority of patients had grade 2 lipohypertrophy which is a massive thickening of fat tissue with higher consistency (n = 38, 43.8%), followed by grade 1 in 22 patients (25%) which is defined as a visible hypertrophy of fat tissue but palpably normal consistency. In a study done in T2DM patients, 62.1% had grade 0, 27.4% had grade 1, 9.7% had grade 2, and 0.2% had lipoatrophy [3]. This difference in clinical grading could be explained by the differences in the observer's perception and the subjective variation in visual findings for grade 1 lesion and the paucity of studies that have utilized this grading system. Further, clinical grading used in our study does not incorporate the subset of insulin-injecting patients who develop palpable but not visible hardening of subcutaneous fat, thus underlying the need for future refinement of this clinical gradation. However, irrespective of the differences in distribution amongst the different grades, the clinical prevalence of lipohypertrophy remains a significant problem in all the studies done so far.

One of the novel features of our study is the ultrasonographic characterisation of the lipohypertrophy using a predetermined grading system [12]. While previous investigators have used high-frequency ultrasound to delineate skin and subcutaneous adipose tissue thickness in insulin-injecting diabetes patients [18], its use in classifying lipohypertrophy has not been widely studied. Ultrasonography detected lipohypertrophy at the insulin injecting sites in 90% of the subjects in our study, which is similar to the study performed by Natalia et al. where in 86.5% of the subjects had evidence of lipohypertrophy when assessed by ultrasonography [19].

On further characterisation of lipohypertrophy based on the ultrasonographic findings, we found that nodular hyperechoic subcutaneous dystrophy was the most common form (33%), followed by the diffuse hyperechoic subcutaneous dystrophy (20.5%), focal and diffuse hyperechoic subcutaneous dystrophy (11.4%), and diffuse and nodular hyperechoic dystrophy (9%). The combination of nodular plus focal and diffuse hyperechoic subcutaneous dystrophy (3.3%) and simplest subcutaneous dystrophy (1.1%) were the least common types. There was substantial agreement amongst the two independent sonologists (kappa value 0.83) involved in our study. The literature on USG characterization of insulin site lipohypertrophy in different ethnic groups is limited, and our study is the first such characterization in Asian Indian patients. However, use of ultrasound for classifying subcutaneous changes of lipohypertrophy can be user-dependent and subjective, thus necessitating the role for expert sonologists in understanding the true clinical significance of the ultrasonographic descriptions of lipohypertrophy (Fig. 2).

The prevalence of lipohypertrophy was higher on ultrasound screening when compared with clinical examination (90% vs 68%) in our study. There was a moderate agreement between the USG and clinical screening of abdominal insulin injecting sites in detecting lipohypertrophy. This suggests that even with meticulous clinical examination, up to 20% or more cases of lipohypertrophy may be missed. Given the significant impact of lipohyertrophy on overall glycemic control, ultrasound evaluation can prove to be a necessary modality in identifying these undetected cases. Though cost and availability issues with routine use of ultrasound in all patients of lipohypertrophy need to be addressed in future multicenter studies, our data strongly suggests that methodical ultrasound evaluation by trained radiologists can be the investigation of choice in suspected abdominal lipohypertrophy, especially in scenarios where there is a presence of multiple risk factors (needle re-use, poor site rotation, etc) but clinical examination is non-conformative. Further, the relationship of various types of lipohypertrophy with respect to glycemic control has not been established and will need a prospective follow-up study to look at the difference in behaviour of individual types of lipohypertrophy with respect to their glycemic variability and their reversibility with the change in insulin injection techniques.

The prevalence of lipohypertrophy on clinical examination was higher in T2DM when compared with T1DM (73.6% vs 46.7%) in our study. This is in contrast to previous studies like Blanco et al. [5]. The decreased prevalence of clinically detected lipohypertrophy in our patients of T1DM when compared with type 2 can be attributed to the fact that T1DM patients included in our study are generally patients who are on our regular follow-up and therefore have been sensitized to the appropriate insulin usage techniques through repeated focussed diabetes education. Further, when compared with the

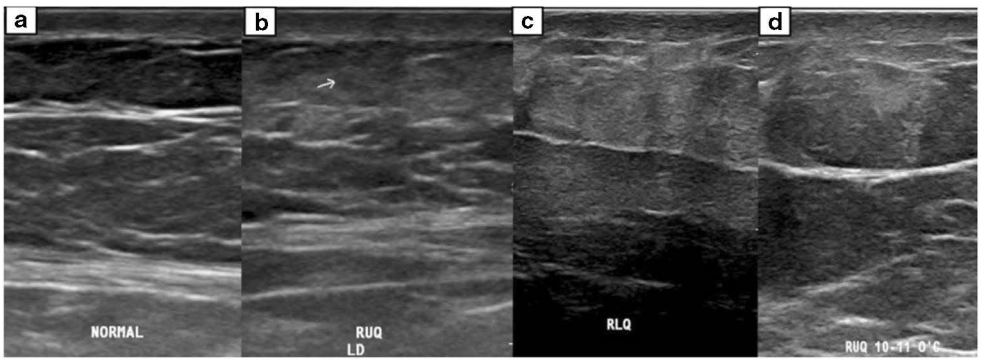

Fig. 2 Ultrasound images: (A) normal, (B) focal and diffuse hyperechoic subcutaneous dystrophy, (C) diffuse hyperechoic subcutaneous dystrophy, and (D) nodular hyperechoic subcutaneous dystrophy

previous studies, the number of T1DM patients in our study was much lower than the T2DM patients.

When we looked at the association of various factors with regard to the development of lipohypertrophy, the clinical evidence of lipohypertrophy was significantly higher in men, obese subjects, those not rotating insulin injecting sites, frequency of needle reuse on more than 5 occasions, and duration of insulin use of more than 60 months (all $p < 0.05$). The needle length, needle calibre, device used, regimen of insulin used, and type of insulin (conventional or analogue) had no influence on the development of lipohypertrophy. Similar findings on the risk factors of lipohypertrophy have been reported in a study by Bahar et al. [4].

The increase in the incidence of lipohypertrophy with the duration of insulin use has been described previously. In our study, the prevalence of lipohypertrophy was 59.1% (29/49) in those who were using insulin for less than 5 years as compared with 87.1% (27/31) in those who were using insulin for 5–10 years. Similar findings were reported previously [5] where the prevalence of lipohypertrophy was 48% in those using insulin for 1–5 years and progressively increased to 90% with increasing duration of insulin use beyond 20 years. Though predominantly attributed to the ability of injected insulin to act as a growth promoting factor for adipose tissue at the local insulin injection site, repeated trauma due to longer duration of injections per se can influence the formation of lipohyperttrophy. The higher prevalence of lipohypertrophy in type 2 diabetes and obese subjects, despite having a lower duration of insulin use than type 1 diabetes subjects, raises the intriguing possibility of insulin volume per injection playing a causative role. Since factors like diabetes education imparted to type 1 diabetes patients may have skewed the results, larger, prospective studies are needed to evaluate the pathological role of cumulative volume of insulin injected.

The prevalence of lipohypertrophy was also higher in those not rotating their injection sites correctly when compared with those who followed the correct rotation of insulin injecting sites which were similar to that reported in previous studies [5].

Another factor influencing the development of lipohypertrophy was the frequency of changing needles. Our study showed that the risk of developing lipohypertrophy increased with the re-use of the same needle more than 5 times (63%) when compared with those re-using needles less than 5 times (37%). In a study by Vardar et al [4], the prevalence of lipohypertrophy was 21% in those who changed their needle at every injection and this proportion increased to 51.2% and 75% in those who changed their needle at every 3rd and 5th injections respectively. The US FDA recommends injection needles for single use only, which may at times be impractical in countries like India, where socio-economic considerations need to be taken into account to arrive at more pragmatic solutions [19].

Amongst all the risk factors studied, the duration of insulin use of more than 60 months and the incorrect rotation of insulin injecting sites appeared to be the most important factors associated with the development of lipohypertrophy when assessed by multiple logistic regression in our study. Though frequency of needle re-use (> 5 times) led to nearly doubling of occurrence of lipohypertrophy (37% to 64%), it failed to show significant correlation on regression analysis. While this can be partly explained by the smaller sample size, it may also suggest that duration of insulin use and site rotation may be more important as contributory risk factors in our study. Overall, findings from correlation analysis point to the fact that issues pertaining to the technique of insulin injection are perhaps more important than the type of insulin being used for the development of lipohypertrophy. Different strategies have been employed worldwide to educate patients regarding insulin injection techniques, especially on injection site rotation and frequency of needle reuse. A prospective, randomized controlled trials to assess the impact of injection technique (IT) education, on insulin-treated patients with clinically observed LH over a period of 6 months, demonstrated a greater and faster improvement in the intervention arm [20]. In our institution, to teach our patients the correct technique of injection, we have included visual aids depicting the grid system of site rotation, which may have a better impact than verbal reinforcement and improve patients' adherence.

In our study, the patients with lipohypertrophy were 4 times more likely to have Hba1c more than 7%. Similar studies have shown that patients with Hba1c more than 7% were at least 3–5 times more likely to have lipohypertrophy [3], which

in turn led to a significantly higher total daily insulin dose requirement (56 IU/day vs 41 IU/day) [5].

At present there are worldwide 150–200 million insulin-using diabetes patients, of which approximately 3.2 million patients with diabetes in India are currently on insulin [21, 22]. This would contribute to a significantly increased financial burden of managing diabetes in India. Thus, a massive impact on healthcare expenditure can be achieved if development of lipohypertrophy in DM patients can be reduced by patient education on correct insulin injecting techniques. Comprehensive therapeutic education, preferably covering all topics related to insulin injection techniques, is one key area that is often overlooked in diabetes patients on insulin-injection therapy [23–25]. Innovative ways to involve the patient in the decision-making process through a discussion format of diabetes education has shown to be more effective than a rigid didactic form [26, 27]. Studies have shown better results with group education, while initiating the health-care provider in formal diabetes education training can ensure lower subsequent Hba1c values and better adherence [28]. Data from Indian studies (ITQ) show only 30% of Indian injectors get their sites checked this frequently with nearly a third only having sites check when they specifically complained and nearly 40% never having had their sites checked [8], while the worldwide data being even more dismal when compared with Indian studies in this regard [1]. This can be a major area of thrust in improving diabetes education in diabetes patients injecting insulin regularly.

Conclusion

Insulin lipohypertrophy is a common under-reported complication of insulin therapy leading to suboptimal glycemic control. While a thorough clinical examination of insulin injection sites has been traditionally used to detect lipohypertrophy, it may prove to be inadequate in more than one-fifth of cases. Our study provides evidence to suggest that systematic ultrasound evaluation may be successful in identifying majority of cases (> 90%) and larger studies identifying its role in standard diabetes care are necessary. Further, ultrasound-based characterization of abdominal lipohypertrophy lesions and its relation to glycemic variations and possible reversibility with correction of injection techniques are areas that need to be critically elucidated in future studies.

Improper insulin injecting technique is the most important risk factor for the development of lipohypertrophy. Increasing awareness about the lipohypertrophy and its risk factors amongst health care providers and educating the patients on correct insulin injection practices are key to solving the problem of insulin lipohypertrophy. The relatively better Hba1c in our type 1 diabetes subjects and lesser lipohypertrophy despite using multiple daily insulin injections for a longer duration emphasizes the beneficial effect of regular, patient-oriented diabetes education, both individually and in groups. For resource-limited countries like India, this can be a simple and cost-effective tool to mitigate lipohypertrophy in insulin-injecting diabetes patients. The strength of our study is the use of a novel ultrasonography-based gradation in addition to clinical examination for the detection of lipohypertrophy and study of various risk factors. The limitation of our study is that the impact of lipohypertrophy and its reversibility on the glycemic control could not be accurately assessed as it is a cross-sectional study and needs larger prospective studies.

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Compliance with ethical standards

The study was approved by the Institutional review board (IRB Min No 9926 dated 05.02.2016).

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

Informed consent Type 1 or type 2 DM subjects of age 18 years and older injecting insulin subcutaneously on the abdomen for at least 6 months duration were recruited after obtaining a written informed consent.

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ORIGINAL ARTICLE

Knowledge, attitude, and practice towards self-management among diabetic patients at Debre Tabor General Hospital chronic diseases follow-up clinic, Northwest Ethiopia

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Abstract

Introduction Self-management in diabetic patients is vital to keep the illness under control and avert any long term complications. Effective management of diabetes is a difficult task without an adequate understanding of the existing level of knowledge, attitude, and practice related to self-management. Knowing the level of knowledge, attitude, and practice towards self-management may help to provide information for health policy-makers to design and implement effective interventions to reduce diabetes-related morbidity and mortality.

Objective To assess the level of knowledge, attitude, and practice towards self-management among patients with diabetes at Debre Tabor General Hospital chronic diseases follow up clinic.

Methods An institution-based cross-sectional study was conducted from February to March 2016. A systematic random sampling technique was employed to select 206 patients. A structured pretested interviewer-administered questionnaire was used to collect data. The data were entered and analyzed using SPSS version 20.

Results More than half of the study participants 114 (55.3%) had poor knowledge about diabetic self-management. Poor attitude of diabetic self-management was detected among 109 (52.9%) of studied patients. Nearly two-thirds 136 (66.0%) of the study participants had poor practice towards self-management.

Conclusion More than half of the participants had poor knowledge and attitude towards self-management and nearly two-thirds of them had poor practice. It is better to emphasize the importance of the patient as the key person in diabetic management.

Keywords Knowledge · Attitude · Practice · Diabetic self-management · Diabetic patients

Introduction

Non-communicable diseases have become one of the major challenges in terms of the damage they cause to humans and the socio-economic condition of the countries. Diabetes mellitus is one of the most common non-communicable diseases and challenging health problems globally [1]. Diabetes 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 [2]. As a result of population growth, unhealthy diets, obesity, aging, urbanization, and sedentary lifestyles, the prevalence of diabetes is increasing worldwide [3]. It is a rapidly worsening, major risk to global public health, with one in 20 deaths attributed to diabetes [4].

It is estimated that the number of people with diabetes is expected to rise to 592 million by 2035. Of which, most people with diabetes live in low- and middle-income countries and these will experience the greatest increase in cases of diabetes over the next 22 years [5]. Diabetes-related mortality in 2013 in Africa region is expected to be over half a million with three-quarter of these deaths occurring in those < 60 years old [6]. World Health Organization (WHO) estimated that in 2011 34% of the Ethiopian population is dying from non-communicable diseases, with a national diabetes mellitus prevalence of 2% [7]. Knowledge of diabetes and diabetes care is needed for the successful management of the disease.

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The low level of knowledge and negative perceptions of diabetes and its complications result in poor glycemic control [8]. Lack of knowledge of diabetes and diabetes care was considered as the primary barrier to diabetes self-management [9].

Diabetes-related morbidity and mortality can be prevented through dedicated self-management behaviors in numerous domains, including food choices, physical exercise, good adherence to medications, and blood glucose monitoring from the patients. To enhance glycemic control, individuals must engage in lifestyle changes and self- management activities [10]. Successful self-management requires knowledge, skills, and a willingness to modify food choices, increase physical activity, perform blood sugar monitoring, take medications, regular checkups, and blood pressure and cholesterol control [11].

Self-management in diabetic patients is vital to keep the illness under control and avert any long term complications. Effective management of diabetes is a difficult task without an adequate understanding of the existing level of knowledge, attitude, and practice related to self-management. Therefore, this study is aimed to assess the level of knowledge, attitude, and practice towards diabetic self-management among patients with diabetes in Debre Tabor General Hospital, Northwest Ethiopia.

Methods and materials

Study design and period

An institution-based cross-sectional study was conducted from February to March 2016.

Study setting

The study was conducted at Debre Tabor General Hospital, the only hospital in Debre Tabor town, South Gondar zone of Amhara Regional State. Debre Tabor town has one governmental hospital, three governmental health centers, two private clinics, and four governmental health posts.

Study participants

Patients with both diabetes type 1 and 2 attending chronic disease follow-up clinic at Debre Tabor General Hospital for their regular follow-up during the study period were included in the study. Those patients who were unwilling to participate and seriously ill were excluded.

Sample size determination and sampling procedure

The sample size was calculated using a single population proportion formula with the assumption of knowledge, attitude, and practice of patients towards diabetic self-management is 50% with a 5% marginal error and 95% confidence interval. The final sample size was 206, after using the correction formula and adding a 5% non-response rate. Study participants were selected using a systematic random sampling technique by taking K-value 2.

Operational definitions

Knowledge Participants who answer the mean and above the mean value of the ten knowledge-related questions were considered having good knowledge and those participants who answer below the mean value were considered as having poor knowledge.

Attitude Participants who answer the mean and above the mean value of the five attitude-related questions were considered as having a good attitude and participants who answer below the mean value were considered as having a poor attitude.

Practice Participants who answer the mean and above the mean value of the nine practice-related questions were considered as having good practice and participants who answer below the mean value were considered as having poor practice.

Data collection instruments and procedures

Data were collected using a structured pretested interviewer-administered questionnaire that was adapted from a questionnaire developed by previous studies [12, 13]. The questionnaire contains thirty-six questions arranged into five sections; the first section contains seven questions regarding the socio-demographic characteristics of the participants, the second section contains five questions regarding health condition/background characteristics of patients, the third section contains ten questions concerning knowledge of patients about diabetes and self-management, the fourth section contains five regarding the attitude of patients towards self-management, and the fifth section contains nine questions regarding the practice of patients towards self-management. The tool's face validity was examined by a public health expert, a diabetic expert, and a statistician. Data were collected with the help of two trained BSc nurse data collectors and one MSc nurse supervisor. A written guideline was given to data collectors to assure that every participant received the same directions and information. Data were collected from the study participants, after guarantying their willingness to take part in the study.

Data quality assurance

The data collection instruments were tested with a pretest by taking 5% of the sample size before the actual data collection time at the University of Gondar Hospital. Amendments on the instrument, such as unclear questions and ambiguous words, were made accordingly. The questionnaire was reviewed by three experts (a public health expert, a diabetic expert, and a statistician) and their suggestions were utilized for improving the questionnaire. The questionnaire originally prepared in English was translated and back-translated to and from Amharic to ensure its consistency. Data collectors and supervisors were recruited based on their experience in research, and half-day training was given on the objective of the study, instrument, and data collection procedures by the principal investigator.

Ethical consideration

Before conducting the study, ethical clearance was obtained from the Institutional Review Board of the University of Gondar on behalf of the ethical review committee of the School of Nursing. A written permission letter was obtained from the clinical director of the hospital. Participants were informed about the purpose of the study, and verbal informed consent was obtained from them. Confidentiality was maintained by omitting direct personal identifiers on the questionnaire, by using code numbers, by storing data locked with a password, and not misuse or wrongfully disclose their information. Participants were also informed that participation was voluntary and they could withdraw from the study participation at any stage if they were not comfortable about the investigation. The investigator prepared a one-page information sheet regarding the purpose and nature of the study.

Data processing and analysis

All the collected data were checked for completeness and consistency, then compiled, coded, and finally entered into SPSS version 20 statistical software from IBM Corporation, Armonk, for analysis. Frequencies and percentages were used to summarize the descriptive statistics of the data, and tables and graphs were used for data presentation.

Results

Socio-demographic characteristics of the respondents

A total of 206 patients have participated in this study, with a 100% response rate. The majority of 129 (62.6%) of the respondents were male. The mean age of the respondents was 45.5 years and 49 (23.8%) of them fell in the age range of 50–59 years. Concerning the educational level, a large proportion of respondents 93 (45.1%) cannot read and write. One hundred fifty-one (73.3%) of the study participants were Orthodox in religion, and more than three-fourths of 160 (77.7%) of them were self-employed. Half 103 (50.0%) of the participants indicated that they live with their wives. A large proportion of the participants 91 (44.2%) indicated that their food was prepared by the spouse (Table 1).

Health condition/background characteristics of respondents

Nearly one-third of 64 (31.1%) and 34 (16.5%) of the respondents were medically diagnosed with type 2 and type 1 diabetes, respectively, and 108 (52.4%) of them did not know the type of diabetes. Of all the participants more than one-third of 75 (36.4%) indicated that they were diagnosed with diabetes in the past 1–5 years. Concerning the type of medication, nearly half 102 (49.5%) of the respondents took insulin to control their diabetes. More than three-fourths of 172 (83.5%) patients had no other chronic conditions and the majority 183 (88.8%) of them had no disability (Table 2).

Knowledge of diabetic patients towards diabetes and diabetic self-management

More than half (56.8%) of 117 of the respondents did not know the causes of diabetes. A large proportion of the participants 61 (29.6%) did not know the early symptoms of diabetes and seventy nine (38.4%) of them could not name some of the things that are beneficial to control diabetes. Nearly half 98 (47.6%) and 97 (47.1%) of the participants did not know the right time to take their medication and the symptoms of low blood sugar respectively. The majority of 297 (95.6%) of the respondents did not know the normal blood glucose level. Sixty one (29.6%) of the participants ate or drank sweets when their blood sugar becomes low. Nearly three-fourths (75.3%) of 155 of the participants did not know the long term complications of diabetes, and 169 (82.0%) of them did not know how often they should visit an eye doctor. Forty six (22.3%) of the respondents said that traditional/spiritual healers can treat diabetes apart from doctors (Table 3).

The attitude of diabetic patients towards diabetic self-management

The majority of 181 (87.9%) of the respondents believed that the food they eat is important in controlling blood sugar levels. Ninety one (44.2%) and only 37 (18.0%) of them thought that exercise and checking their foot every day are important in managing diabetes respectively. More than half 114 (55.3%)

Table 1 Socio-demographic characteristics of diabetic patients at Debre Tabor General Hospital chronic care clinic, Northwest Ethiopia, 2016 ($n = 206$)

Variables	Category	Frequency ($n = 206$)	Percentage (100%)
Age	< 20 years	4	1.9
	20–29 years	35	17.0
	30–39 years	44	21.4
	40–49 years	34	16.5
	50–59 years	49	23.8
	≥ 60 years	40	19.4
Sex	Female	77	37.4
	Male	129	62.6
Living conditions	With both parents	11	5.3
	With mother	11	5.3
	With wife	103	50.0
	With husband	55	26.7
	Alone	26	12.7
Educational status	Cannot read and write	93	45.1
	Primary	50	24.3
	Secondary and above	63	30.6
Religion	Orthodox	151	73.3
	Muslim	37	18.0
	Protestant	18	8.7
Occupation	Government employed	27	13.1
	Self-employed	160	77.7
	Student	19	9.2
Food preparation	Self	90	43.6
	Spouse	91	44.2
	Children	22	10.7
	Relatives	3	1.5

of the participants responded that the most important person in managing diabetes is self and only 35 (17.0%) of them thought that stopping smoking/alcohol consumption is beneficial to control diabetes (Table 4).

Table 2 Health condition/ background characteristics of diabetic patients at Debre Tabor General Hospital chronic care clinic, Northwest Ethiopia, 2016 ($n = 206$)

Variables	Category	Frequency (n = 206)	Percentage (100%)
Type of diabetes	Type 1	34	16.5
	Type 2	64	31.1
	Not sure	108	52.4
Duration since diagnosis	< 6 months	19	9.2
	1–5 years	75	36.4
	5–10 years	62	30.1
	Above 10 years	50	24.3
Type of medication	Pills only	92	44.7
	Injection only	102	49.5
	Both pills and injection	12	5.8
Other chronic conditions	Present	34	16.5
	Not present	172	83.5
Any disability	Present	23	11.2
	Not present	183	88.8

Table 3 Knowledge of patients about diabetes and self-management at Debre Tabor General Hospital chronic care clinic, Northwest Ethiopia, 2016 ($n = 206$)

Questions	Response	Frequency (n = 206)	Percentage (100%)
Can you name some of the causes of diabetes?	Family history of diabetes	8	3.9
	Overweight	34	16.5
	Eating too much sugar	29	14.1
	Stress	18	8.7
	Not sure	117	56.8
What can be the early symptoms of diabetes?	Passing lots of urine	42	20.4
	Excess thirst	18	8.7
	Increased hunger	39	19.0
	Tiredness	25	12.1
	Headache	21	10.2
	Not sure	61	29.6
Can you name some of the things that are beneficial to control diabetes?	Regular exercise	33	16.0
	Dietary modification	49	23.4
	Stop smoking/alcohol	7	3.4
	Adhere to medications	38	18.4
	Not sure	79	38.4
Do you know the right time to take your medication?	1 h after a meal	51	24.8
	30 min before a meal	5	2.4
	30 min after a meal	52	25.2
	Not sure	98	47.6
How would you feel if your blood sugar is low?	Hanger	20	9.7
	Mood swings	29	14.1
	Irritability	28	13.6
	Sweaty	32	15.5
	Not sure	97	47.1
What is the normal blood sugar level?	4–6 mmol/l	6	2.9
	10–12 mmol/l	3	1.5
	Not sure	297	95.6
What should you eat or drink if your blood sugar is low?	Juice	52	25.2
	Sweets	61	29.6
	Sugar	56	27.2
	Not sure	37	18.0
What are the long term complications of diabetes?	Blindness	13	6.3
	Kidney damage	26	12.6
	Heart problem	12	5.8
	Not sure	155	75.3
How often should you visit an eye doctor?	Yearly	19	9.2
	2–3 times yearly	9	4.4
	More than 3 times yearly	9	4.4
	Not sure	169	82.0
Who else apart from doctors can treat diabetes?	Traditional/spiritual healers	46	22.3
	No one	160	77.7

The practice of diabetic patients towards diabetic self-management

More than two-thirds (68.0%) 140 of the participants adjusted the way they eat since they had diabetes of which 20 (14.2%), 25 (17.9%), and 95 (67.9%) of them still follow their eating plan sometimes, always, and mostly respectively. Regarding exercise, nearly half 102 (49.5%) of the respondents perform regular exercise mostly since they had diabetes, and 16 (7.8%) of them never perform. The majority of 172 (83.5%) of the participants never regularly test their blood sugar at home. Concerning foot care, only 6 (2.9%) of the respondents check their feet for the color change, wound, cracks, and swellings always and 63 (30.6%) of them never check their feet. On the other hand, 148 (71.8%) and 149 (72.3%) of them did not inspect the inside of their shoes and dry between their toes after washing respectively. Regarding medication, one hundred thirty three (64.6%) of the participants always took their pills/injections according to how they were told to do. More than three-fourths of 164 (79.6%) of the respondents did not drink alcohol (Table 5).

Table 4 Attitude of patients towards diabetic self-management at Debre Tabor General Hospital chronic care clinic, Northwest Ethiopia, 2016 ($n = 206$)

Questions	Response	Frequency ($n = 206$)	Percentage (100%)
Is the type of food you eat important in controlling blood sugar levels?	Yes	181	87.9
	No	2	0.9
	Not sure	23	11.2
Do you think exercise is important in managing diabetes?	Yes	91	44.2
	No	14	6.8
	Not sure	101	49.0
Do you think checking your feet every day is important in managing diabetes?	Yes	37	18.0
	No	30	14.5
	Not sure	139	67.5
Who is the most important person in the management of diabetes?	Doctor	59	28.6
	Self	114	55.3
	Not sure	33	16.1
Do you think that stop smoking/alcohol consumption is beneficial to control diabetes?	Yes	35	17.0
	No	16	7.8
	Note sure	155	75.2

Overall knowledge, attitude, and practice of patients towards diabetic self-management

The current study revealed that 55.3% of the respondents had poor knowledge and 44.7% of them had good knowledge regarding diabetes and diabetic self-management. Poor attitude of diabetic self-management was detected among 52.9% of studied patients, and 47.1% of them had a good attitude towards diabetic self-management. Nearly two-thirds (66.0%) of the participants had poor practice towards diabetic self-management, whereas 34.0% of them had a good practice (Fig. 1).

Discussion

The finding of this study showed that 55.3% of the respondents had poor knowledge regarding diabetes and self-management. This finding was relatively consistent with a study conducted in China (54.4%) [14]. On the other hand, it was lower than studies conducted in Rwanda (63%), the urban area of south India (65%), and Rural Sullia (75.8%) [15–17]. This discrepancy might be due to differences in sample size and study setting. The study conducted in Rwanda was conducted among only 80 participants whereas in this study 206 patients were involved. A community-based study was conducted in south India and Sullia, whereas the current study is institutional-based and patients may have recent information about the issue and answer the questions correctly. Patients may not recall information received from health professionals if they were asked by the house to house survey and the reported knowledge will become low. However, it was higher than studies conducted in Dilla University Referral Hospital, South Ethiopia (20.6%), Nekemete Hospital, west Ethiopia (45.7%), Egypt (40.6%), Nigeria (20.5%), Saudi Arabia (40%), India, Kapa Kathmandu (38%), and rural Nepal (31.8%) [12, 13, 18–22]. The possible explanation for this difference might be due to variations in geographical location, developmental level, assertive programs, and media used to create awareness about diabetes and its self-management, the instrument used, and methods of data collection. For example, the study conducted in Dilla University Referral Hospital used both quantitative and qualitative methods. Besides, the large proportion of participants with poor knowledge in this study may be attributed to a lack of diabetes and self-management related information from health professionals.

Poor attitude towards self-management was detected among 52.9% of studied patients. This finding was lower than a study conducted in the urban area of south India (59.4%) [16]. The difference might be due to variation in the level of knowledge among study participants. In the previous study, only 35% of the participants had good knowledge about self-management whereas, in the current study 44.7% of the participants had good knowledge. However, it was higher than studies conducted in Dilla University Referral Hospital, South Ethiopia (22%), Nekemete Hospital west Ethiopia (32%), Egypt (41.3%), and Saudi Arabia (24%) [12, 13, 18, 19]. The large proportion of participants with poor attitudes in this study might be due to a lack of self-management related knowledge. Because in this study only 44.7% of the participants had good knowledge whereas, in previous studies, 79.4%, 54.3%, 59.4%, and 60% of the study participants had good knowledge, respectively.

Table 5 Practice of patients towards diabetic self-management at Debre Tabor General Hospital chronic care clinic, Northwest Ethiopia, 2016 (n = 206)

Questions	Response	Frequency ($n = 206$)	Percentage (100%)
Have you adjusted the way you eat since you had diabetes?	Yes	140	68.0
	No	66	32.0
If yes, are you still following the above eating plan?	Always	25	17.9
	Mostly	95	67.9
	Sometimes	20	14.2
Have you been exercising since you had diabetes?	Always	6	2.9
	Mostly	102	49.5
	Sometimes	82	39.8
	Never	16	7.8
Do you test your blood sugar at home regularly?	Always	8	3.9
	Mostly	5	2.4
	Sometimes	21	10.2
	Never	172	83.5
Do you check your feet for the color change, wound, cracks, and swellings?	Always	6	2.9
	Mostly	44	21.4
	Sometimes	93	45.1
	Never	63	30.6
Do you inspect the inside of your shoes?	Always	7	3.4
	Mostly	9	4.4
	Sometimes	42	20.4
	Never	148	71.8
Do you dry between your toes after washing?	Always	7	3.4
	Mostly	20	9.7
	Sometimes	30	14.6
	Never	149	72.3
Do you take your pills/injection according to how you were told to do?	Always	133	64.6
	Mostly	64	31.1
	Sometimes	4	1.9
	Never	5	2.4
Do you drink alcohol?	Yes	42	20.4
	No	164	79.6

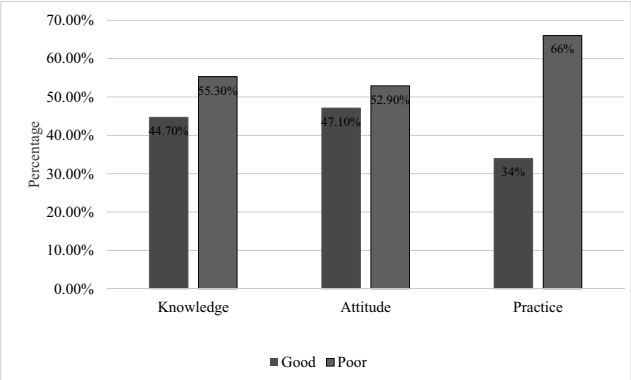

Fig. 1 Level of knowledge, attitude and practice towards diabetic self-management among diabetic patients at Debre Tabor General Hospital chronic care clinic, Northwest Ethiopia, 2016 ($n = 206$)

Nearly two-thirds (66.0%) of the participants had poor practice towards diabetic self-management. This was relatively consistent with studies conducted in Rwanda (60.6%), India (58%), and rural Sullia Karnataka (58.4%) [15, 21, 22]. This finding was lower than a study conducted in the urban area of south India (75%) [16]. The possible explanation for this difference might be due to differences in the socio-economic and socio-demographic characteristics, differences in study instruments used, number of study participants, and study design used. On the other hand, it was higher than studies conducted in Dilla University Referral Hospital south Ethiopia (24%), Nekemete Hospital, west Ethiopia (45.3%), Saudi Arabia (44%), south India (52%), and China (50.3%) [12, 14, 18, 19, 23]. The difference might be due to gaps in patient counseling practice about the role of the patient in the management of diabetes. It might also be due to good information

dissemination using different technologies which made their patients good in self-management in the previous studies. Self-monitoring of blood glucose (SMBG) was the most neglected practice which is not performed by 83.5% of the participants even if performing SMBG regularly helps diabetics maintain good blood glucose control. Similar findings were reported in China and Assela General Hospital, Ethiopia in which 81.02% and 83.2% of respondents did not perform SMBG respectively [24, 25]. The low level of adherence to SMBG might be due to the unavailability of blood glucose self-monitoring equipment (glucometer), low economic status, and low educational level. Proper education and follow-up are very important to increase the level of adherence [26].

Strengths of the study The response rate in this study was high (100%). Data collectors provide enough information to the study participants regarding the purpose of the study to achieve this high response rate.

This study has some limitations. The study assessed self-care activities by self-report questionnaires, and this may differ from what patients practiced. The study was also only descriptive and unable to identify the factors associated with knowledge, attitude, and practice towards self-management.

Conclusion

More than half of the participants had poor knowledge and attitude towards diabetic self-management, and nearly two-thirds of them had poor practice. It is better to emphasize the importance of the patient as the key person in diabetic management.

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Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

Abbreviations *DSM,* diabetic self-management; *KAP,* knowledge attitude practice; *SMBG,* self-monitoring of blood glucose; *SPSS,* Statistical Package for Social Sciences; *WHO,* World Health Organization

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ORIGINAL ARTICLE

Function of family of origin and current quality of life: exploring the mediator role of resilience in Chinese patients with type 2 diabetes

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Abstract

Objectives Early physical and mental experiences from family of origin and parents might influence individuals' later adulthood quality of life (QOL). The present study was undertaken to examine the inter-relationships among function of family of origin, resilience, and current quality of life in a T2DM sample from China.

Methods Three hundred T2DM participants were included in this investigation. A Chinese version of Connor-Davidson Resilience Scale 25, an APGAR family functioning scale, and a Diabetes Specificity Quality of Life Scale were used to assess the levels of mental resilience, function of family of origin, and QOL of these patients, respectively. Multiple stepwise regression analysis was performed to identify the predictors of QOL. A 3-step composite analysis was used to examine the predicted mediating effect.

Results QOL total score was negatively related to resilience ($r = -.299$, $p < 0.01$) and family function ($r = -.246$, $p < 0.01$). In contrast, a significantly positive correlation between resilience and family function ($r = .302$, $p < 0.01$) was found. Two subscales of resilience (strength and optimism) and function of family of origin explained an additional 4.5% of the variance in QOL changes after controlling for demographic variables. Resilience had a 26.3% mediating effect between function of family of origin and current QOL.

Conclusion In conclusion, the present work suggested a synthetic and stable association between function of family of origin and QOL level in the later life in a sample of Chinese T2DM population, with resilience acting as a mediating factor. Adult individuals who have grown up in an unfavorable family setting may be low in mental resilience, and would have worse QOL in their mid- and later life, especially when they are confronted with certain adversity or stress, such as having diabetes.

Keywords Quality of life · Resilience · T2DM · Family function · Family of origin

Introduction

Chinese society is now confronted with a series of challenges including aging populations, soaring proportion of obese and overweight individuals, and increasing prevalence of unhealthy lifestyles such as excessive consumption of high-energy and high-fat diet as well as insufficient physical activity [1–3]. All the changes put people at greater risk of type 2 diabetes mellitus (T2DM) [4, 5]. According to a latest epidemiological study, approximately 11% of Chinese population has this disease [6]. T2DM is associated with various acute and chronic complications, disability, and impaired physical and mental functioning that greatly threaten the quality of life (QOL) of patients [7–9].

Family of origin refers to the family that one was born into, where he grows up in with other family members, such as his parents, siblings, grandparents, single parents, or other relatives. Family of origin strongly influences the development of an individual through family function, which refers to the roles of family in human life and social development. Accumulating studies have shown that early family environment (e.g., parenting style) can affect the child development and resilience level significantly [10]. Of note, remembered family atmosphere and parenting behaviors from childhood

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continue to influence physiological well-being and depressive symptom across the life span [11]. Early physical and mental experiences from family of origin and parents would also deeply impact individuals' later adulthood development and outcomes, such as QOL, career achievement, mental health, and resilience [12, 13].

Up to date, an explanation regarding the role of childhood family environment in the psychological development and QOL level in mid- and later life of Chinese adult patients with type 2 diabetes is lacking. The purpose of this study was to examine the relationships among function of family of origin, mental resilience, and QOL in a Chinese T2DM population. We hypothesized that individuals growing up under undesirable family atmosphere would be less resilient and would report poorer QOL than would those enjoying a positive family parenting environment during childhood and that resilience would mediate the relationship between childhood family atmosphere and adulthood QOL of diabetic patients. This work was aimed to provide a novel perspective on the interrelationship between family of origin function, mental resilience, and their current QOL in Chinese T2DM patients.

Materials and methods

Design and sample

A cross-sectional study was conducted among 300 T2DM patients at two major tertiary hospitals in Jinzhou, China, from May to September 2019. Data were collected by researchers together with four well-trained research assistants. They assigned the questionnaires to the T2DM patients when they routinely visited the outpatient department. Participants were told to complete the questionnaires voluntarily and anonymously, and they were not required to complete the survey if they were not willing to go further out of whatever reasons. Inclusion criteria were as follows: age over 18 years; diabetes identified as type 2; diabetes diagnosed ≥ 6 months; and can speak and understand mandarin (standard spoken Chinese). Patients who had history of malignant tumor or other severe comorbidities and gestational diabetes were excluded from the study. Following collection of 306 questionnaires, it was found that 6 were invalid and thus excluded.

Measures

Mental resilience

The 25-item Chinese version of the Conner-Davidson Resilience Scale (CD-RISC25) was utilized to evaluate the three dimensions of patients' resilience. The three dimensions of this scale were tenacity (13 items), strength (8 items), and optimism (4 items). Each item uses a 0-to-4 rating method, and the total score ranges from 0 to 100, with higher scores indicating higher level of resilience. Cronbach's α coefficient of internal consistency of the three subscales ranged from 0.705 to 0.879.

Family function

The Chinese version of APGAR score was used to evaluate family function. This scale contains five items/dimensions: adaptability, partnership, growth, affection, and resolve. Each item/dimension is scored from 0 to 2, and the total score ranges from 0 to 10. Higher APGAR scoring means better family function. Cronbach's α coefficient of internal consistency of the scale was 0.824.

Quality of life

The Chinese version of Diabetes Specificity Quality of Life Scale (DSQL) was applied to assess QOL among patients with T2DM. DSQL is a reliable and validated instrument for QOL measurement, and contains 27 items that measure four different domains of health: physiology, psychology, social, and therapy. DSQL was scored ranging from 27 to 135, with higher score indicating worse QOL. Cronbach's α coefficient of internal consistency of the four subscales ranged from 0.909 to 0.987.

Statistics analysis

Data analysis was carried out using Statistical Package for the Social Sciences Version 17.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics for sociodemographic and clinical variables are expressed as frequencies and percentages. Pearson correlation analysis was performed to assess correlations among resilience, family function, and QOL. Multiple linear regression was performed using the DSQL total score as the outcome variable and family function and resilience as continuous independent variables, controlling for demographic and clinical variables.

Variables were considered as mediators when the following correlation was identified: (a) independent variables are strongly related to dependent variables; (b) independent variables are associated with mediating variables; (c) independent variables and mediating variables are related to dependent variables [14]. Based on the correlation framework, a 3-step composite analysis was used to examine the mediating effects, as routinely

performed in many previous reports [15–17]. A two-tailed probability (p) value of less than 0.05 was considered to be statistically significant.

Results

Sample characteristics

A total of 300 outpatient T2DM patients were recruited in this investigation and answered the questionnaires completely. Respondent distribution by demographic and disease characteristics is shown in Table 1. This shows that 43.3% of respondents were male, and 66.3% were married. The percentages of participants aged 18–45, 46–60, and > 60 were 29.3%, 59.7%, and 11.0%, respectively. 85.3% of respondents were enrolled in medical insurance.

Correlation analysis for the relationship between current QOL, function of family of origin, and resilience

Table 2 shows that the level of DSQL QOL total score (where higher score indicating worse QOL) was significantly and negatively related to resilience ($r = -.299$, $p < 0.01$) and family function ($r = -.246$, $p < 0.01$). In contrast, a significantly positive correlation between resilience and family function ($r = .302$, $p < 0.01$) was found.

Table 1 Demographic and clinical characteristics of the sample ($n = 300$)

Factors	Group	*n*	%
Gender	Male	130	43.3
	Female	170	56.7
Age	18–45	88	29.3
	46–60	179	59.7
	> 60	33	11.0
Education level	Primary school or less	54	18.0
	Middle school	105	35.0
	High school/secondary professional education	56	18.7
	Associate degree education or above	85	28.3
Marital status	Married	199	66.3
	Single/divorced/widowed	101	33.7
Average income level	Low	121	40.3
	Middle	149	49.7
	Upper	30	10.0
Medical expenditure mode	Medical insurance	256	85.3
	Self-supporting	44	14.7
Employment	Yes	245	81.7
	No	55	18.3
Diabetic duration (year)	< 5	26	8.7
	5~10	157	52.3
	11–15	57	19.0
	> 15	60	20.0
HbA1c	< 7	23	7.7
	≥ 7	277	92.3
Therapy regimen	Diet/exercise	27	9.0
	Oral drugs	43	14.3
	Insulin	72	24.0
	Combined treatment	158	52.7
Number of complications	0	135	45.0
	≥ 1	165	55.0

Table 2 Correlation analysis for the relationship between function of family of origin, resilience, and current quality of life

	Function of family of origin	Resilience	Current quality of life
Function of family of origin	1	.302**	− .246**
Resilience	.302**	1	− .299**
Current quality of life	− .246**	− .299**	1

**$p < 0.01$

Multiple linear regression analysis for the relationship between current QOL, function of family of origin, and resilience

To further explore the relationship of QOL with family function and resilience, we conducted a thrice repeated multiple linear regression analysis, in which QOL was used as the explained variables, sociodemographic characteristics as the controlled variables, and family function and resilience dimensions as principal significant variables. According to the final model in Table 3, namely model R_3, two subscales of resilience (strength and optimism) and family function were relevant to the level of QOL.

The mediation effect of resilience between function of family of origin and current QOL

A 3-step composite analysis was conducted to identify a potential mediator. As shown in Fig. 1, in the first step, resilience was significantly regressed on function of family of origin ($\beta = .285$, $p < 0.001$). In the second step, current QOL was significantly regressed on function of family of origin ($\beta = -.170$, $p < 0.001$). In the third step, when both functions of family of origin and resilience were included in the same model, both factors remained significant predictors of current QOL ($\beta = -.125$ and $-.157$, respectively; both $p < 0.01$). Through 3-step regression, resilience had a significant mediating effect between function of family of origin and current QOL, with a mediation effect of .285 * (− .157) / (− .170) ≈ 26.3%.

Discussion

Principal findings

Against the background of continuously rising diabetic incidence, this study investigated the comprehensive relationships among function of family of origin, mental resilience, and their current QOL. Our data indicated that function of family of origin had a significant role in current QOL status in type 2 diabetic patients, directly and indirectly via mediation by mental resilience. As far as we know, this might be the first report regarding exploration of the influence of function of family of origin of type 2 diabetic patients on their current QOL status. Although certain studies have also examined the role of family function in QOL of type 2 diabetic patients [18–20], they exclusively focused on exploring the contribution of "current family function" rather than "function of family of origin" as in our present study.

Table 3 Multiple linear regression analysis for the relationship between current quality of life, function of family of origin, and resilience

Explanatory variables		Model R_1		Model R_2		Model R_3	
		t	*p*	*t*	*p*	*t*	*p*
Sociodemographic variables	Number of complications	6.703	.000	6.491	0.000	6.544	0.000
	Marital status	− 7.253	0.000	− 6.629	0.000	− 6.418	0.000
	Education level	− 2.992	0.003	− 3.195	0.002	− 2.924	0.004
	Age	2.920	0.004	3.051	0.002	3.304	0.001
	Therapy regimen	− 2.973	0.003	− 3.103	0.002	− 3.087	0.002
Resilience	Tenacity			− 2.920	0.004	–	–
	Strength			–	–	− 2.108	0.036
	Optimism			− 2.418	0.016	− 2.442	0.015
Function of family of origin						− 3.733	0.000
F value		37.152		30.359		28.330	
p value		0.000		0.000		0.000	
Adjusted R^2		0.377		0.407		0.422	

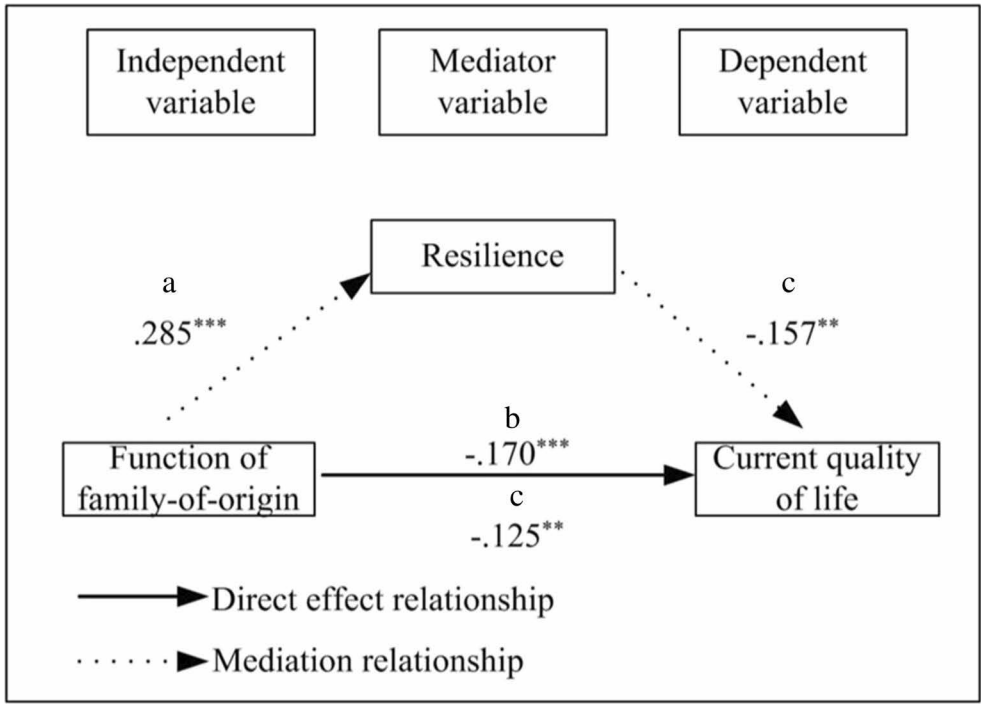

Fig. 1 The mediator model of mental resilience. ***$p < 0.001$, **$p < 0.01$. (**a**) The first step representing mental resilience regressed on function of family of origin. (**b**) The second step representing current quality of life regressed on function of family of origin. (**c**) The third step representing current quality of life regressed on function of family of origin and mental resilience

QOL condition of Chinese T2DM patients

In China, the prevalence of DM in adults aged 20 and older has reached a worrying rate of 11%, with a significant proportion remaining undiagnosed [6]. T2DM accounts for 90–95% of all diagnosed diabetic cases [21]. QOL in health field refers to the overall well-being of individuals and societies and is used to assess how an individual's well-being is affected negatively by a disease, a disability, or a disorder [3]. Based on the bio-psycho-social medical model, QOL should be understood in terms of a combination of physical, mental, and social factors [22]. As such, except for traditional blood glucose control and complication treatment, health care providers should pay more attention to the physical, emotional, and social aspects of chronic diseases such as T2DM [7, 23, 24]. Numerous studies have shown that QOL among diabetics is much lower than that reported among non-diabetics [25–27].

Interrelationship between resilience, function of family of origin, and QOL among Chinese T2DM patients

Mental resilience, or resilience in short, can be defined as an individual's ability to properly handle stress and adversity. Generally, resilience can be regarded as a positive adaptation to adversity or traumatic events [28, 29]. It is regarded that resilience may be enhanced by assets, resources, family, and support system, etc., of an individual [13]. Studies have suggested positive relationships between resilience and QOL in patients with diabetes or other types of diseases [30–32]. Interventions aiming to enhance resilience level of diabetic patients may produce a positive impact over their QOL.

Level of an individual's resilience is determined both by internal (such as genetic) and external (such as environmental) factors [33]. Internal factors are of diverse biological and psychological determinants, arising from within an individual. External factors refer to the nature and quality of relationships formed within and outside the family group. Family is a basic social unit and functions to gratify the needs of family members physically and mentally and is related to their QOL levels. Among others, resilience represents as an extremely important mediator of the association between family function and QOL. For example, family function has been shown to impact QOL of the elderly [34]. Additionally, resilience also mediates the relationship between family function and mental health in type 2 diabetic patients [35]. These studies indicated that family function may largely influence the QOL level of human being, and in many cases in a resilience-mediating manner. It should be pointed out that the "family function" in previous studies is "current." As to whether and how an individual's current QOL is influenced by function of family of origin, it is completely unknown.

Based on the correlation analysis between function of family of origin, resilience, and QOL in T2DM patients, QOL of the DM patients is closely related to the original family status and their resilience level. In our multiple linear regression analysis, the final model R_3 showed that two subscales of resilience (strength and optimism) and function of family of

origin had a significant influence on QOL: the comparison between R_3 and R_1 indicated that these two factors explained an additional 4.5% of the variance in QOL changes. In addition, the 3-step composite analysis confirmed a 26.3% mediation ratio of resilience between the relationship of function of family of origin and current QOL of the subjects.

In our study, resilience exhibited a positive influence on QOL level of T2DM population, which is in line with previous studies [30, 35, 36]. This seems easy to understand, as individuals with high resilience are often life satisfactory, optimistic, and having a tranquil mind. These fine psychological qualities would facilitate their coping with difficulties and adversities when they are faced with stressful occasions [37]. In compatible with this notion, our current finding also found a significant positive effect of optimism and strength on QOL. Family setting and parenting represent an initial and extremely important context for the physical and mental development of individuals and would mold and even maintain their resilience in the whole life [13, 38–40]. Previous results have shown that adolescents growing up in chronically distressed families are more likely to be socially and emotionally problematic, and cannot effectively address a variety of adversities. As such, the negative influence of unfavorable family setting on adolescent individuals seems to be long-termed and consecutive, going all the way through the whole life of the victims. This might help explain why the function of family of origin could produce a significant influence on the individuals' mental resilience and QOL, as shown in our study. Similar to the results presented herein, it was shown that elderly individuals who had grown up under a warm, supportive, and loving parenting style (authoritative parenting) tend to exhibit greater resilience and a lower level of depression. In contrast, cold, unsupportive, and high demanding parenting style (authoritarian parenting) was related to less resilience, and resulted in worse mental health outcomes [13].

Strengths of the study

In contrast to previous studies which indicated that the "current" family function may largely influence the QOL level of human being, and in many cases in a resilience-mediating manner, our present study for the first time reveals that an individual's current QOL is also significantly influenced by function of family of origin where the type 2 diabetic patients lived with during childhood. Furthermore, we found that the influence of function of family of origin on the current QOL of T2DM patients was partially mediated by their mental resilience. These novel findings would help understand and realize the importance of the early family environment on the later adulthood life of an individual, especially when they are confronted with an adversity, such as having T2DM.

Limitations

The present study bears several major limitations. Firstly, the subjects were limited to the urban community, which may limit the generalizability of our study results. Secondly, the study design was cross-sectional, so one cannot draw any causal relationships between QOL and mental resilience. Thus, future longitudinal studies or randomized controlled trials will be warranted to further confirm our arguments. Thirdly, the sample size was relatively small, and the heterogeneity in our sample characteristics might have brought bias. Thus, the results should be interpreted with caution. Fourthly, the function of family of origin rating by diabetic population in our sample would be subject to recall bias.

Conclusion

The findings of the present study suggest a close and stable correlation between function of family of origin and the current QOL in Chinese adults with T2DM, which is partly mediated by mental resilience. Adult individuals who have experienced unfavorable family setting may be low in mental resilience. This negative influence continues to function in their later life, and would decrease their QOL, especially under a certain adversity or stress, such as having diabetes. The findings of this study also highlight the importance of function and setting of family of origin for the health-related QOL of minor family members in their mid- and later life.

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Authors' contributions Hongliang Dai formulated the research questions, designed and supervised the study, developed the preliminary search strategy, and drafted the manuscript; Guizhi Jia, Xin Li, Yuying Chu, and Hongliang Dai collected and analyzed the data for study. Hongliang Dai wrote the manuscript. Guizhi Jia and Yuying Chu conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

Compliance with ethical standards

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

Ethical consideration All the participants were informed beforehand regarding the purpose and process of this study. Afterwards, the written informed consent was obtained from the eligible participants who readily agreed to participate in this research before they completed the questionnaires. They were also informed to have the right to withdraw from this

survey if for any reason they were not interested in doing so. All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was also reviewed and approved by Jinzhou Medical University Ethics Committee.

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CASE REPORT

De novo mutation in HNF-1β gene as a cause for Maturity-onset Diabetes of the Young type 5 with sustained hypomagnesemia

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Abstract

Background Maturity-onset Diabetes of the Young type 5 (MODY5) is clinically heterogeneous, and the genetic examination is important to provide the accurate diagnosis. Identification of more cases will better understand the genotype-phenotype correlations of this disorder.

Methods We collected the clinical and biochemical data, using the whole-exome gene detection and multiplex ligation–dependent probe Amplification to detect the pathogenic gene variants.

Results The proband is a 39-year-old female, and presenting with symptoms including polyuria, polydipsia, and weight loss for 6 months. Her BMI was 17.6 kg/m^2. Laboratory tests indicated hypokalemia (3.1 mmol/L), hypomagnesemia (0.4 mmol/L), and hypocalcemia (1.91 mmol/L). Glycated hemoglobin (HbA1c) was 13.7%, fasting C-peptide was 0.24 ng/mL (normal range: 0.3–3.73 ng/mL). Both glutamic acid decarboxylase and islet cell antibodies were negative. Abdominal magnetic resonance image showed the agenesis of the tail and body of the pancreas and the presence of disseminated cysts of the left kidney. Genetic examination displayed a de novo heterozygous deletion of the whole HNF-1B gene (NM_000458.3). Three-year follow-up after the diagnosis showed that the patient has sustained hypomagnesemia and cannot maintain an appreciable increase in serum magnesium levels (0.52–0.61 mmol/L), although she was using the double-dose magnesium aspartate. Moreover, she cannot achieve good glucose control either.

Conclusion Our findings indicted that MODY is highly heterogeneous and patients with additional extrapancreatic clinical features and hypomagnesemia should be screened for MODY5.

Keywords Maturity-onset Diabetes of the Young · Hypomagnesemia · Hepatocyte nuclear factor-1βeta (HNF-1β) · Mutation · Diabetes mellitus

Introduction

Maturity-onset Diabetes of the Young (MODY) is a rare group of dominantly inherited and clinically heterogeneous diabetes mellitus [1]. MODY type 5 (MODY5) accounts for 2–6% of MODY diagnoses, whose typical characterization is relatively worse beta cell function and additional extrapancreatic clinical features, like liver dysfunction, renal disease, and genital malformation [2]. This disorder is caused by mutations of the hepatocyte nuclear factor-1beta (*HNF1β*) gene. *HNF1β* is an important transcription factor in the development of the pancreas, kidney, liver, and genital tract [3]. *HNF1β* gene located on chromosome 17q12 and more than 100 different mutations in this gene have been identified since it was associated with MODY5 in 1997 [1, 4].

Stiles et al. reported *HNF1β* deletion as a cause for a patient with chronic, treatment-resistant hypomagnesemia, but without diabetes mellitus (DM) [5]. In this report, we described a rare heterozygous whole-gene deletion in *HNF1β* gene that was identified in a proband with MODY5 and sustained hypomagnesemia.

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Methods

Ethics

This study was approved by the ethics institutional review board of the Laiwu Central Hospital of Xinwen Mining Group. Written informed consents were obtained from the proband and her parents.

Case presentation

Clinical features

The proband is a 39-year-old Chinese female without a prior documented remarkable medical history. She presented with symptoms including polyuria, polydipsia, and weight loss for 6 months. Hyperglycemia (fasting plasma glucose ranges from 8.3 to 13.6 mmol/L and 2-h postprandial glucose was over 20 mmol/L) and ketosis but without metabolic acidosis were identified at presentation. She was diagnosed as type 2 DM and treated with insulin in another hospital. Due to poorly controlled blood glucose, she was admitted to our hospital. Further investigation revealed that she (1) was a premature infant, (2) was feeling fatigue from a young age, (3) had suffered from paroxysmal extremities numbness and spontaneous hand tremor for several years, and (4) was aborted at 6-month gestation for unknown reasons.

Her BMI was 17.6 kg/m^2. A physical examination revealed no obvious abnormalities. Laboratory tests indicated hypokalemia (3.1 mmol/L), hypomagnesemia (0.4 mmol/L), and hypocalcemia (1.91 mmol/L). Fasting plasma glucose was 7.6 mmol/L and 2-h postprandial glucose 19.3 mmol/L. Glycated hemoglobin (HbA1c) was 13.7% determined using high-performance liquid chromatography (HPLC) with the Hemoglobin A1c analyzer (TOSOH Corporation, Japan). Used an automatic biochemistry analyzer (Beckman Coulter Analyzer AU58 Series, USA) to analyze the following parameters. Fasting C-peptide was 0.24 ng/mL (normal range: 0.3–3.73 ng/mL), 1-h and 2-h postprandial C-peptides were 0.44 and 0.15 ng/mL, respectively. Levels of serum ALT, AST, BUN, and creatinine were normal. Both glutamic acid decarboxylase and islet cell antibodies were negative.

Abdominal magnetic resonance image showed the agenesis of the tail and body of the pancreas and the presence of disseminated cysts of the kidney (Fig. 1).

The genetic analysis

Genetic tests were carried out on the patient and her parents 2 years later after the diagnosis of DM. Genomic DNA was isolated from peripheral blood leukocytes using QIAamp DNA Mini Kit (Qiagen, Germany) following the manufacturer's instructions. Whole-exome sequencing (WES) was performed using SeqCap EZ Med Exome Enrichment Kit (Roche NimbleGen, USA) and the Illumina HiSeq sequencing platform. Genetic examination by the WES and multiplex ligation–dependent probe amplification (MLPA) detected a 1.26-Mbp heterozygous deletion (Chr17:34842450-36105089) that includes *HNF1β* gene (NM_000458.3, Fig. 2). It was proved to be a de novo mutation because neither her parents shared the deletion. Therefore, our patient was genetically confirmed MODY5.

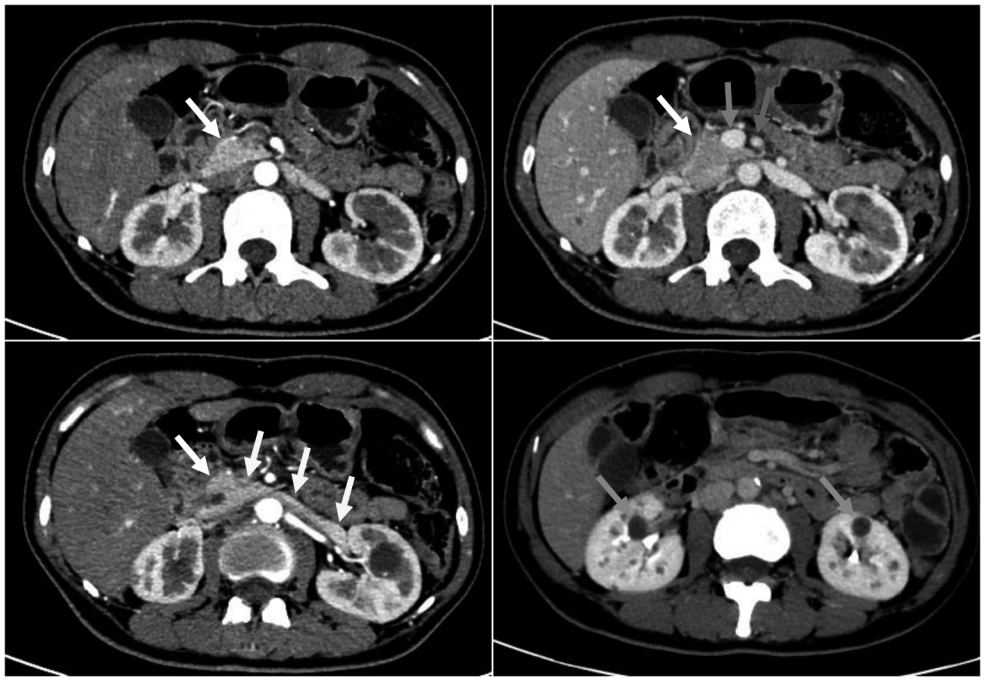

Fig. 1 Abdominal magnetic resonance image showed the agenesis of the tail and body of the pancreas and the presence of disseminated cysts of the kidney. Arrow in white, the pancreatic uncinate process. Arrow in green, superior mesenteric vein. Arrow in red, superior mesenteric artery. Arrow in yellow, body and tail of pancreas. Arrow in blue, disseminated cysts of the kidney

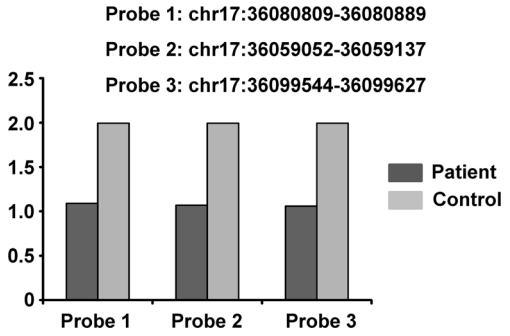

Fig. 2 Genetic examination by multiplex ligation–dependent probe amplification (MLPA) displayed a heterozygous deletion of the whole *HNF1β* gene (NM_000458.3)

In addition, the WES revealed two heterozygous missense variants in *PPP1R3A* (NM_002711 c.1465T>A, p.F489I) and *PLIN1* (NM_002666, c.929A>G, p.E310G) genes, respectively (Fig. 3). The variation c.1465T>A in *PPP1R3A* gene results in a change in the 489th amino acid of the encoded protein from F to I. The variation c.929A>G in *PLIN1* gene results in a change in the 310th amino acid of the encoded protein from E to G. Neither of the variations was reported in the database of the Exome Aggregation Consortium (ExAC) (http://exac.broadinstitute.org/) or the Human Gene Mutation Database (HGMD) (http://www.hgmd.cf.ac.uk/). Both the patient and her mother carried these two mutations; however, her mother had no diabetes and hypomagnesemia. Therefore, these are likely to be variations with unknown significance and benign.

Follow-up

Serum magnesium was 0.4 mmol/L (normal range: 0.7–1.0 mmol/L) at presentation to our department and dropped to 0.31 mmol/L, despite the oral replacement therapy (magnesium 395.7 mg daily) for 7 days. Later, this dose was doubled for a trial period, with a slight increase in serum magnesium (0.46 mmol/L). Since then, the patient is using the double-dose magnesium aspartate. However, she could not maintain an appreciable increase in serum magnesium levels (0.52–0.61 mmol/L) and achieve reduction of her symptoms.

Three-year follow-up after the diagnosis of DM showed that the patient could not achieve good glucose control although by intensified insulin therapy (insulin glargine and insulin lispro). HbA1c was 8–9%.

Discussion

We herein reported a heterozygous deletion of the whole *HNF1β* gene in a Chinese patient with the phenotypes of MODY5 and sustained hypomagnesemia.

Due to relatively poor beta cell function and progressive hyperglycemia, patients with MODY5 usually required an intensive insulin treatment. Notably, MODY5 encompasses a wide extrapancreatic clinical spectrum [1, 6]. Renal disease, especially the presence of renal cysts, is the most frequently detected feature. Other features include pancreatic atrophy, exocrine pancreatic dysfunction, liver dysfunction, genital tract malformation, and early-onset gout [7, 8]. Analysis for mutations of *HNF1β* is recommended in young diabetic patients particularly when pancreatic atrophy, kidney, or genital abnormalities are present.

A whole *HNF1β* gene deletion is the most common mutation, occurring in half of patients with MODY5. Because the *HNF1β* gene located on chromosome 17q12 in humans, the *HNF1β* deletion has recently been regarded to be linked with the 17q12 deletion syndrome in all cases [9]. The 17q12 deletion syndrome is an extremely rare microdeletion syndrome whose estimated prevalence is 1.6 per 100.000 people. The penetrance of this disorder is high, but its expressivity is variable [10]. The 17q12 deletion syndrome can either be inherited from an affected parent in an autosomal dominant

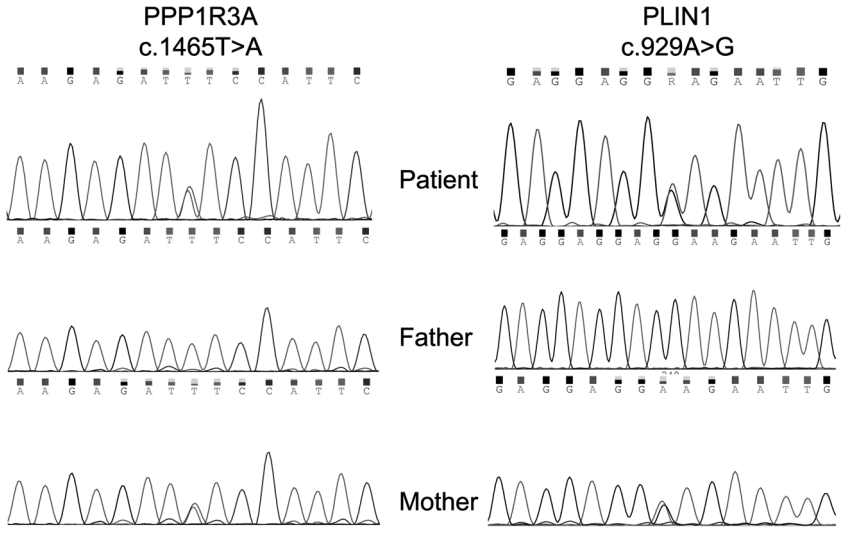

Fig. 3 Whole-exome sequencing (WES) revealed two heterozygous missense mutation in PPP1R3A (NM_002711 c.1465T>A, p.F489I) and PLIN1 (NM_002666, c.929A>G, p.E310G) gene, respectively

manner or occur de novo. Actually, the deletion mutation in 70% of the cases is de novo [11]. Thus, presence of DM and typical clinical features in our patient indicates 17q12 deletion syndrome as possible diagnosis. The patient in this case required insulin treatment because of impaired insulin secretion accompanied by pancreatic atrophy. She had renal cysts and hypomagnesemia. Based on the above findings, her phenotype was compatible with MODY5.

Hypomagnesemia has been associated with disorders resulting from mutations in the *HNF1β* gene [2]. The occurrence of hypomagnesemia is described with various types of *HNF1β* mutations [6, 12, 13]. It is believed to occur through magnesium wasting in the renal distal convoluted tubule. Stiles et al. reported a 29-year-old female patient who suffered from an unexplained hypomagnesemia for 8 years, but without DM. Genetic analysis showed that this disorder was also caused by a heterozygote 1.5-Mb deletion on chromosome 17q12 encompassing *HNF1β* gene [5]. It was noted that our patient developed DM at about 39-year old, though MODY5 generally occurred before the age of 30 years. Therefore, the patient reported by Stiles et al. should be followed up regularly on her glycemic state to detect DM earlier.

In summary, features caused by *HNF1β* deletion are highly heterogeneous amongst patients and genotype/phenotype correlation is still unclear up to now. *HNF1β* mutations can be part of the 17q12 deletion syndrome which are one of the most common causes of MODY5 characterized by congenital anomalies of the pancreas and kidney. Sustained and treatment-resistant hypomagnesemia are also associated with the *HNF1β* mutation.

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Author contributions Y.Z. conceived of and supervised the project, and revised the manuscript content. B.R. and Y.C. collected and analyzed the data, and drafted the manuscript. S.Z., Q.Z., J.W., and S.C. took responsibility for the integrity of the data analysis. All the authors have read and approved the final submitted version.

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Data availability All data generated or analyzed during this study are included in this published article.

Compliance with ethical standards

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

Ethics approval and consent to participate This study was approved by the ethics institutional review board of the Laiwu Central Hospital of Xinwen Mining Group. Prior to sample collection, written informed consent was obtained from the proband and her parents.

Patient consent for publication All subjects provided consent for publication.

Code availability Not applicable.

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CASE REPORT

Extremely low HDL and residual cardiovascular risk—a case report

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Abstract
Introduction Extremely low high-density lipoprotein cholesterol (HDL-C) is defined as levels below 20 mg/dL. Association between extremely low HDL-C levels may occur from artifactual, primary monogenic disorders or from secondary causes. We present a 55-year-old known diabetic male with extremely low HDL, in the absence of severe hypertriglyceridemia, with apolipoprotein A1 deficiency and presenting with acute myocardial infarction.
Results Transradial angiography revealed triple vessel disease, for which the patient was medically managed and sent home in a stable condition and is presently on follow-up.
Conclusion Such cases are infrequent and pose a diagnostic challenge.

Keywords Apo AI deficiency · Hypoalphalipoproteinemia · Reverse cholesterol transport · Extremely low HDL · Residual cardiovascular risk

Introduction

In addition to its role in reverse cholesterol transport, high-density lipoprotein (HDL) shows many other protective properties towards atherosclerosis. It has an inhibitory effect on chemotaxis of monocytes, prevents endothelial dysfunction and apoptosis, prohibits low-density lipoprotein (LDL) oxidation, and stimulates the proliferation of endothelial cells and smooth muscle cells. These anti-inflammatory, antioxidative, antiaggregatory, anticoagulant, and pro-fibrinolytic activities are exerted by apolipoproteins, enzymes, and phospholipid components of HDL [1]. HDL also enhances insulin sensitivity and promotes insulin secretion by pancreatic beta islet cells. Elucidation of the HDL proteome has highlighted the "hormonal" characteristics of HDL in that it carries and delivers messages systemically [2]. Low serum high-density lipoprotein cholesterol (HDL-C) is known to be an important component of the metabolic syndrome.

We present a case of extremely low HDL (less than 20 mg/dL) and apolipoprotein A1 (Apo A1) deficiency, presenting with acute myocardial infarction (AMI). Such patients with HDL-C less than 20 mg/dL in the absence of severe hypertriglyceridemia are infrequently encountered in clinical practice and fall below the 5th percentile [3]. The most common pattern of dyslipidemia found in India is a combination of borderline high LDL cholesterol, low HDL cholesterol, and high triglycerides [4]. To our knowledge, there is no documented case from India of extremely low HDL, in the absence of severe hypertriglyceridemia, presenting with AMI.

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Case report

A 55-year-old known diabetic male presented to cardiology outpatient department with complaint of recurrent typical chest pain [3–4 episodes] for the last 5 days. His vitals at presentation were as follows: blood pressure 128/80 mm Hg, pulse 70/min, respiratory rate 20/min, normal vesicular breath sounds, normal peripheral pulses, and S1 and S2 heart sounds were audible. His body mass index (BMI) was 19.2 kg/m^2 (18.5–24.9). His abdomen was soft, non-tender, and non-distended, and there was no organomegaly. There was no

neurological deficit. There was depression of ST wave in V4–V6 leads and elevation of AVR. Echocardiography showed regional wall motion abnormalities in basal inferior lateral wall in left circumflex coronary artery territory, with fair left ventricular systolic function. Left ventricular ejection fraction was 52% (> 55%).

There was no significant allergy history, medication history, and past or family history, except that he was a known case of diabetes mellitus on medication for 6 years. He reported a family history of mildly reduced HDL-C, with his mother and father demonstrating levels of 24 and 27 mg/dL, respectively. He had no family history of cardiovascular disease. He denied taking prescription medications or over-the-counter supplements. He was not a known alcoholic. No significant findings were seen in examination of the skin, eyes, tonsils, and spleen.

The laboratory blood reports at admission were as follows: high sensitive troponin I > 40,000 ng/L (0–19), NT-proBNP 409.7 pg/mL (0–125), CKMB mass 141.55 ng/mL (0–7), hemoglobin 13.6 g/dL (13–17), red blood cell count 4.47 million/μL (4.5–5.5), packed cell volume 40% (40–50), MCV 89.5 femtoliter (83–101), MCH 30.4 pg (27–32), MCHC 34 g/dL (32–36), RDW 14.4% (11–16), platelet count 1.84 lacs/μL (1.00–3.00), total leucocyte count 15000 per μL (4–10), with neutrophils 84% (40–80), lymphocytes 14.5% (20–40), monocytes 1% (0–1), eosinophils 0.5% (1–6), aspartate transaminase 218 U/L (0–35), alanine transaminase 47 U/L (0–45), gamma glutamyl transferase 28 U/L (0–55), alkaline phosphatase 99 U/L (40–130), total protein 6.1 g/dL (6.4–8.3), albumin 4 g/dL (3.5–5), prothrombin time 13.5 s (11–16), glycosylated hemoglobin 6.5% (4–6%). Random plasma glucose, urea, creatinine, electrolytes, and bilirubin were within reference range. His serology reports were negative for HIV, HbsAg, and HCV. 12–14h overnight fasting serum tested the next morning showed the following results: cholesterol 81 mg/dL (0–200), triglyceride 235 mg/dL (0–150), high-density cholesterol 8 mg/dL (35–65), low-density cholesterol 26 mg/ dL (0–100), thyroid-stimulating hormone 4.6 μIU/mL (0.50–8.90), high sensitive C reactive protein 0.9 mg/L (< 3), homocysteine 10.2 μmole/L (5.46–16.2).

Further investigations revealed the following results: total serum lipids: 888.8 mg/dL (450–800), apolipoprotein A1 94.40 mg/dL (110–205), apolipoprotein B 77.40 (55–140), apolipoprotein B/A1 0.82 (0.35–1.0), lipoprotein [a] 24.90 mg/dL (0–30), apolipoprotein E 0.05 g/L (0.023–0.063). Lipoprotein electrophoresis revealed the following results: beta lipoproteins 46 % (38.6–69.4), pre-beta lipoproteins 34.5% (4.4–23.1), alpha lipoproteins 19.5% (22.3–53.5), chylomicrons absent. Urine albumin creatinine ratio and urine routine examination were within reference range.

NCCT whole abdomen and HRCT CHEST showed no significant abnormality, except thin subpleural band in the right lower lobe.

After proper workup and investigations, transradial coronary angiogram was done under aseptic conditions, which showed triple vessel coronary artery disease. There was 70% lesion in the left anterior descending, 50% lesion in the left circumflex, and 100% lesion in the right coronary artery (chronic total occlusion). Medical management was advised and patient discharged in stable condition. He was prescribed fenofibrate 160 mg/day for 6 months, rosuvastatin 10 mg/day for 6 months, niacin 1 g/day for 6 months, and metformin 500 mg/day sustained release tablets to continue. He was also given antiplatelets clopidogrel 75 mg per day and aspirin 150 mg per day for 6 months. He was advised 30–40-min brisk walk for at least 4 days per week and low cholesterol, low carbohydrate diet.

At 6 months follow-up, HDL was 21 mg/dL, triglyceride 132 mg/dL, LDLC 28 mg/dL, and cholesterol 76 mg/dL. He was advised to continue aspirin and rosuvastatin until the next follow-up.

Discussion

Apolipoprotein A1 (Apo AI) is the major HDL protein (65%) and cofactor for lecithin cholesterol acyl transferase (LCAT). Other proteins in HDL include apoA-II, apoC, apoA-IV, and paraoxonase (PON). Mutation, glycation, and oxidative modification of apoA-I destroy the structural and functional integrity of apoA-I and markedly impair its ability to act as substrates for LCAT. Both PON1 and PON3 are almost exclusively associated with HDL, and reduced function of PON cripples their protection of lipoproteins against oxidative modifications [5].

Evaluation of our patient revealed that he had the risk factors of male gender, type 2 diabetes mellitus, low Apo A1 levels, and extremely low HDL with high (though not severely high) triglyceride levels. He presented with acute myocardial infarction. Low HDL is a cause for residual risk for cardiovascular disease, even at LDL levels below 70 mg/dL [6]. Our patient had LDL value at presentation of 26 mg/dL. Residual risk also arises from established risk factors, such as dyslipidemia, high blood pressure, hyperglycemia, inflammation, and unhealthy lifestyles and emerging or newer risk factors [7].

In pathological conditions like diabetes mellitus, as in our patient, oxidative modification and glycation of the HDL protein occur and the HDL proteome changes into a proinflammatory protein. HDL loses its antiatherogenic properties, including reverse cholesterol transport, and oxidative and anti-inflammatory properties and becomes dysfunctional. The relative composition of lipids and proteins and enzymatic activities associated to HDL, such as paraoxonase 1 (PON1) and lipoprotein-associated phospholipase 11 (Lp-PLA2), are altered [8].

Approximately 10% of individuals with extremely low HDL-C levels are heterozygous for mutations in the genes of APOA1, ABCA1, LCAT, or Apo E gene polymorphisms, although data on the risk of atherosclerosis in these individuals are contradictory [9]. We could not perform mutational studies due to financial constraints. Patients exhibiting

extremely low HDL-C often have severe hypertriglyceridemia (triglyceride > 500 mg/dL). HDL-C of less than 20 mg/dL in the absence of severe hypertriglyceridemia, as reported in our patient, arise from severe perturbations in the metabolic pathways of HDL [3]. Compared to isolated low HDL-C, the risk of CVD is 30 to 60% higher when low HDL-C is accompanied by elevated triglyceride [10].

Extremely low HDL levels in the absence of hypertriglyceridemia have also been reported in Tangier disease, anabolic steroid intake, and autoimmune lymphoproliferative disease [3, 11, 12].

Various strategies for increasing levels of HDL or its components and the rationale for these approaches have been documented. Niacin when prescribed at a dose of 1 to 2 g per day can increase HDL-C levels up to 25% [13, 14]. Fibrate therapy lowers triglycerides while raising HDL-C ≈ 10 to 20% [15], and its effects occur via peroxisome proliferator–activated receptor alpha (PPARα) activation. Statins modestly increase HDL-C by 5 to 10% and offset the risk of very low HDL [16].

Conclusion

Case-control studies have reported that there is significant association of acute coronary events with raised apolipoprotein B, total cholesterol, LDL cholesterol, and non-HDL cholesterol and inverse association with high apolipoprotein A and HDL cholesterol. Subjects with HDL-C levels < 25 mg/dL have been shown to have higher mortality than those with HDL levels 26–49 mg/dL [17]. Further large-scale prevalence studies on extremely low HDL and trend studies of risk factor interrelationships in acute myocardial infarction are required. Physicians should be aware of the high possibility of low HDL cholesterol, especially in patients with type 2 diabetes or the metabolic syndrome, and the best treatment options employed to optimize the lipid profile. There is also a need to find a standard method to evaluate HDL functionality and quality, given the challenges posed by the multifarious roles played by HDL.

Authors' contributions All authors contributed to the study conception and design. Moushumi Lodh and Ashok Kumar Parida performed material preparation, data collection, and analysis. Moushumi Lodh wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability Not applicable.

Compliance with ethical standards

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

Ethics approval Not required for case report.

Consent for participation Informed consent was obtained.

Consent for publication The participant has consented to the submission of the case report to the journal.

Code availability Not applicable.

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LETTER TO THE EDITOR

A global view on prevalence of diabetes and the Human Development Index

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Diabetes is caused by a combination effect of genetic, environmental, and social factors, and the incidence is increasing rapidly, especially in low- and middle-income countries. The burden of diabetes has steadily increased over the last decades across the globe and the Global Diabetes Report of the World Health Organization, 2016, pointed out that approximately 463 million people live with diabetes worldwide [1, 2]. The Human Development Index (HDI) is a summary measure of achievements in three key dimensions of human development: a long and healthy life, access to knowledge, and a decent standard of living. The HDI is the geometric mean of normalized indices for each of these dimensions [3]. In this study, we aim to find the underlying relationship between the HDI scores and the prevalence of diabetes using the general additive model (GAM).

The data was collected from World Health Organization (WHO) reports and United Nations Development Programme (UNDP) reports, including the HDI scores, prevalence of physical inactivity, tobacco use rate, alcohol use rate, and salt/sodium intake rate [4, 5]. According to the UNDP, countries with HDI score above 0.788 ($HDI \geq 0.788$) are regarded as developed, while all others are developing. The HDI score levels were also defined by UNDP as low ($HDI < 0.550$), medium ($0.550 \leq HDI \leq 0.699$), high ($0.700 \leq HDI \leq 0.799$), and very high ($0.800 \leq HDI$) [3]. We constructed a general additive model with physical inactivity, tobacco use, alcohol use, and salt intake to explore the pattern of association between the HDI and diabetes.

Among 182 countries, the prevalence rates of diabetes ranged from 3 to 23%. The highest HDI score was 0.949 and the lowest was 0.352. The prevalence rates of diabetes among male, female, and total population were positively correlated with the HDI, and Spearman's rho values were estimated as 0.508, 0.311, and 0.409 respectively (all $p < 0.001$). Two models were conducted in this study and model 2 included four covariates (physical inactivity, tobacco use, alcohol use, and salt intake). The R squares were improved in model 2, and the values were 0.599, 0.660, and 0.639 among male, female, and total population respectively. Positive linear associations were found, and the regression coefficients were respectively 13.411, 9.835, and 12.419 in the three groups ($p < 0.001$). In addition, the natural cubic smoothing splines were statistically significant ($p < 0.01$).

Generally, S-shaped curve was obtained from the final model. In the three populations, the prevalence of diabetes has a rising trend in low and medium HDI scores, reaching a peak and turning point in the high-HDI range and a downward trend in the very high–HDI range (Fig. 1).

The results indicated that the high prevalence of diabetes was found not only in low- or medium-HDI countries but also in some countries with high HDI and in which the problems are easier to be ignored. Therefore, sufficient attention should be paid to these countries with high HDI, and the inflection point should be moved ahead in order to prevent diabetes better.

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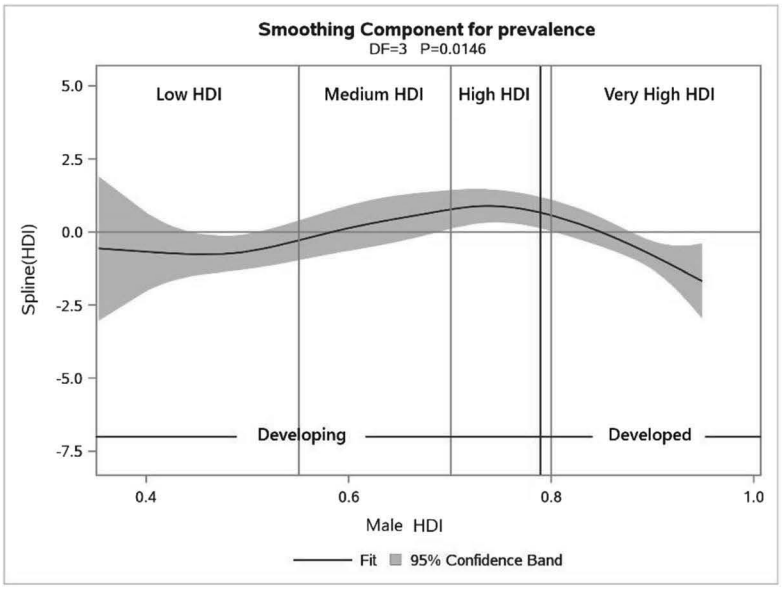

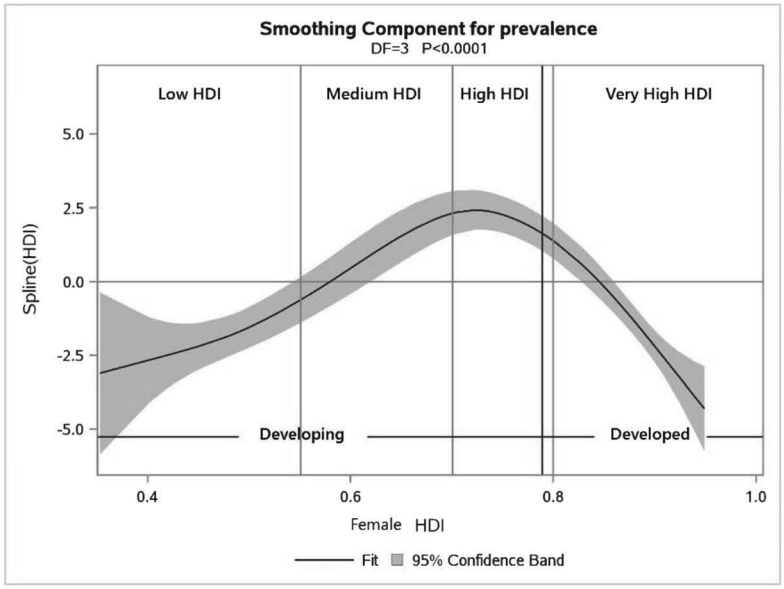

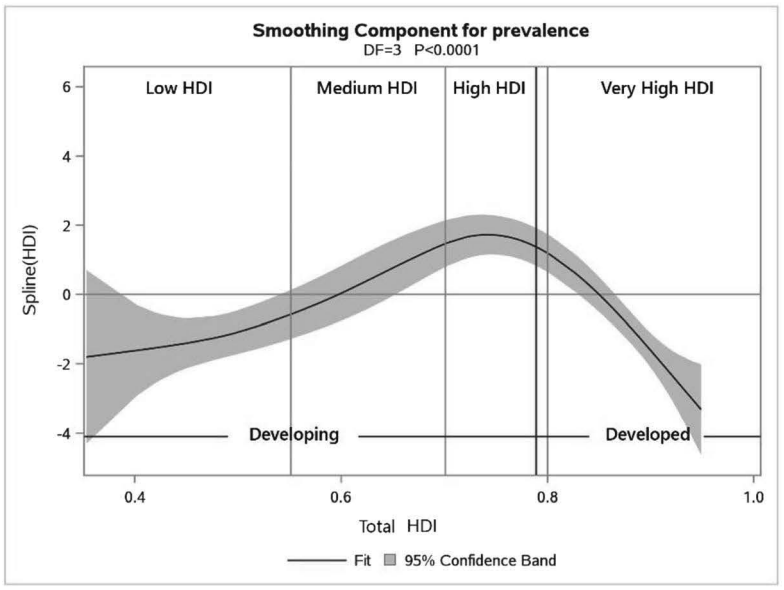

Fig. 1 Smoothing components of spline HDI and prevalence in male, female, and total population

Compliance with ethical standards

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

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EULOGY FOR DR. OM PRAKASH GUPTA,
BRILLIANT DIABETOLOGIST, TEACHER AND MENTOR

This is our chance to say 'thank you' to a man who is a symbol of diabetes in India of the past, present, as well as of the future. Born in December 1929, Dr. Om Prakash Gupta had a bright, unstoppable, career, securing first position in MBBS from Agra University, passing MD (Medicine), MRCP (Endocrinology-UK) and MS (Medical Education-USA) in first attempts and receiving FRCP (UK) for his outstanding contributions with a winning spree of 26 medals, prizes and awards during his undergraduate, postgraduate and later career. Little did anyone know at that stage that Dr. Gupta was to become a doyen of diabetology in India!

We all affectionately remember Dr. Gupta in our own different ways; yet there was always something common amongst us. To all of us, he was the epitome of humility, gentleness and level-headedness which underpinned all his other wonderful attributes. He touched the lives of his countless colleagues, students and mentees. He had such an extraordinary appeal and was so great a towering personality, that any person who attempts to describe Dr. Gupta's greatness would find it difficult to do full justice to him.

His contemporaries and compatriots and whosoever had come in contact with him, will recollect Dr. Gupta's pivotal role not only in promoting the discipline of diabetology but also in the fields of teaching, patient care and administration. After a short stint as Assistant Professor of Medicine at All India Institute of Medical Sciences, New Delhi, he had a rapid, but tranquil, ascent to the highest positions any medical doctor could aspire for. His appointment as Professor and Head of the Department of Medicine at the young age of 31 and Dean (Principal) of B, J. Medical College at Ahmedabad which was soon followed by his appointment as Director, Medical Education and Research and as Director, Health and Medical Services, Medical Education and Research, Government of Gujarat serve as a testament to Dr. Gupta's professional attributes. Apart from being a much sought after physician, diabetologist and endocrinologist (both among the elite and the downtrodden alike), Dr. Gupta had successfully added a valuable sheen to his professional career by publication of a large number of research papers and book chapters. His skills were also made abundantly clear through numerous orations, national and international awards, and several recognitions. To name a few, these were the Government of India Fellowship for advanced training and research in Endocrinology at the Royal Post Graduate Medical School and

associated Hammersmith Hospital in London, England, WHO Fellowship for medical educational technology at University of Southern California, USA, the prestigious B C Roy Award from the Medical Council of India and the training received at world renowned Joslin Clinic in Boston, USA, among several other glorious achievements. Furthermore, Dr. Gupta's continuing engagement as a consultant physician and diabetologist for over 30 years, even after his formal retirement, speaks volumes about his commitment towards his patients.

Dr. O.P. Gupta's seminal paper published 50 years ago titled 'A survey of the prevalence of diabetes mellitus by means of a house to house survey in Ahmedabad (Gujarat), India' came just before the first collaborative nation-wide study on Epidemiology of Diabetes Mellitus began under the sponsorship of the Indian Council of Medical Research (ICMR). Indeed, it is fair to state that Dr. Gupta's publication was one of the papers which ignited the interest of Indian diabetologists in the field of diabetes epidemiology. When the Research Society for the Study of Diabetes in India (RSSDI) was established in 1972, Dr. Gupta was invited to lead this organization as its first President. Not only did he motivate youngsters to join the RSSDI, but, for the next half a century, he ensured his own participation in practically every annual RSSDI scientific meeting. Same was the story with regard to his participation in successive Diabetes Congresses of International Diabetes Federation (IDF) held all over the world. He was also appointed as the Chairman of the ICMR Expert Committee on Endocrinology for two years from 1972 to 1974 during which he coordinated and guided the Committee Members regarding the large number of research proposals submitted to ICMR for funding. Though an astute scientist, Dr. Gupta was open to all ideas. His work on Ayurveda drugs in diabetes reflects his inquisitiveness to explore new directions.

Sadly, Dr. Om Prakash Gupta left for his heavenly abode in April, 2021 but not without brightening our lives, not without serving countless patients and organizations and not without enlightening our way into the future of science and humanity. Dr. Gupta is survived by his wife and a daughter. All we can say that a glory has departed but he will live on in our hearts, forever. Let us feel beholden to our association with this gracious and mighty person and be worthy of him.

Dr. Vinod Kumar, Patron, RSSDI
Dr. V. Mohan, Patron, RSSDI

Dated: May 5th, 2021

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

NEW EXECUTIVE COMMITTEE AND OFFICE BEARERS 2021

Patrons of RSSDI

Dr. H.B. Chandalia, Mumbai
Dr. C. Munichhoodappa, Bengaluru
Dr. Ashok K. Das, Puducherry
Dr. Binode K. Sahay, Hyderabad
Dr. V. Seshiah, Chennai
Dr. P.V Rao, Hyderabad
Dr. Jitendra Singh, New Delhi
Dr. V Mohan, Chennai
Dr. Vinod Kumar, New Delhi

President

Dr. Banshi Saboo, Ahmedabad

President Elect

Dr. Ch.Vasanth Kumar, Hyderabad

Immediate Past President

Dr. Rajeev Chawla, New Delhi

Secretary

Dr. Sanjay Agarwal, Pune

Vice-President

Dr. Anuj Maheshwari, Lucknow

Vice-President

Dr. Vijay Viswanathan, Chennai

Joint Secretary

Dr. Sujoy Ghosh, Kolkata

Treasurer

Dr. Sunil Gupta, Nagpur

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Dr. Sudhir Bhandari, Jaipur
Dr. J K Sharma, New Delhi
Dr. Bikash Bhattacharjee, Guwahati
Dr. Pratap Jethwani, Rajkot
Dr. L. Sreenivasa Murthy, Bengaluru
Dr. Sanjay Reddy, Bengaluru
Dr. Shalini Jaggi, New Delhi

Co-opted

Dr. Vijay Panikar, Mumbai
Dr. Brij Makkar, New Delhi
Dr. Rakesh Sahay, Hyderabad

TRAINEE GRANTS (Up to 10 grants)

Research Grants upto INR 200000 to support outstanding thesis/ research work by first year MD/DNB/ PHD students/Research fellows from India.

Eligibility Criteria
All Postgraduates in First year MD, DM /DNB from any of the institutions in the country are eligible to apply

How to apply?
Send in your Research proposals by email to the RSSDI Secy/ Chairman research committee by email/ apply directly on web site.

Research proposal should have following proofs-

1. A supporting letter from your guide/ head of department stating that this is a bonafide project for your thesis and also mentioning the dates of you joining the program and expected date of graduation. The guide must also state that he/she will stand guarantee for the work done
2. A detailed budget
3. Thesis proposal approved by the department/appropriate institutional authority
4. Approval by the ethics committee

Selection Process
Proposals will be reviewed by the research committee of the RSSDI.

Disbursement of Grant
A minimum of 50% of the grant amount will be disbursed initially. Further disbursement will be done annually based on submission of progress reports on the work done and utilisation of sanctioned amount. These reports must be filed to the secretary of the RSSDI

Responsibility:
All grant awardees are expected to present their work at RSSDI Annual Conference during research presentation's session. Failure to file progress reports annually and when requested by the RSSDI and failure to present progress at RSSDI Annual conf may result in the forfeiture of the grant.

All awardees are expected to follow the tenets of responsible and ethical conduct of research. Unethical or fraudulent use of RSSDI research funds will warrant adverse action from the society including

forfeiture of grant, black listing in the society's databases and other legal recourses that are available to the society.

Publication
The RSSDI expects that the grant source be acknowledged in all publications and submissions made with regards to the research done with the grant.

All awardees are encouraged to submit their work to the RSDDI Journal IJDDC

CALL for RESEARCH PROPOSALS for GRANTS (up to 5 lacs)

Research proposals are invited from Indian scientists, who are members of RSSDI interested in conducting research in the field of Diabetes, Endocrinology& Metabolism, for funding by RSSDI

The proposals may of clinical or translational research importance. A maximum grant amount of INR 5 Lakhs will be sanctioned. All grants will be reviewed by the research committee.

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 & bibliography.

Brief biodata of principal investigator and other co-investigators.

Importance of work
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.

Ethics Committee clearance of the Institution or other bonafide body.

How to apply
All applications should be addressed to:
1. The Secretary , RSSDI
2. Soft copy of the research proposal should be sent to Secretary, RSSDI

When to apply
Proposals will be accepted Twice a year. Once between 1st Jan - 31st April & then July 1st to 30th Nov.

All research proposals will be reviewed by Research committee over a period of 4-6 weeks & approved proposals will be provided Research Grant after fulfilling all documentation by 30th June & then 31st December of each year.

MAJOR RESEARCH GRANT PROPOSALS- usually not more than one at a given time.

Above 10 Lacs upto a total amount of 50 Lacs will be Granted to RSSDI initiated, owned, multi-centric, clinical or translational research, having long term application of scientific and clinical findings, which can translate into strategies for improving health-care delivery, patient outcomes, and community health in India.

Such research proposals will be carried out in only centres with research capabilities across India.

TRAVEL GRANTS FOR YOUNG DIABETES RESEARCHERS TO ATTEND INTERNATIONAL CONFERENCES

Criteria 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

List of RSSDI Accredited Centres

Sl. No	Institute Name	Institute Location
1.	Diacon Hospital	Bangalore, Karnataka
2.	North Delhi Diabetes Centre	New Delhi, Delhi
3.	Prithvi Hospital	Tumkur, Karnataka
4.	Total 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.	Sunil's Diabetes Care N' Research Centre	Nagpur, Maharashtra
10.	Marwari Hospital and Research Centre	Guwahati, Assam
11.	Down Town Hospital	Guwahati, Assam
12.	St.Theresa's Hospital	Hyderabad, Telangana
13.	Aegle Clinic	Pune, Maharashtra
14.	Lilavati Hospital & Research Centre	Bandra West, Mumbai
15.	Srajan Hospital	Udaipur, Rajasthan
16.	Endeavour Clinics & Dr. Sambit's Centre of Diabetes and Endocrinology	Bhubaneswar, Odisha
17.	ILS Hospital, Salt Lake	Salt Lake City, Kolkata
18.	Belle Vue Clinic	Dr. U N Brahmacahri Sreet, Kolkata
19.	Arthur Asirvatham Hospital	Mdurai, Tamil Nadu
20.	M V Hospital for Diabetes	Chennai, Tamilnadu
21.	Sarvodaya Hospital and Research Centre	Faridabad, Uttar Pradesh
22.	Galaxy Speciality Centre	Sodala, Jaipur

carefully looked into all aspects of this course & has accredited & recognized 22 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.

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 !

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.

Dates for Admission in ACCD 2021

1) Last date of submission of Application Form – 30th June 2021
2) Screening Interview - 7th July 2021
3) Declaration of Interview Result – 10th July 2021
4) Last date of payment of course fee - 15th July 2021
5) Commencement of course - 16th July 2021

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.

49th Annual Conference of RSSDI-RSSDI 2021

Date: 11th - 14th November 2021

Registered with Registrar of News Papers, India vide no. RNI-43019/85

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