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Incorporating Diabetes Bulletin

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The prevalence of metabolic syndrome in South Asia: a systematic review

Nirmal Aryal[1] · **Sharada P. Wasti**[2]

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Abstract The objective of this study was to estimate the prevalence of metabolic syndrome and its individual components in South Asia region. A search was conducted on PubMed, Scopus and OvidSP (MedLine and EMBASE) using the term 'metabolic syndrome', 'prevalence' and the name of each South Asian country for studies published on or after the year 2000. Reference lists and citation references of the included papers were also checked. Eligibility criteria were mainly population-based studies on both gender and healthy participants aged ≥18 years. Four definitions of metabolic syndrome were considered: the World Health Organisation (1999), Third Adult Treatment Panel (2001) and its modified version (2005) and International Diabetes Federation (2005). A total of 558 papers were retrieved from all sources, of which 16 relevant studies were identified comprising 14,515 males (44.1 %) and 18,390 females (55.9 %). The weighted mean prevalence of metabolic syndrome was 14.0 % (WHO), 26.1 % (ATPIII), 29.8 % (IDF) and 32.5 % (modified ATPIII). Low levels of HDL cholesterol and hypertension were prevalent in half of the study population. Overall, females had a higher prevalence of MS under all definitions except WHO. Females were more likely to have low levels of HDL cholesterol (68.8 vs 37.9 %) and central obesity (47.9 vs 37.9 %), whereas males were comparatively more hypertensive (42.3 vs 38.1 %). Despite the high rates of metabolic risk factors, research is extremely sparse in South Asia preventing knowledge of actual burden. Along with the increased access to clinical intervention, prevention strategies should be intensified with special attention to females.

Keywords Metabolic syndrome · Prevalence · Cardiovascular disease · South Asia

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Introduction

Metabolic syndrome (MS) refers to the constellation of risk factors related to cardiovascular disease (CVD) and diabetes. MS represents the clustering of mainly hyperglycaemia, hypertension, dyslipidemia and central obesity. These metabolic factors are co-occurring, inter-related and commonly share underlying causes, features and mechanisms [1]. Patients with MS are at two-fold risk of developing CVD over a period of 5 to 10 years and at five-fold risk of having type 2 diabetes compared to individuals without MS [2]. The major advantage of MS is not to function as a risk assessment tool, but rather to identify patients with a shared pathophysiology who are at high risk of developing CVD and diabetes [3]. MS also helps to induce and intensify lifestyle changes in clinical practice [4].

The prevalence of MS is high worldwide—35 % in the USA [5], 24.9 % in Latin America [6] and in the range between 20.7 and 37.2 % in the Gulf countries [7] under the Adult Treatment Panel (ATP III) criteria. South Asia is home to nearly one fourth of the world population and has the highest absolute burden of CVD in the world [8]. Also, CVD mortality rates in this region are higher than those in Western and East Asian countries [9]. The Global INTE

RHEART study reported that CVD prevails at a younger age in South Asians than in any other population [10].

The burden of CVD and its risk factors are escalating alarmingly in South Asia. For example, the global burden of disease has projected that India alone will have the highest number of individuals with CVD than in any other region by the year 2020 [11]. Likewise, the prevalence of MS components such as obesity, hypertension, dyslipidemia, along with lifestyle factors such as smoking is increasingly high in this region [9].

With this backdrop, the aims of this systematic review are to identify robust epidemiological evidence of MS in the South Asia region and to estimate the prevalence of MS and its individual components.

Methods

Inclusion and exclusion criteria

The main inclusion criterion was English language full text articles published on or after the year 2000 to July 2013. Likewise, only population-based studies on apparently healthy subjects aged ≥18 years, consisting both genders and sample size of more than 500, were included. Studies on patients, targeted to particular occupational groups, conducted in hospital settings and among South Asian immigrants were excluded.

Search and selection methods

The search yielded a total number of 558 papers: 369 from PubMed, 133 from Scopus, 49 from OvidSP (MedLine/EMBASE) and 7 from reference search. A search was conducted in three major biomedical databases: PubMed, OvidSP (MedLine and EMBASE) and Scopus. The search terms 'prevalence' and 'metabolic syndrome' were combined with the name of each South Asian country: Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka. Studies were searched by titles and/or abstracts. Other search terms for 'metabolic syndrome'—'metabolic syndrome X', 'syndrome X', 'insulin resistance syndrome X', 'Reaven Syndrome X'—were also considered. In addition, reference lists were also scrutinized to find relevant published articles.

Study characteristics

This systematic review examined a total of 16 studies comprising 14,515 males (44.1 %) and 18,390 females (55.9 %). Ten studies were conducted in India [12–21], two each in Sri Lanka [22, 23] and Bangladesh [24, 25] and one each in Pakistan [26] and Nepal [27]. Eight studies were carried out in urban settings [12–15, 18, 19, 21, 22], three in rural [24–26], four in both urban and rural [16, 17, 20, 23], and one study did not mention setting [27]. No single study was found from Maldives, Bhutan or Afghanistan. Fifteen included studies that were cross-sectional and one was longitudinal. Ten studies mentioned the study year, out of which six were conducted between 2005 and 2010. Three studies had a participant range of 500–1000, nine had between 500 and 2500 participants and four studies had more than 2500 participants.

Thirteen studies selected study participants by randomized sampling method, whereas in two studies [21, 27], they were selected non-randomly. The response rate of the participants varied from 61.3 to 98.2 %.

The detailed summary of the included studies is presented in the supplementary material 2.

Data extraction and quality appraisal

A data extraction form was developed using the Centre for Reviews and Dissemination guidance template [28]. The data form recorded basic information (authors, study year, title of paper, journal details), detailed information of each short-listed article (study design, study location, study objectives, study population, sample size, key findings), and finally the reviewers comments. The accuracy of the extracted data was double checked, and amendments were made. The quality of the studies was assessed using the Critical Appraisal Skill Program (CASP) checklist for systematic reviews [29].

The flow diagram of article selection process is shown in Fig. 1.

Definitions

This study considered the four key definitions of MS: the World Health Organisation (WHO, 1999) [30], the National

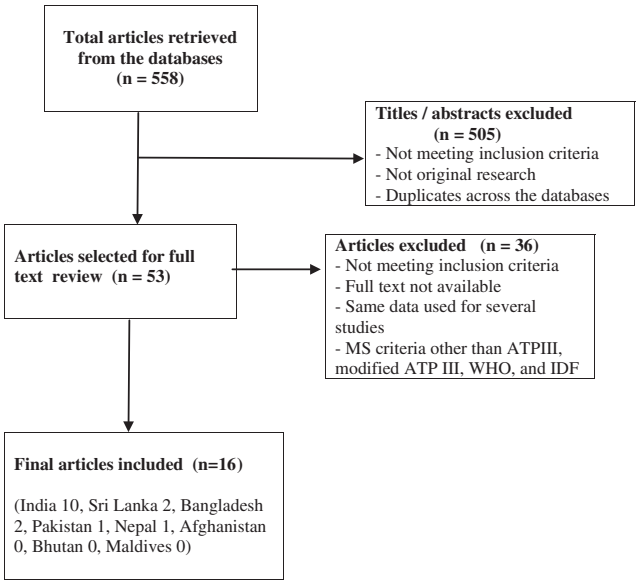

Fig. 1 Flow diagram for selection of the articles

Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII,2001) [31], and its modified version 2005 [32], and the definition defined by the International Diabetes Federation (IDF, 2005) [33]. These definitions mostly consisted of fasting glucose, blood pressure, triglycerides, high-density lipoprotein cholesterol (HDL) and obesity as components. However, these definitions vary in cut-off points and have differences in the terms of prioritizing certain components. Details of these definitions are presented in the supplementary material 1.

Use of MS definitions

Four studies used ATP III definition only [14, 15, 20, 25], three studies considered modified ATP III definition only [13, 18, 21] and one study used IDF definition only [23]. Likewise, three studies followed ATP III and IDF definitions [16, 26, 27], one study followed modified ATP III and IDF definitions [22] and one study considered ATP III and modified ATP III definitions [17]. Further, one study each used WHO, ATP III and IDF definitions [12]; WHO, modified ATP III and IDF definitions [24]; and ATP III, modified ATPIII and IDF definitions [19].

We calculated mean prevalence (weighted) of MS and its individual components as follows: sum of number of cases in all or relevant studies/sum of number of participants in all or relevant studies × 100. In a few studies, prevalence data were available only in certain categories, mainly by gender, urban and rural setting and ethnicity. In such cases, we calculated the overall prevalence by combining the existing data. The sex standardized mean prevalence of MS was calculated considering total study participants as a standard population.

Results

Prevalence of metabolic syndrome

The mean prevalence of MS (weighted) was 26.1 % (ATP III), 29.8 % (IDF), 32.5 % (modified ATP III) and 14.0 % (WHO). By any definitions, the prevalence ranged from 8.6 to 46.1 %. The sex standardized mean prevalence of MS was 25.4 % (ATPIII), 28.8 % (IDF), 36.2 % (modified ATPIII) and 13.9 % (WHO). The weighted mean prevalence of MS and its individual components are shown in Table 1.

The prevalence of MS was highly reported in the Punjabi community in India (35.8 %) [19] by ATP III criteria; in rural area of Pakistan (40.0 %) [26] by IDF criteria; in Colombo, Sri Lanka (46.1 %) [22] by modified ATP III criteria; and in Chennai city, India (23.2 %) [12] by WHO criteria.

The weighted mean prevalence of MS was higher in females than that in males [ATP: 29.5 vs 22.1 %; IDF: 34.3 vs 18.8 %; modified ATP III: 35.8 vs 28.8 %], except when considering the WHO definition (12.8 vs 15.6 %). The gender difference in the prevalence of MS was more pronounced in rural areas of Pakistan [26] where the difference in the prevalence was 37 % by the IDF criteria (males, 13 %; females, 50 %) and 20 % by ATP III criteria (males, 20 %; females, 40 %). However, examining the studies individually, only one study under ATP III criteria [15], none of the studies under IDF criteria, three studies under modified ATP III criteria [13, 17, 21], and one study under WHO criteria [12] reported higher prevalence in males. The prevalence of MS was found nearly two-fold higher in males than in females in a study carried out in Mumbai city, India [21].

Seven studies [14, 15, 17–19, 22, 23] reported age-adjusted prevalence, of which four [14, 18, 19, 23] studies compared it with crude prevalence. Age-adjusted prevalence was lower in all of the studies.

Nine studies provided prevalence of MS by age group. In eight studies [14, 15, 18, 19, 22–24, 27], the prevalence was observed to be increased with the increment in age, and it was highest in the age group above 50 years. However, an Indian study [21] demonstrated fairly equal prevalence in the age group 20–40 and 41–60 years (20.6 and 20.7 %, respectively) and decrement in the subjects older than 61 years.

The weighted mean prevalence of MS in the countries of South Asia is presented in Fig. 2.

Prevalence of individual components of MS

Nine studies [12–14, 16–19, 22, 27] provided all individual components of MS, whereas five [15, 20, 21, 23, 26] provided some of them, and two [24, 25] provided none. Four studies [14, 15, 21, 26] analysed individual components of MS by age group.

Low HDL cholesterol

Fourteen studies reported the prevalence of low levels of HDL cholesterol. The weighted mean prevalence was 57.9 %. The prevalence range was 31.6 % [22] to 79.6 % [26]. In seven studies [12, 14, 17, 20, 23, 26, 27], low HDL cholesterol was found in more than half of the study participants. Eleven studies reported the prevalence by gender which provided weighted mean prevalence of 37.9 % for males and strikingly 68.8 % for females. All of the studies showed higher prevalence in females than in males. Four studies presented the prevalence of low levels of HDL cholesterol with age group. In general, the prevalence trend was observed to be higher in younger age groups for both genders. A Pakistani [26] and Indian [21] study identified a highest prevalence in the youngest age group (20–40 years). An Indian study [15] reported highest in the age group of 30–39 years in both genders, whereas another Indian study [14] reported highest in the age group

Table 1 The weighted mean prevalence of metabolic syndrome and individual components

Variables	Male (%)	Female (%)	Total (%)	Range (%)
MS definition				
ATP III	22.1	29.5	26.1	18.3–35.8
IDF	18.8	34.3	29.8	11.2–40.0
Modified ATPIII	28.8	35.8	32.5	19.5–46.1
WHO	15.6	12.8	14.0	8.6–23.2
Individual MS components				
Low HDL-C	37.9	68.8	57.9	31.6–79.6
Hypertriglyceridemia	37.2	36.1	37.2	25.2–55.1
Hyperglycaemia	27.9	27.6	28.9	9.2–65.1
Hypertension	42.3	38.1	48.5	21.2–81.1
Adbominal obesity	11.2	29.8	23.4	10.0–70.9
Abdominal obesity (South Asian cut-off)	37.9	47.9	43.2	21.6–60.3

of 30–39 years among females and in 40–49 years among males. The mean value of HDL cholesterol in males and females was given in four studies, out of which three [15, 17, 22] documented higher values in females, one [16] reported higher in males, one [26] showed similar value in both.

Hypertriglyceridemia

The weighted mean prevalence of hypertriglyceridemia was 37.2 %. Thirteen studies included the prevalence of high levels of triglycerides in the range varying from 25.2 % [12]

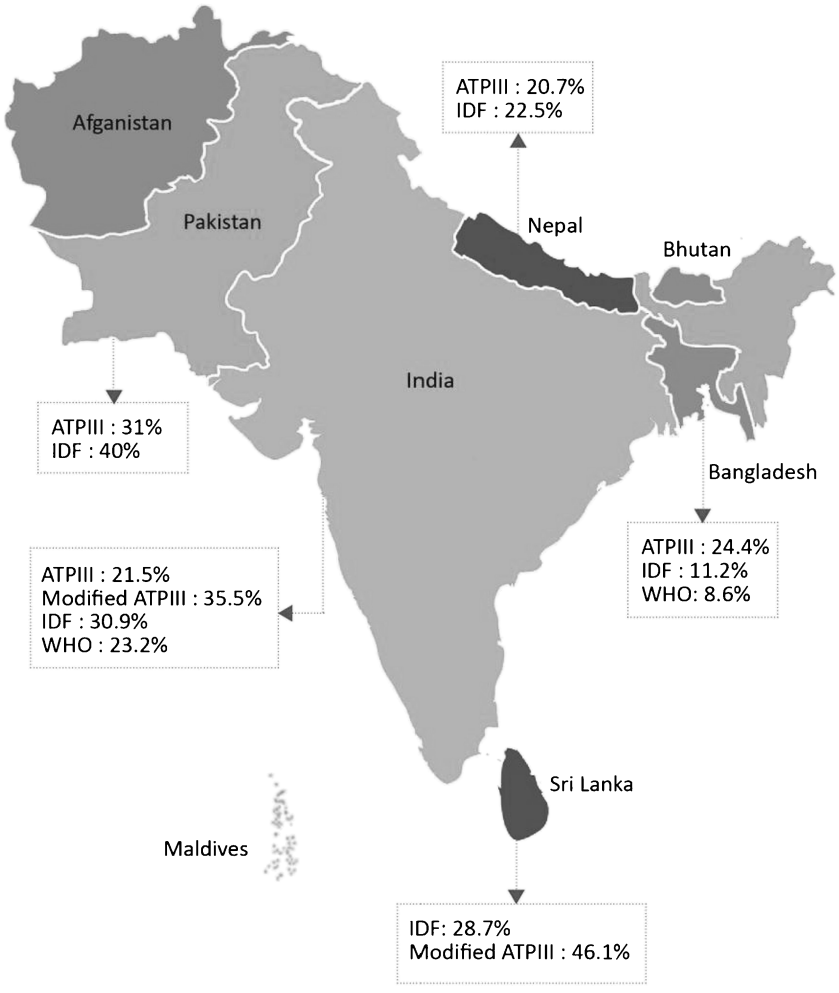

Fig. 2 The weighted mean prevalence of metabolic syndrome by country of South Asia

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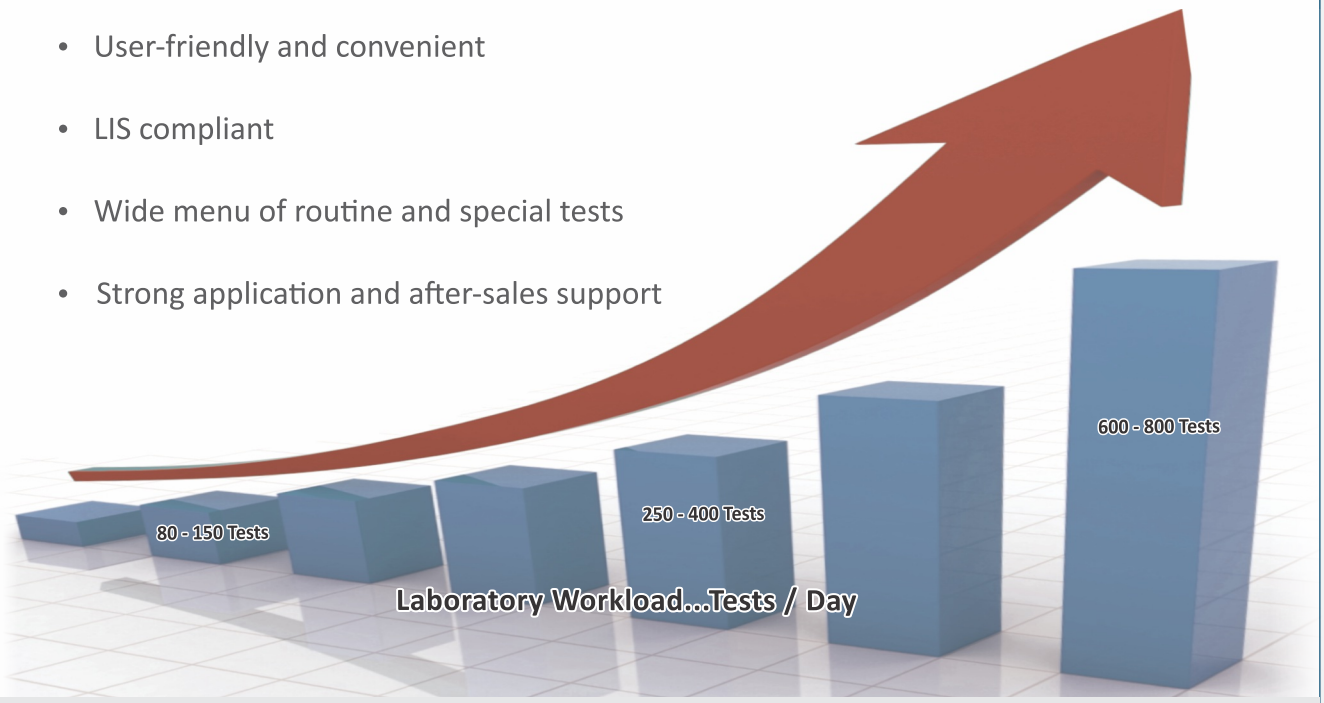

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to 55.1 % [23]. The weighted mean prevalence was marginally higher in males (37.2 %) than that in females (36.1 %). Eleven studies provided the prevalence of hypertriglyceridemia by gender; however, only three studies [19, 20, 26] showed higher prevalence of triglyceride in females. According to age groups, hypertriglyceridemia was mostly observed among participants in middle age of 40–60 years for both genders.

Hyperglycaemia

The prevalence of hyperglycaemia was given in 11 studies. The weighted mean prevalence was 28.9 %, and the prevalence range was between 9.2 % [17] and 65.1 % [22]. Ten studies described the prevalence by gender which demonstrated that males and females had fairly equal weighted mean prevalence (males 27.9 % vs females 27.6 %). While considering individual studies, only three [18, 19, 26] reported higher prevalence in females. For both genders, increased prevalence of hyperglycaemia was observed with increasing age.

Hypertension

Nine studies provided the prevalence of hypertension with the weighted mean prevalence of 48.5 %. This prevalence varied from 21.2 % [13] to 81.1 % [23]. Males had higher weighted mean prevalence of hypertension compared to females (males, 42.3 %; females, 38.1 %). Among the eight studies which showed gender wise prevalence, only two studies [17, 22] reported slightly higher prevalence in females than that in males. Hypertension was found increase along with increasing age for both genders.

Abdominal obesity

The prevalence of abdominal obesity was presented in 11 studies. Not considering the South Asian cut-off point, the weighted mean prevalence was 23.4 %, in the range of 10.0 % [27] to 70.9 % [21]. Females had nearly three times higher weighted mean prevalence than males (females, 29.8 %; males, 11.2 %). Gender wise prevalence was shown in six studies, and females had decidedly greater prevalence in all of these. The difference in the prevalence was at least 9.5 % [17] and 29.3 % [19] in maximum.

Moreover, the weighted mean prevalence of abdominal obesity increased sharply to 43.2 % while considering the South Asian cut-off point for waist circumference (male, ≥90 cm; female, ≥80 cm) [33]. Six studies [13, 16–19, 22] presented abdominal obesity with the South Asian cut-off point. According to this cut-off, females had considerably higher weighted mean prevalence (females 47.9 % vs males 37.9 %). Similarly, by age group, abdominal obesity was observed highly prevalent among middle age (40–60 years) participants for both genders. Six studies reported the mean value of WC by gender, of which five [13, 15–17, 22] noted higher mean value in males, but one [26] showed higher in females.

Urban and rural difference

The weighted mean prevalence of MS in urban areas was higher than in the rural areas by all definitions except WHO (ATPIII, 28.7 vs 21.6 %; modified ATPIII, 38.8 vs 11.7 %; IDF, 34.1 vs 19.2 %; and WHO, 23.2 vs 30.7 %). The difference was more striking in modified ATPIII criteria. In both settings, females had usually higher weighted mean prevalence of MS than in males. Table 2 shows the weighted mean prevalence of MS by urban and rural setting for both genders.

Discussion

The findings of this review suggest that more than one quarter of the participants had MS, with more propensity in females. South Asians residing in urban areas had markedly higher prevalence of MS, in both genders. Low levels of HDL-cholesterol were found in nearly 70 % of females and were more prevalent in young people of both genders. Another striking finding was that hypertension was observed in nearly half of the participants and central obesity in more than one third. Further, we found that males were more likely to have increased levels of hypertension, whereas females were

Table 2 The weighted mean prevalence of metabolic syndrome in urban and rural setting

MS definitions	Male (%)	Female (%)	Total (%)
ATPIII			
Urban	23.9	33.2	28.7
Rural	16.7	24.8	21.6
Modified ATPIII			
Urban	34.6	42.9	38.8
Rural	11.9	11.6	11.7
IDF			
Urban	25.8	41.1	34.1
Rural	10.4	24.7	19.2
WHO			
Urban	27.3	19.7	23.2
Rural	30.0	31.1	30.7

comparatively more likely to have low levels of HDL-cholesterol and central obesity.

Our findings indicate that the prevalence of MS in South Asia stands neither in a lower position nor in a higher position across the globe, while comparing it with the systematic reviews or best available studies from other parts of the world. Our findings are fairly similar to the results of systematic reviews of Latin American countries [24.9 % (ATP III)] [6], a nationally representative study of Australia [22.1 % (ATP III), 30.7 % (IDF)] [34] and combined prospective studies of Europe [15 % (WHO)] [35]. In contrast, our study reported distinctly higher prevalence than in the African studies (0 to 7.9 % by any definitions) [36, 37], and a nationally representative study of Eastern Asia (China) [13.7 % (ATP III)] [38]. However, our figure is lower than the prevalence identified in a national survey of America [35 % (ATP III), 39 % (IDF)] [5] and in a systematic review of the Gulf countries [20.7–37.2 % (ATP III), 29.6–36.2 % (IDF)] [7].

This study demonstrated low HDL cholesterol as the most frequent individual component of MS with weighted mean prevalence of 57.9 %, and considerably higher among the females. A Latin American systematic review [6] also displayed highest prevalence of low HDL cholesterol (62.9 %), and also at greater proportion among the females, but the gender difference was much wider in our finding. Hypertension was shown to be the most prominent MS component in Europe (63.5 %) [35] and in Eastern Asia (41.2 %) [38]. Central obesity, which was the third most prevalent MS component in our study (44.5 %), was the most prevalent one in the USA (38.6 %) [5] and in Africa [37].

The underlying factors behind the high prevalence of dyslipidemia, hypertension and central obesity among South Asians could be multifarious. However, an increasing trend of urbanization and predilection towards 'westernized' lifestyle are mainly implicated [39–41], which could influence glucose intolerance, abdominal obesity and dyslipidemia. Misra et al. [42] suggested the possible role of body composition in the genesis of atherogenic dyslipidemia among South Asians. They argued that a higher percentage of body fat, excess truncal fat and increased intra-abdominal fat accumulation may be linked with insulin resistance and consequent dyslipidemia. Moreover, the INTERHEART study also found lower prevalence of protective factors in South Asian controls compared with controls from other countries (moderate or high intensity exercise, 6.1 vs 21.6 %; daily intake of fruits and vegetables, 26.5 vs 45.2 %) [10].

Some of the studies showed a genetic susceptibility of South Asians to central obesity and MS [43], low levels of HDL-cholesterol [44] and serum lipids and obesity [45]. Moreover, some genetically based hypotheses have also been postulated which may explain South Asians propensity to central obesity, namely 'the thrifty genotype' [46], 'the thrifty phenotype' [47], 'adipose tissue compartment overflow hypothesis' [48], 'variable disease selection hypothesis' [49] and 'the mitochondrial efficiency hypothesis' [50]. The vast majority of these genetic studies were limited to Indians and migrant Indian populations. In addition, the prevalence of MS among migrant South Asians living in western countries was also higher when compared with multiple ethnic group populations [51, 52] which suggests that modifiable correlates of MS may not be solely responsible for its increasing rates.

In this study, higher prevalence of MS in females was found compared to males. This finding can be partly explained by the explanation that culturally South Asian females are mostly engaged in the household tasks and have a more sedentary lifestyle than males. South Asian women also have poor access to the health services resulting in both late diagnosis and poor management of the disease [53].

Limitations of this review included not being able to search grey literature, only considering articles published in English language on or beyond the year 2000, and heterogeneity in the methodological quality of the studies (mainly discrepancies in measuring waist circumference and some variations in the cut-off value). Similarly, we could not rule out the possible bias due to the disproportionately higher representation of Indian studies. The main strength of this review is that we explored three major medical databases PubMed, OvidSP (MedLine and EMBASE) and Scopus. Also, we considered the most common definitions of MS.

Conclusion

South Asian countries have witnessed increasing burden of risk factors and diseases related with metabolic root. Nonetheless, they are grappling with limited health care resources and capacity. The actual burden of MS in South Asia is still obscure because none of the South Asian countries have nationally representative studies. The research environment should be consolidated, and research capacity should be strengthened. This systematic review suggests that MS is very common in this region and deserves urgent attention from both the clinical and public health viewpoint. Along with affordable and increased access to medical treatment, an intensified approach on primordial and primary prevention of metabolic disorders should be the utmost priority for South Asian countries, with special attention to females. Finally, heterogeneity of included studies limits our ability to conduct a meta-analysis. This needs to be addressed in the future.

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ORIGINAL ARTICLE

Lack of knowledge about diabetes in Pune—the city of knowledge!

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Abstract India is experiencing an escalating epidemic of diabetes for which the most cost-effective solution is prevention. Awareness is the first step towards prevention. We undertook a questionnaire-based study to evaluate gaps in awareness of different implications of diabetes among various sections of the urban population of Pune. Individuals aged ≥13 years (378 diabetic, 1122 non-diabetic) from different socio-economic backgrounds were interviewed using a structured questionnaire. Awareness regarding causes, symptoms, complications, treatment and preventive measures, curability of diabetes and long-term implications of diabetes in pregnancy was evaluated. An awareness score was calculated based on the percent of total questions correctly answered. Of those surveyed, 78 % scored less than 50 %, 44 % did not know the meaning of diabetes, 30 % could not name any of the risk factors, symptoms, complications and preventive measures for diabetes, and 70 % were unaware of the long-term risks of diabetes in pregnancy. As a group, diabetic participants scored marginally better than non-diabetic participants (mean score 39 vs. 31 %; $P<0.001$). Participants at high risk of diabetes (sedentary workers, non-diabetic participants with first-degree family history of diabetes and non-diabetic hypertensive participants) had poor knowledge about the condition (mean scores <40 %). Lower age, lower education and male gender were independently associated with poor awareness; education was the strongest predictor. Awareness regarding different implications of diabetes is poor in the population of Pune. There is a need for widespread and extensive public education campaigns to raise awareness and contribute to the national diabetes prevention initiatives.

Keywords Diabetes · Awareness · Diabetes education · India

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Introduction

India is one of the diabetes capitals of the world and had 65.1 million people with type 2 diabetes mellitus (T2D) in 2013; this number is expected to reach 109 million by 2035 [1]. It is estimated that half of those who have diabetes are unaware of their condition [1]. In addition, 77.2 million have pre-diabetes [2]. The rise in diabetes has been partly attributed to the rapid socio-economic and nutritional transition occurring in India, mostly in urban areas, reflected by energy-dense diets, physical inactivity and stress [3]. Indians develop diabetes at a younger age and at a lower body mass index compared to western populations [4]. In addition, younger women in urban India are increasingly developing gestational diabetes mellitus (GDM) with implications for future generations. As the epidemic affects young and economically productive groups, it has significant socio-economic consequences for patients, their families and society. It is estimated that treatment and other related expenditure

amounts to INR 19914 per person with diabetes per annum [5].

The conventional thinking is that diabetes results from an interaction between genetic susceptibility and precipitating factors such as diet, physical inactivity and obesity. Therefore, preventive measures have included modification of lifestyle. This can only be achieved if individuals are aware about various implications of diabetes. Assessing awareness of diabetes in the population is the first step towards designing appropriate educational and intervention programmes. We conducted a questionnaire-based survey to evaluate awareness about diabetes and its implications among different sections of the residents of Urban Pune. We also aimed to assess the influence of demographic and socio-economic factors on awareness levels. This survey was a part of our department's prevention programme consisting of lifestyle modification.

Materials and methods

Study design This was a one-time, questionnaire-based survey involving 1500 participants.

Participants As young people are increasingly affected with diabetes [6], we included a wide age range of participants starting with teenagers. We included both diabetic and non-diabetic individuals. We approached three schools (students and teachers), three police stations, three information technology (IT) companies and three multispecialty hospitals (nursing staff, patients visiting outpatient department and their relatives) in Pune and requested permission to conduct the survey. Only one IT company refused. We requested the managements of these institutes to circulate an invitation to attend our session.

Questionnaire We designed a questionnaire based on published literature [7] and modified it in consultation with diabetologists. The questionnaire was initially administered to 20 participants to assess the suitability of the contents, clarity and flow of the questions. We modified it, taking into account feedback from these participants. The questionnaire was available in both English and Marathi (local language).

The first section covered demographic details (age, gender, level of education, occupation and average annual income of the participants). First-degree (parents, siblings and children) family history of diabetes was recorded. Those with known diabetes and hypertension were asked to specify duration of disease. The second section consisted of four closed-ended questions on the meaning of diabetes, curability of diabetes and future implications of GDM for mother and baby. There were five multiple-choice questions (MCQs) on risk factors, symptoms, complications, treatment and preventive measures; participants were asked to tick as many choices as appropriate (Fig. 1).

Scoring system We used a scoring system to assess knowledge about diabetes. Correct answers were scored as 1 and incorrect answers (inclusive of 'don't know') as 0 (Table 1).

Total score was derived by adding scores from individual sections; percentage score was calculated by dividing the total score by the maximum possible score.

Data collection The survey was conducted between June 2011 and January 2013. A team of two research fellows and two research assistants administered the questionnaires. They discussed the purpose of the study and the contents of the questionnaire with the participants. Questionnaires were self filled; the research assistants helped in recording responses for those who were unable to read or write. Care was taken not to influence responses. Each questionnaire was checked by a research assistant to ensure that all questions were answered. The participants were asked to complete unanswered questions if any. The session ended with a discussion about diabetes and distribution of information leaflets.

Classification To compare awareness among participants as a dichotomous variable, we used a cut-off of 50 % (total score ≥20 out of 40). Participants were categorized into good (≥50 %) or poor (<50 %) awareness groups.

Statistical methods We assessed awareness scores in the whole group and subgroups (teenagers and young adults, sedentary workers, non-diabetic hypertensive participants and non-diabetic participants with first-degree family history of diabetes). We also compared awareness levels between diabetic and non-diabetic participants. Continuous variables were compared between groups using *t* test. Associations between different categorical variables (exposures) and degree of awareness (outcome) were studied using chi-square test. Variables influencing awareness (age, education, annual income, gender, family history and presence of diabetes) were assessed using multiple regression analysis. Statistical Package for Social Sciences (SPSS-16) was used for data analysis.

Results

Demographic details Of 1500 participants (53 % men), 46 % were teenagers and young adults whereas 37 % were middle-aged adults and 17 % were elderly. Eighty-eight percent had completed secondary education while only 3 % were illiterate (Table 2).

1. Do you know what diabetes is? MAX SCORE: 1

Yes	No

2. What increases risk of diabetes? MAX SCORE: 6

Family history of diabetes		Stress	
Excessive intake of sweets		High fat diet	
Inactivity		Obesity	
Don't know			

3. What are the signs & symptoms of diabetes? MAX SCORE: 10

Frequent urination		Delayed wound healing		Weight loss	
Excessive hunger		Excessive thirst		Giddiness	
Loss of sensation		Tiredness		No symptoms	
Sweating		Don't know			

4. Which organs are affected by diabetes? MAX SCORE: 8

Heart		Kidneys		Lungs	
Eyes		Foot and nerves		Joints	
Digestive system		Teeth		Don't know	

5. Which measures can be taken to prevent diabetes? MAX SCORE: 5

Balanced diet		Regular exercise	
Weight management		Stress management	
Awareness and education		Don't know	

6. What are the measures for preventing complications of diabetes? MAX SCORE: 7

Taking medicines as prescribed		Diet control	
Regular checkup		Regular exercise	
Stress management		Weight management	
Awareness and education		Don't know	

7. Can diabetes be cured completely? MAX SCORE: 1

Yes	No	Don't know

8. Do women with diabetes in pregnancy have a higher risk of developing diabetes later in life? MAX SCORE: 1

Yes	No	Don't know

9. Are children born to diabetic mothers prone to develop diabetes in future? MAX SCORE: 1

Yes	No	Don't know

Fig. 1 Questions used for obtaining data on diabetes awareness (Section 2 of the questionnaire)

Fifty-two percent diabetic and 24 % non-diabetic participants had first-degree family history of diabetes. Diabetic participants were older (mean age 56 vs. 36 years; $P<0.001$) and had completed fewer years of education (11 vs. 13 years; $P<0.001$) than non-diabetic participants.

Sufficiency of knowledge Of the total participants, 136 (9 %) scored 0 and only 1 participant could achieve the maximum possible score. The mean score of all participants was 33 %. A total of 1170 (78 %) participants were classified as having poor awareness (score <50 %).

On univariate analysis, younger age, lower education, lower income, male gender and absence of family history of diabetes were associated with poor awareness. Multiple regression analysis revealed that younger age, lower education and male gender were independently associated with poor awareness; education was the strongest predictor (Table 3).

Table 1 Contribution of different questions to the diabetes awareness score (see Fig. 1)

Questions	Maximum possible score
Closed-ended questions	4
MCQs	
i. Risk factors	6
ii. Signs and symptoms	10
iii. Complications	8
iv. Treatment	7
v. Prevention	5
Total score	40

Meaning of diabetes Overall, 44 % did not know what diabetes was; this proportion was fairly similar in the different groups, except diabetic participants (31 %).

Risk factors Twenty-four percent participants could not name any risk factor for diabetes. Commonly listed risk factors were family history, excess sweet consumption, stress and inactivity (Fig. 2a). Sixty-five percent teenagers and young adults did not perceive 'obesity' while 55 % sedentary workers did not perceive 'physical inactivity' as risk factors. Forty-five percent of non-diabetic participants with first-degree family history of diabetes failed to report 'family history' as a risk factor.

Table 2 General characteristics of the participants

	N=1500
Men	796 (53)
Age (years)[a]	40.6 (17)
Teenagers (13–19)	225 (15)
Young adults (20–39)	468 (31)
Middle-aged adults (40–59)	551 (37)
Elderly (≥60)	256 (17)
Education (years)[a]	12.4 (4)
Illiterate (0)	48 (3)
Up to secondary education (1–9)	143 (9)
Secondary and higher secondary education (10–12)	612 (41)
Higher education (≥13)	697 (47)
Annual income (INR)	
No income	461 (31)
<1,50000	578 (38)
1,50000–4,99999	388 (26)
≥5,00000	73 (5)
Cardiometabolic risks	
Diabetes	378 (25)
Hypertension	235 (16)
Coexisting diabetes and hypertension	145 (10)

Numbers are *n* (%)

[a] Indicates mean (SD)

Symptoms Twenty-nine percent participants were unaware of any symptom of diabetes. Delayed wound healing, frequent urination and tiredness were commonly reported symptoms. Merely 2 % of participants were aware that diabetes can occur without any symptoms (Fig. 2b). More diabetic participants were aware of the symptoms than non-diabetic participants ($P<0.001$). More than a third of high-risk participants and more than half of teenagers and young adults were unaware of the common presenting symptoms (excessive urination, hunger and thirst).

Complications Thirty-six percent participants were unaware of organ-related complications of diabetes. Among those aware, a majority named eyes and kidneys as commonly affected organs. A lesser number knew about the effect of diabetes on heart, foot and nerves (Fig. 2c). More diabetic participants were aware of the complications than non-diabetic participants ($P<0.001$). In diabetic participants, longer duration of diabetes was associated with better awareness about complications ($P=0.004$). More than half of participants with coexisting diabetes and hypertension did not know that eyes, kidneys, heart, foot and nerves are affected.

Preventive measures Thirty-three percent participants were not aware of any preventive strategy for diabetes while 27 % were unaware of any measure for prevention of complications of diabetes. Over half of the participants knew about diet and exercise as preventive measures for diabetes and its complications. Education and weight management, which are important contributors, were appreciated only by a third (Fig. 2d, e). There were no significant differences between diabetic and non-diabetic participants when knowledge of treatment and preventive measures were compared.

Curability More than half the participants (57 %) believed that diabetes could be cured completely including a third of diabetic participants.

GDM and its future implications Seventy-seven percent participants were unaware that women with GDM have a higher risk of developing diabetes in the future. Sixty-eight percent of participants did not know of the long-term risks in the offspring of diabetic mothers. This awareness was marginally better in women compared to men although two thirds of women in adolescent and childbearing age did not know these facts.

Discussion

Our study highlights poor awareness about diabetes and its health implications among residents of urban Pune. This was

Table 3 Associations of poor awareness of diabetes

Predictors	Age quartiles		Education quartiles		Income group		Gender		Family history of T2D		Presence of T2D	
Groups[a]	Q1[b]	85 %	Q1[b]	95 %	1	82 %	Men	80 %	Yes	72 %	Yes	77 %
	Q2	75 %	Q2	85 %	2	77 %	Women	76 %	No	81 %	No	78 %
	Q3	79 %	Q3	70 %	3	75 %						
	Q4	74 %	Q4	63 %	4	53 %						
P (For trend)	0.003		<0.001		<0.001		0.051		<0.001		0.559	
*P*1*	<0.001		<0.001		0.310		0.002		0.082		0.909	

[a] Numbers are % participants belonging to poor-awareness group

[b] Q1 refers to those in the lowest quartile of age or education

*$P1$ = adjusted for other factors in the table (age, education, annual income, gender, family history and presence of diabetes, as appropriate)

particularly evident in those at high risk of diabetes and its complications. Younger age, lower education and male gender predicted poor awareness. These results stress the need for widespread and extensive public education about diabetes.

Being aware of the risk factors is important for primary prevention of T2D. The most common perception that excessive sweet intake leads to diabetes needs to be modified as the aetiology of diabetes is multifactorial and avoiding sweets may not be sufficient to prevent diabetes. Family history is a non-modifiable risk factor, and family members of all diabetic patients should be sensitized to take preventive action. Among modifiable risk factors, obesity is commonly

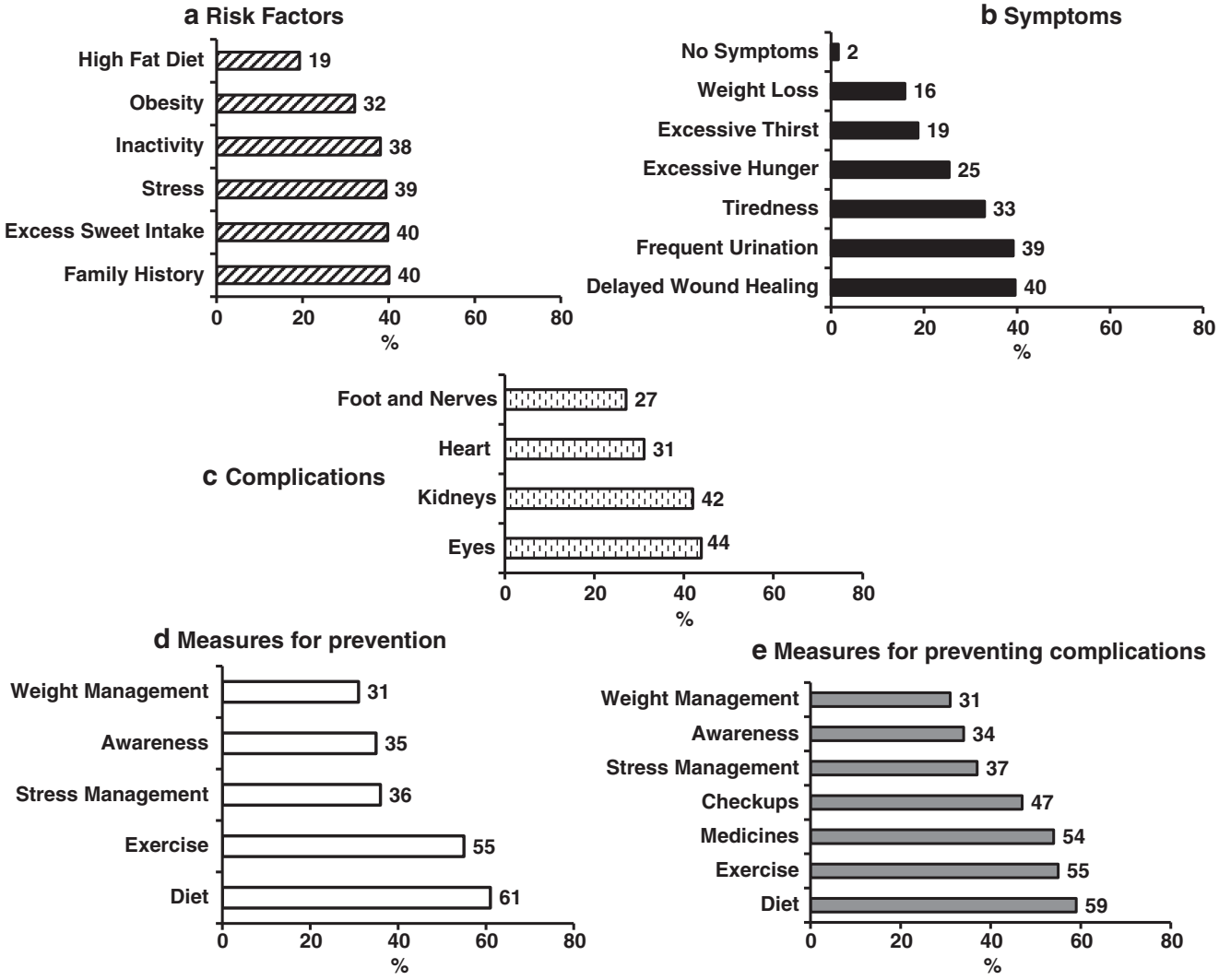

Fig. 2 **a**–**e** Percentage of participants who were aware about different implications of diabetes

Table 4 Summary of Indian studies that have assessed awareness regarding diabetes and its different implications

Reference	Place	Setting	Year	Target population			Proportion of participants who were unaware of different attributes of diabetes					
				N	Diabetes status of the participants	Age (years)	What is diabetes	Risk factors	Symptoms	Organs affected	Prevention	Long-term risks of diabetes in pregnancy
Mohan D et al. [7]	Chennai	Urban	2005	26001	Diabetic and non-diabetic	≥20	25 %	37 %	–	56 %	78 %	–
Murugesan N et al. [15]	Chennai	Urban	2007	3681	Diabetic and non-diabetic	20–65	10 %	–	–	70 %	9 %	–
Muninarayana C et al. [16]	Kolar	Rural	2010	311	Diabetic and non-diabetic	≥30	49 %	55 %	–	75 %	–	–
Khapre MP et al. [17]	Wardha	Rural	2011	100	Diabetic	31–70	18 %	32 %	16 %	32 %	–	–
Ghadage A et al. [18]	Pune	Urban	2013	100	Non-diabetic	≥18	30 %	–	–	–	–	–
Shriraam V et al. [19]	Tamil Nadu	Rural	2013	120	Women attending antenatal clinic	18–33	–	–	–	–	–	47 %
Deepa M et al. [20]	Chandigarh, Tamil Nadu, Jharkhand, Maharashtra	Urban and rural	2014	16607	Diabetic and non-diabetic	≥20	U[a], 42 % *R*[b], 63 %	–	–	49 %	44 %	–
Current study	Pune	Urban	2014	1500	Diabetic and non-diabetic	≥13	44 %	24 %	29 %	36 %	33 %	75 %

[a] Urban

[b] Rural

neglected as 'chubbiness' is still considered a sign of good health. Considering the increasing trends of obesity in childhood [8], spreading awareness about this risk factor should begin at an early age. Sedentary behaviour is a major risk factor for diabetes, worsened by urbanization and mechanization. With Pune becoming an IT hub and home to an increasing number of sedentary workers, it is imperative to promote physical activity at workplaces. All diabetes prevention programmes [9] have highlighted the important role of weight management, regular physical activity and healthy diet in reducing the risk of T2D. These findings should reach the grassroot level, and preventive activities should be part of the school curriculum from early childhood to show beneficial effects in later years.

The fact that diabetes most often does not cause any overt symptoms needs to be stressed in all education programmes. This will highlight the importance of regular blood glucose testing for diagnosis of T2D. Simultaneously, the well-known symptoms (polyuria, polyphagia, polydypsia) also need to be highlighted to anticipate severe hyperglycaemia and avoid acute metabolic complications in diabetic patients. The crucial roles that hypertension and lipid abnormalities play in diabetic organ damage [10] need to be highlighted in diabetes clinics to promote awareness and prevention of complications. A common belief that 'diabetes is curable' can prove harmful in many cases and should be specifically addressed in all education programmes to avoid many more attempting expensive and useless remedies in the hope of permanent cure [11].

Indian women with GDM have more than 50 % chance of developing T2D within 5 years of delivery [12], and the child is at higher risk of developing obesity and insulin resistance in later life [13]. As rates of GDM are increasing [14], education of adolescents and inclusion of routine diabetes screening in antenatal care deserve consideration.

There is limited literature on diabetes awareness in India (Table 4). These studies assessed awareness on only a few aspects. There was only one study which assessed awareness regarding future implications of GDM and reported low awareness in pregnant women attending antenatal clinics [19].

Our population-based study has a moderately large sample size and includes both men and women with a wide age range and those in high-risk groups. The questionnaire was specially designed and tested for clarity and validity. It included a range of questions directed at a variety of high-risk groups (sedentary workers, non-diabetic people with family history of diabetes, non-diabetic hypertensive people) to assess their perceptions about the disease. We included a sizable number of participants in different groups to give meaningful results. We explained the purpose and meaning of questions to promote better understanding. Though the representativeness of the study sample cannot be assured, the purposive sampling reflects the issues we wanted to address. Despite these limitations, the results are important and have given us a good understanding of the situation in urban India. The scenario in rural areas may be different and the level of awareness is likely to be even lower; this needs to be investigated.

In summary, there is need for pervasive public health education campaigns to raise awareness and contribute to the national diabetes prevention initiatives. This can be achieved by identifying and approaching high-risk groups through personal meetings, group sessions, workshops and mass screenings. Opportunistic education can be delivered in hospitals, outpatient departments, referral centres, diabetes clinics, schools, colleges and workplaces. Extending the education programmes to school and college curricula will help primary prevention while efforts in diabetes clinics will promote secondary and tertiary prevention. Adolescent girls and women in childbearing age should be a particular target to help prevent diabetes in two generations. Larger sections of society may be reached through mass media approaches (newspapers, radio and television) and mobile/internet technologies (mobile messages, applications, games, emails and social media updates). Authentic information on diabetes should be made widely available to the general public like the one made available by the American Diabetes Association (http://www.diabetes.org/). Programmes on diabetes education designed to train health care professionals can form a pool of paramedics, educators, nutritionists, social workers and volunteers who can act as mediators for spreading awareness. One such programme has already been implemented (the India Diabetes Educator Project—IDEP; recognized by the International Diabetes Federation) under which more than 3000 allied health professionals were educated over a period of 4 years [21]. Eventually, increased levels of awareness are likely to facilitate acceptance of prevention and treatment programmes and will contribute to a reduction in the growing epidemic of this silent killer and its complications.

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Conflict of interest None

Authors' contribution Chittaranjan Yajnik, Tejas Limaye and Sonali Wagle planned the study and wrote and edited the manuscript. Kalyanaraman Kumaran and Arun Nanivadekar wrote and edited the manuscript. Charudatta Joglekar analysed the data and edited the manuscript.

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ORIGINAL ARTICLE

Diabetic foot in patients below 40 years of age

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Abstract Data on diabetic foot ulcers (DFU) in young patients are scarce. We aimed to examine the risk factors, clinical presentation, wound characteristics, and outcome of DFU among young diabetic patients and to compare them with similar age diabetics without foot ulcer and those of older age diabetics with foot ulcers. A prospective cohort of 745 patients (834 ulcers) below 40 years of age, 7620 patients (9405 ulcers) ages 40 years and above, and 992 patients below 40 years diabetics without foot ulcers in a single multidisciplinary diabetes center were studied. Registered patients with foot ulcers in Jabir Abu Eliz Diabetes Centre (JADC) in Khartoum, Sudan from March 2001 to Dec 2011 were reviewed. Below 40 years of age constituted 8.9 % (n=7450) of all patients with DFU. Male-to-female ratio was 1.7:1. IDDM type was prevalent in 60.9 %. Thirty-six per cent of below 40 years had peripheral neuropathy compared to 61.6 % of older group (p<0.0002) and 8.7 % of below 40 without DFU (p<0.0002). ABI <0.9 was found in 38.7 % (n=288) in below 40 years with ulcers compared to 41.4 % in older patients (p=0.8989) and 36.3 % (n=360) of below 40 without DFU (p=0.3125). HbA1c >7 % was significantly more in diabetics below 40 years with foot ulcers compared to those without foot ulcers (83.5 vs. 75.1 %) (p=0.0002). In below 40 years of age, 80.1 % of ulcers healed compared to 70.6 % in older age group (p>0.0002). Major lower extremity amputation was performed in 4.8 % in below 40 years patients compared to 7.3 % in older group (0.0105). Young diabetics with foot ulcers had significantly longer duration of the disease, more foot deformities, and callus formation and more severe neuropathy than young diabetics without ulcers but had a lesser duration of diabetes than elderly diabetics with foot ulcers. HbA1c in young diabetics with foot ulcers was significantly higher than young diabetics without ulcers, and their foot ulcers healed better and with less major lower extremity amputation than elderly patients.

Keywords Diabetic foot · Foot ulcer · Amputation · Diabetes · Diabetic complications

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Introduction and background

Diabetic foot ulcers (DFUs) have been recognized as a major diabetes-related complication with significant morbidity and mortality [1, 2]. It represent a global burden in terms of distribution, socioeconomic, and psychological impaction [3, 4]. Despite the well-studied pathophysiology of the disease and the continuing efforts in therapeutic and preventive measures, 4–10 % of diabetic patients are at risk of DFU with a lifetime risk approximating 25 % [5, 6].

Ulcerated diabetic foot is a complex problem. Ischemia, neuropathy, and infection are the three pathological components that lead to diabetic foot complications, and they frequently occur together as an etiologic triad. Neuropathy and

ischemia are the initiating factors, most often together as neuroischemia, whereas infection is mostly a consequence [7]. Thus, diabetic foot ulcers can be divided into two groups: those in neuropathic feet (so called neuropathic ulcers) and those in feet with ischemia often associated with neuropathy (so called neuroischemic ulcers) [8].

About half of people with diabetes will develop peripheral neuropathy. Most of the time, symptoms do not begin until 10 to 20 years after diabetes has been diagnosed. Being the most recognized risk for the development of ulceration in neuropathic and neuroischemic feet, its presence explains the high prevalence of DFU among elderly diabetic population. However, DFU do occur in young diabetics.

This study was designed to identify the risk factors, clinical presentation, wound characteristics, and outcome of DFU among young diabetic patients below 40 years of age and to compare them with those of older ages.

Research design and methods

Registered patients with DFU in Jabir Abu Eliz Diabetes Center in Khartoum, Sudan from March 2001 to Dec 2011 were reviewed. A total of 8209 were identified. Among those, 745 patients were found to be below 40 years of age (group A). Those at 40 years of age or above (7620 patients) were considered as group B. Diabetic patients below 40 years of age without DFU were also included as a control group (group C = 992 patients).

Both groups' data were retrieved from an electronic data sheet present in the center registry office. Variables studied included age, gender, origin, duration of DM, presence of co-morbidity, and presenting symptoms (pain, fever, swelling, cellulitis, discharge, and local signs). Sensory neuropathy was tested using 10 g monofilament test. Besides wound characteristics, the presence of osteomyelitis and microbiology of wounds were recorded after wound biopsy for culture and sensitivity. Offending organism(s) and antibiotic sensitivities were recorded. Relevant investigations (HbA1c, AB Index, X-ray, and CT angiography when needed) were also recorded as appropriate. All patients with major sepsis were shifted to soluble insulin (Actrapid) until sepsis is being controlled. Surgical interventions (drainage, debridement, revascularization, skin graft, flap coverage) were done as needed. The final outcome (complete healing without amputation, toe amputation, minor foot amputation, and major amputation) were recorded.

The main risk factors included duration of diabetes >10 years, Hemoglobin A1c >7.0, callus, deformities, ABI <0.9, and absent 10 g monofilament test.

Wound characteristics studied included the site (toes, metatarsal head, medial aspect, lateral aspect, plantar, dorsal, heel, and others). Size of wounds was measured in cm^2 and wounds were subdivided into <2 cm^2, 2–5 cm^2, and >5 cm^2. The depth of wounds was assessed by layers and subdivided into full thickness skin ulcers, penetrating to fascia or muscle, and penetrating to bone or joint. Infection was identified by clinical assessment and classified into grades as follows:

Clinical description	Grade
No purulence or evidence of inflammation	I
Two signs of inflammation, such as pain or induration; cellulitis, 2 cm or less around ulcer; infection limited to skin and subcutaneous tissues	II
At least one of the following: cellulitis >2 cm around ulcer, lymphangitis, spread beneath fascia, abscess, gangrene, or involvement of muscle, tendon, or bone	III
Evidence of local infection as well as systemic toxicity, such as fever, hypotension, leukocytosis, or azotemia	IV

Osteomyelitis was diagnosed when a foot ulcer reached the bone by probing or the presence of radiological evidence by X-ray, MRI, or bone scan.

Data was processed and analyzed in a computer using SPSS version 14.

Statistical significance was calculated by Z-ratio and two-tail probability of <0.05 was considered as significant.

Results

A total of 745 patients with 834 DFUs, less than 40 years of age, were studied (group A) compared to 7620 patients with 9405 DFUs of 40 years or older (group B). Diabetic patients below 40 years of age without DFU were also included as a control group (group C = 992 patients). Less than 40 years patients constituted 8.9 % of the total number of registered DFU patients (n=8365). The most affected age group were those between 31 and 39 years old (67.1 %). The male-to-female ratio was 1.7:1.0; type 1 diabetes mellitus was prevalent in 60.9 % (n=454). Most of ulcers were new ones (85.8 %). Recurrent wounds whether on the same site, same foot, or the other foot accounted for 14.2 % of patients compared to 18.8 % among older age group, (p value=0.005).

Seven hundred fifty-one ulcers (90.1 %) from group A reached the end point of either complete healing, minor or major amputation compared to 7806 ulcers (83.0 %) from group B. Table 1 shows the risk factors comparing diabetics with foot ulcers in <40 years versus those >40 years. Older patients had significantly longer duration of diabetes, more sensory neuropathy, and more deformities. Table 2 shows that <40 years diabetics with foot ulcers had significant longer duration of diabetes, higher HbA1c, more sensory neuropathy, deformities, and callus formation than those <40 years diabetics without foot ulcers. Table 3 shows the wound characteristics with more affection of the forefoot and toes in the older patients and more heel ulcers in the young diabetics. Table 4 shows more systemic presentation of sepsis like fever

Table 1 Risk factors comparing diabetics with foot ulcers below versus above the age of 40 years

Risk factor	<40	=>40	*P* value
Duration of diabetes >10 years	237 (31.8 %)	4714 (61.9 %)	<0.0002
Hb A1C >7.0 %	622 (83.5 %)	6180 (81.1 %)	0.1105
Callus	254 (34.1 %)	2817 (37.0 %)	0.1202
Deformity	296 (39.7 %)	4744 (62.3 %)	<0.0002
10 g monofilament (absent or impaired)	268 (36.0 %)	4695 (61.6 %)	<0.0002
ABPI <0.9	288 (38.7 %)	3158 (41.4 %)	0.8989

but better outcome and wound healing in <40 versus more gangrene and amputation and less wound healing in >40 years diabetics. Wound healing without amputation occurred in 88.9 % of those <40 years compared to 85.1 % in those >40 years (p=0.0043). Major lower extremity amputation was also more in >40 years (n=570, 7.3 %) versus (n=36, 4.8 %) in those <40 years (p=0.0105).

Intractable sepsis and life-threatening infection was the main cause of major lower extremity amputation (MLEA) in 33 patients (out of 36) <40 years accounting for (91.7 %) while it was the main cause (in 400 patients out of 570), (70.2 %) in those >40 years of age (p<0.005). Critical limb ischemia was the main cause of MLEA in 170 (29.8 %) patients (out of 570) >40 years of age versus 3 out of 36 (8.5 %) in those <40 years of age (p<0.005).

Conclusion

Diabetic foot is always regarded as a disease of elderly patients. However, it does occur in younger diabetics. We believe that this is the first study describing the characteristics of this problem among young patients.

It is well known that the combination of peripheral neuropathy, deformities, peripheral vascular disease, and infection constitute the major causation of diabetic foot ulcers, making it more or less a geriatric problem. These complications of diabetes usually take time to develop and manifest as diabetic foot, raising a question on what risks the development of diabetic foot in young patients.

Duration of diabetes of more than 10 years seems to play a significant role as a risk factor for ulceration in below 40 years diabetes patients. It is clear from the results that peripheral neuropathy and foot deformities increase with age with a statistically significant difference. However, the only independent factors with no difference between young and elderly patients were glycemic control reflected by HbA1c and callus formation. In the absence of obvious deformities, callus formation can be due to local shoes with hard base without an off loading pad. However, walking bare foot is common in farmers and in those coming from remote areas, though no accurate figures could be given. Thus, younger diabetic patients should be aware of the importance of appropriate foot wear, evading barefoot walking, and glycemic control to avoid diabetic foot ulcers.

Surprisingly, below 40 years of age showed a significantly higher prevalence of heel ulcers than older patients. Heel ulcers in diabetics are challenging and considered as one of the risk factors for major lower extremity amputation [9]. Risk factors for the development of diabetic ulcers on a specific site in the foot is very complex and include many variables like peripheral neuropathy, peripheral vascular disease, pressure distribution, and shear forces. However, the mechanisms involved and predictability are not well understood [10]. This may explain the characteristic site distribution of DFU among below 40 years patients which mimics older ages in most but with some special predilections.

Infection severity in diabetic foot is an important factor in determining treatment policy, hospital stay, and risk of major amputation [11]. Patients below 40 years had more fever, pain, and swelling with better healing and less amputation. This could be due to the fact that they have less neuropathy, less ischemia, and are more symptomatic so they present earlier and hence have better response to sepsis, early diagnosis, and better outcome with less amputation and more wound healing. In elderly patients with more neuropathy and ischemia,

Table 2 Risk factors in <40 diabetics with and without foot ulcers

Risk factor	<40 with DFU	<40 diabetics without DFU	*P* value
Duration of diabetes >10 years	237 (31.8 %)	70 (7.1 %)	<0.0002
Hb A1C >7.0 %	622 (83.5 %)	745 (75.1 %)	<0.0002
Callus	254 (34.1 %)	100 (10.1 %)	<0.0002
Deformity	296 (39.7 %)	308 (31.0 %)	<0.0002
10 g monofilament (absent or impaired)	268 (36.0 %)	86 (8.7 %)	<0.0002
ABPI <0.9	288 (38.7 %)	360 (36.3 %)	0.3125

Table 3 Wound characteristics: comparing <40 versus >40 with foot ulcers

Characteristic	<40 (out of 834 ulcers)	≥40 (out of 9405 ulcers)	*P* value
Site			
Toes	265 (31.8 %)	4150 (44.1 %)	<0.0002
Head of metatarsals	137 (16.4 %)	1442 (15.3 %)	0.4015
Medial aspect	63 (7.6 %)	680 (7.2 %)	0.7301
Lateral aspect	61 (7.3 %)	608 (6.5 %)	0.3416
Plantar	68 (8.2 %)	685 (7.3 %)	0.356
Heel	112 (13.4 %)	785 (8.3 %)	<0.0002
Dorsum	79 (9.5 %)	886 (9.4 %)	0.9609
Other	49 (5.9 %)	169 (1.8 %)	<0.0002
Size			
<2 cm^2	121 (14.5 %)	1298 (13.8 %)	0.5707
2–5 cm^2	390 (46.8 %)	4618 (49.1 %)	0.1953
>5 cm^2	323 (38.7 %)	3489 (37.1 %)	0.3503
Depth			
Full thickness	408 (48.9 %)	4730 (50.3 %)	0.4479
Penetrating to fascia or muscle	302 (36.2 %)	2840 (30.2 %)	0.0003
Penetrating to bone or joint	124 (14.9 %)	1835 (19.5 %)	0.0011
Infection grade			
I	324 (38.9 %)	3922 (41.7 %)	0.1092
II	354 (42.4 %)	3395 (36.1 %)	0.0003
III	142 (17.0 %)	1890 (20.1 %)	0.0332
IV	14 (1.7 %)	198 (2.1 %)	0.4071
Osteomyelitis	208 (27.9 %)	2978 (39.1 %)	<0.0002
Offending organism (swab culture)			
Staph aureus	308 (36.9 %)	2098 (22.3 %)	<0.0002
Streptococcus	46 (5.5 %)	497 (5.3 %)	0.7749
Pseudomonas aeruginosa	48 (5.8 %)	752 (8.0 %)	0.0209
E. coli	52 (6.2 %)	486 (5.2 %)	0.1855
Other	108 (13.0 %)	178 (1.9 %)	<0.0002
Mixed	14 (1.7 %)	677 (7.2 %)	<0.0002
No growth	258 (30.9 %)	4717 (50.1 %)	<0.0002

patients presents late until gangrene appears. Older patients have more predilections to mixed growth and possibly anaerobes. This together with the significant presence of osteomyelitis among older patients entails different strategies in treatment beside a different outcome in terms of limb salvage.

Table 4 Clinical presentation and outcome of diabetic patients with foot ulcer above and below 40 years

Symptom/sign	<40 (out of 745 patients)	≥40 (out of 7620 patients)	*P* value
Pain	414 (55.6 %)	3753 (49.3 %)	0.001
Fever	216 (29.0 %)	1860 (24.4 %)	0.0057
Swelling	434 (58.3 %)	4083 (53.6 %)	0.0146
Cellulitis	323 (43.4 %)	3449 (45.3 %)	0.3183
SIRS	6 (0.8 %)	102 (1.3 %)	0.2187
Gangrene	17 (2.3 %)	503 (6.6 %)	<0.0002
Complete healing	668 (88.9 %)	6643 (85.1 %)	0.0043
Minor amputation	47 (6.3 %)	593 (7.6 %)	0.1829
Major amputation	36 (4.8 %)	570 (7.3 %)	0.0105

This difference is possibly explained by the specific immune response characterizing patients with long standing diabetes [12]. The diagnosis and classification of diabetic foot infections in below 40 years patients is a straight forward task.

Older age is identified as one of the independent baseline predictor of non-healing in diabetic foot ulcer [13]. In our series, 80.1 % of ulcers in below 40 years of age healed without amputation compared to 70.6 % in older age group ($p>0.0002$). Eighty-three ulcers (10 %) in below 40 years and 1599 (17 %) in 40 years and above group were either in continuous treatment or not being on follow up. We can assume that younger patients have a higher rate of healing with or without minor amputation. Although, the rate of major amputation remained significantly higher among older patients; however, young diabetics still have major amputation rate comparable to general rates observed in diabetic foot elsewhere [14–16]. Higher rates among older diabetics are attributed to peripheral vascular disease and peripheral neuropathy. This could be observed when we find that ischemia contributed to nearly one third of amputations in this group, together with nearly two thirds affected by complete or partial peripheral neuropathy. In contrast, young diabetics suffer the consequences of ascending uncontrolled sepsis which was behind most of their major amputations. The effect of hyperglycemia in decreasing tissue tolerance to ischemia and thus inducing ischemic necrosis has been reported [17]. Hence, hyperglycemia in young diabetics plays a major role in determining the outcome, especially in borderline ischemic limbs.

One of the contradictions to this theory was the finding of ABI in both groups which has shown similarity of peripheral arterial disease (PAD) when identified as ABI <0.9. However, major lower extremity ischemia was the main indication for major LEA in those >40 years (29.8 %) versus 8.5 % in those <40 years ($p=0.005$). This shows the limitations of AB Index in predicting the clinical outcome. Several studies that correlate ABI with PAD among diabetic patients showed unreliability and insensitivity of ABI. In the diabetic foot, the pressure measured in one distal artery is less representative of atherosclerotic disease in the lower extremity [18]. The efficacy of ABI is limited in the presence of clinical peripheral neuropathy [19], and is also less sensitive in elderly patients, blaming medial calcinosis which leads to false higher readings. This is greatly observed in elderly diabetic population with below knee PAD [20].

Another factor that may play a significant role in determining the outcome of DFU in young diabetics by influencing resistant infections is colonization by *Staphylococcus aureus* bacteria which was isolated significantly more from young diabetics' wounds in this series. With the ongoing emergence of methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *S. aureus* (VRSA) [21, 22], young diabetics acquire another risk factor for major lower extremity amputation. Young diabetics still carry the unique characteristics of diabetic foot and its disastrous complications regardless the possible different pathological consequences. They need the same specialized and skillful interventions to prevent limb loss.

There are several limitations to this study. Risk factors like smoking and dyslipidemia were not recorded in all patients. We could not estimate the outcome in a limited time frame of follow up. Patients who were lost during the study period were not included in the final outcome, a fact that may alter some results especially the rate of major amputation. Also we did not report and analyze the surgical interventions implemented in sequence. Of particular interest are revascularization and reconstructive procedures which may significantly affect the outcome.

In conclusion, DFU do occur in young diabetic patients. It may have a different pathophysiology and clinical presentation seen in older patients. Yet it carries most of the characteristics and morbid outcome. With specialized care, early appropriate wound control, proper interventions, and microbiological control young diabetics with foot complications have a better chance to achieve complete healing with or without minor amputation.

Conflict of interest The authors declare that there is no duality of interest associated with this.

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ORIGINAL ARTICLE

Interaction of poor sleep quality, family history of type 2 diabetes, and abdominal obesity on impaired fasting glucose: a population-based cross-sectional survey in China

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Abstract This study aims to explore the interaction of sleep quality, family history of type 2 diabetes, and obesity in relation to impaired fasting glucose in a Chinese population. A representative population-based cross-sectional study was conducted, and 15,145 residents aged between 18 and 75 years were selected from 11 districts of Xuzhou City, Jiangsu Province. The Pittsburgh Sleep Quality Index was used to evaluate sleep conditions, with categories of good and poor. Impaired fasting glucose (IFG) was assessed by fasting blood glucose. Interaction of sleep quality, obesity, and family history of diabetes (FHD) on IFG was analyzed by logistic regression. Relative excess risk due to interaction (RERI) and the synergy index (SI) were applied to evaluate the additive interaction between the two factors. Either poor sleep or positive FHD was independently associated with an increased odds ratio (OR) for IFG. Those with both poor sleep and positive FHD had a significantly increased risk compared with those without poor sleep and FHD (OR 20.6, 95 % confidence interval (CI) 16.4–29.0, $P<0.001$). The corresponding RERI and SI was 14.6 (8.6–20.6) and 3.7 (1.4–5.1), respectively. Both abdominal obesity and FHD significantly increased the risk of being IFG. The synergistic effect of abdominal obesity and FHD on IFG was statistically significant (OR 40.1, 95 % CI 28.8–61.5). The results suggest that additive interactions exist between poor sleep quality, abdominal obesity, and family history of diabetes in relation to impaired fasting glucose.

Keywords Impaired fasting glucose · Sleep quality · Family history of diabetes · Abdominal obesity · Interaction

Background

Many epidemiological surveys [1–5] and experimental studies [6–9] have shown that sleep duration and sleep quality contribute to decreased glucose tolerance, reduced insulin sensitivity, and increased risk of developing type 2 diabetes.

As the most important risk factor for type 2 diabetes, impaired fasting glucose (IFG) is also one of the prediabetes cases. Based on a prospective cohort of IFG subjects, the average annual incidence of diabetes was 11 % during the 6-year follow-up period without intervention [10]. Many aspects contribute to the risk of developing prediabetes including aging, positive family history of diabetes (FHD), obesity, abdominal obesity, etc. [11–13]. Some studies have shown that IFG was associated with sleep quantity and quality [7, 11]. The Western New York Health Study which included 1455 participants over 6 years of follow-up indicated that sleep duration of less than 6 h was associated with increased prevalence of IFG, compared to 6–8-h sleep duration every night [14]. Our previous study also confirmed that relatively healthy individuals with poor sleep quality and short sleep time were associated with a higher risk of IFG [11].

Although each of the above risk factors plays a role, the development of IFG is attributable to the combined effect of genetic and environmental factors rather than to one single factor. So far, there is little understanding of these multivariate

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explanations of IFG in a relatively healthy population and there are no studies on the interaction of sleep, positive family history of diabetes, and obesity on IFG in these subjects. Therefore, the aim of this cross-sectional study is to examine the combined effect of poor sleep quality, positive family history of diabetes, and abdominal obesity on IFG among relatively healthy populations in Chinese primary care settings.

Methods

The study was conducted from March to November in 2012, and the sampling was selected with probability proportional to size from all of the 11 regions in Xuzhou City. In the first stage, five sub-districts/townships in urban/rural areas were selected from each region. In the second stage, five communities/villages were selected from each sub-district/township. In the final stage, one person at least 18 years old who has lived in their current residence for at least 5 years was selected from each household using a Kish selection table [15].

All participants received a health examination and completed a structured questionnaire, including demographic information, medical history, medication history, sleep assessment, cigarette smoking, alcohol drinking, and exercise habits. All participants underwent 12-h overnight fasting, and blood sampling was drawn for measurement of plasma glucose. Face-to-face interviews were carried out by trained physicians and public health professionals. Then, each individual completed the Pittsburgh Sleep Quality Index (PSQI) [16]. In our study, we excluded participants who were pregnant or were suffering from diseases such as cardiovascular disease, stroke, neuropathy, psychosis, depression, chronic obstructive pulmonary disease, obstructive sleep apnea, diabetes, and chronic pain. Those with incomplete sleep duration or sleep quality information were also excluded. A total of 15,145 subjects participated in the survey, and the overall response rate was 91.8 %.

This study was approved by the ethics committee of Xuzhou Center for Disease Control and Prevention. All participants provided written informed consent.

Key measurements

The blood samples were obtained by venipuncture after overnight fasting for at least 12 h. Extracted plasma was stored at −70 °C for glucose determination using the hexokinase method. According to the recommendations from the American Diabetes Association, IFG was defined as fasting plasma glucose between 5.6 and 7.0 mmol/L [17]. FHD was defined as having at least one first-degree family member (father, mother, and/or siblings) with diabetes, regardless of diabetes types.

Sleep quality and disturbance over a 1-month interval was assessed using the PSQI, a validated self-rated questionnaire [16]. Seven component scores reflected sleep problems including sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. The sum of the scores for these seven components produced the global sleep quality score which varied from 0 to 21 points. The diagnostic sensitivity and specificity were 89.6 and 86.5 %, respectively, in differentiating poor from good sleepers when the global PSQI score was higher than 5. The Chinese version of the PSQI, used with permission from the original PSQI authors, has an overall reliability coefficient of 0.82–0.83 and an acceptable test–retest reliability coefficient of 0.77–0.85 [18].

Body height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were measured. Body mass index (BMI) (in kg/m^2) was calculated as the weight (in kg) divided by the height (in m^2). BMI was then categorized as underweight ($\leq$18.5 kg/m^2), normal weight (18.5–23.9 kg/m^2), overweight (24.0–27.9 kg/m^2), and obesity ($\geq$28.0 kg/m^2) [19]. Abdominal obesity was defined as waist circumference $\geq$85 cm for men and $\geq$80 cm for women [19].

Covariates

Employment status was categorized into manual and non-manual. Education level was categorized into below high school, high school, and above high school. Lifestyle variables included cigarette smoking, alcohol use, and physical activity level. Cigarette smoking was defined as the subject having smoked at least 100 cigarettes in their lifetime. Information on the amount and type of alcohol consumed during the previous year was obtained. Alcohol drinking was defined as total consumption of alcohol at least 30 g every week over a period of at least 1 year. Regular leisure time physical activity was defined as participating in moderate or vigorous activity for no less than 30 min every day and at least 3 days every week. Family history of diseases included hypertension, heart disease, and cancer. Hypertension was defined as having been diagnosed with hypertension with treatment or field measurement of SBP $\geq$140 mmHg and/or DBP $\geq$90 mmHg [20].

Statistical analysis

t test and chi-square test were used to analyze the difference between continuous and category variables between groups, respectively. Odds ratios (OR) and 95 % confidence interval (CI) were estimated for the interaction between two exposures in association with IFG by logistic regression analysis. The additive interaction between the two factors was evaluated with two indicators: the relative excess risk due to interaction (RERI) and the synergy index (SI). The RERI was the excess risk attributed to interaction relative to the risk without exposure. SI was the excess risk after both exposures when there is a biological interaction relative to the risk

from both exposures without interaction. Additive interactions were defined as either statistically significant RERI >0 or SI >1. A P value <0.05 (two-tailed) was considered statistically significant. All analyses were performed using the statistical analysis program SPSS 11.5 (SPSS, Chicago, IL, USA).

Results

A total of 15,145 adults (7557 men and 7588 women) with complete data were included in our analysis. The average age was 47.6±15.1 years. Among them, 634 (4.2 %) individuals had IFG. The prevalence of IFG significantly increased with age and BMI. Manual workers, cigarette smokers, and hypertensive individuals had a higher prevalence of IFG. The prevalence of poor sleep quality was 26.0 %. Individuals with poor sleep quality had a higher prevalence of IFG than those with good sleep quality (6.7 vs. 3.3 %, χ^2=85.98, P<0.001). The prevalence of IFG in individuals with abdominal obesity was significantly different from that in those without abdominal obesity (8.5 vs. 2.3 %, χ^2=313.65, P<0.001). As compared with individuals without FHD, those with FHD had a higher IFG prevalence (25.1 vs. 2.5 %, χ^2=541.55, P<0.001) (Table 1).

Either poor sleep or positive FHD was independently associated with an increased OR for IFG. Those with both poor sleep and positive FHD had a significantly increased risk compared with those without poor sleep and FHD (OR 20.6, 95 % CI 16.4–29.0, P<0.001). The corresponding RERI and SI were 14.6 (8.6–20.6) and 3.7 (1.4–5.1), respectively (Table 2).

Both abdominal obesity and FHD significantly increased the risk of being IFG. The synergistic effect of abdominal obesity and FHD on IFG was statistically significant (OR 40.1, 95 % CI 28.8–61.5, P<0.001). The corresponding RERI and SI were 27.9 (15.4–40.3) and 2.4 (1.1–3.7), respectively (Table 3).

Discussion

Our study showed joint interactions between poor sleep quality and FHD, and also, FHD and abdominal obesity increased the risk of IFG, independent of potential confounders. Few epidemiologic studies have demonstrated joint effect of risk factors on the prevalence of type 2 diabetes mellitus. A 6-year US National Health and Nutrition Examination Survey indicated a strong additive interaction between abdominal obesity and insufficient 25(OH)D in regard to insulin resistance [21]. The MONICA/KORA Augsburg cohort study reported an additive effect of overall and abdominal obesity on diabetes [22]. Joint effects of genetic risk scores and obesity had been reported to have contributed to the risk of diabetes [23, 24].

Table 1 Characteristics of the study population

Variables	Number	IFG (%)	P
n	15,145	634	
Age (years)			
18+	3495	39 (1.1)	<0.001
30+	2312	66 (2.9)	
40+	2373	96 (4.1)	
50+	2716	135 (5.0)	
60+	2267	157 (6.9)	
70+	1982	141 (7.1)	
Gender (%)			
Male	7557	316 (4.2)	0.94
Female	7588	318 (4.2)	
Residents (%)			
Urban	4180	172 (4.1)	0.58
Rural	10,965	462 (4.2)	
Marriage statues (living with partners) (%)			
Married	13,403	547 (4.1)	0.07
Single	1742	87 (5.0)	
Manual worker			
Yes	10,833	474 (4.4)	0.02
No	4312	160 (3.7)	
Educational level			
High school or above	3246	165 (4.2)	0.99
Below high school	11,899	499 (4.2)	
Cigarette smoking			
Yes	3514	174 (5.0)	0.01
No	11,631	460 (4.0)	
Alcohol drinking			
Yes	2872	120 (4.2)	0.98
No	12,273	514 (4.2)	
Regular exercise			
Yes	2559	107 (4.2)	0.99
No	12,586	527 (4.5)	
BMI (kg/m^2)			
<18.5	597	1 (0.2)	<0.001
18.5–23.9	9491	191 (2.0)	
24–27.9	4259	208 (4.9)	
≥28	798	134 (16.8)	
Hypertension			
Yes	3060	159 (5.2)	0.002
No	12,085	475 (3.9)	
Sleep quality			
Poor	3936	265 (6.7)	<0.001
Good	11,209	369 (3.3)	
Abdominal obesity			
Yes	4613	394 (8.5)	<0.001
No	10,532	240 (2.3)	
Family history of diabetes			
Yes	483	121 (25.1)	<0.001
No	14,662	513 (3.5)	

Abdominal obesity was classified as waist circumference ≥85 cm for men and ≥80 cm for women. Hypertension was defined as having been diagnosed hypertension with treatment or field measurement of SBP ≥140 mmHg and/or DBP ≥90 mmHg. Poor and good sleep quality were categorized by a cutoff of PSQI >5 and ≤5, respectively

IFG impaired fasting glucose

Table 2 Additive interaction between the sleep quality and impaired fasting glucose by family history of diabetes among participants

FHD	Sleep quality	IFG	No IFG	OR (95 % CI)	RERI (%)	SI (95 % CI)
No	Good	327	10,600	1		
	Poor	186	3549	1.5 (1.4–2.0)		
Yes	Good	42	240	5.5 (3.9–8.2)		
	Poor	79	122	20.6 (16.4–29.0)	14.6 (8.6–20.6)	3.7 (1.4–5.1)

Adjusted for age, gender, region, marital status, education level, occupation smoking, drinking, physical activity, abdominal obesity, BMI and history of hypertension

IFG impaired fasting glucose, *FHD* family history of diabetes, *RERI* relative excess risk due to interaction, *SI* the synergy index

However, these studies did not take sleep quality into consideration and, so far, no published paper has shown the joint effect of risk factors on IFG.

The risk of development of type 2 diabetes was related to either end of the distribution of sleep duration or qualitative disturbances of sleep. One recent meta-analysis from ten prospective studies with a 3-year follow-up concluded that sleep duration and sleep disturbances consistently predicted the risk of incidence to type 2 diabetes [25]. Our study showed a higher prevalence of IFG in individuals with poor sleep quality than those with good sleep quality. Consistently, the Western New York Health Study indicated that short sleep duration was associated with an elevated risk of IFG [14]. Trouble initiating sleep and waking up too early were shown to be associated with IFG [26]. Another recent study in China suggested that individuals with prediabetes and newly diagnosed diabetes had a significantly higher global PSQI score than those with normal glucose tolerance [27].

The family history of diabetes has a significant, independent, and graded association with the prevalence of diabetes [28, 29]. Our study showed a higher risk of being IFG in individuals with FHD than those without FHD. Rodriguez-Moran et al. indicated that presence of FHD in first-degree relatives was associated with IFG in children and adolescents, which implicated early detection of diabetes [30]. In respect to sleep quality, a Japanese study showed that poor sleep was associated with a higher risk of developing diabetes in workers without FHD [31]. Inconsistently, we found a joint effect of poor sleep quality and FHD on IFG. To the best of our knowledge, it is the first report on this additive interaction. FHD is a surrogate marker for both genetic susceptibility and clustering family behavioral and environmental risk factors [32]. Sleep deprivation is accompanied by impaired insulin secretion and sensitivity [8]. Insulin resistance in both muscle and hepatic tissue is genetically determined and fully established in the early life of those with FHD [33]. Short sleep duration/poor quality of sleep may be more influential in the early phase of the process of impaired glucose metabolism or developing diabetes before obvious clinical abnormalities [31].

A meta-analysis with 18 cohort studies indicated a relative risk of 7.28 for obese individuals to develop diabetes [34]. Lee et al. found that obesity increased the risk of IFG and diabetes by approximately similar magnitudes [35]. The cutoff values for obesity and abdominal obesity vary according to ethnic and sex, and we used the cutoff for Chinese adults. Our study showed a higher prevalence of IFG in individuals with abdominal obesity than those without abdominal obesity. Another study in Chinese population reported that waist circumference was strongly associated with diabetes [36]. Waist circumference is a simple measure of abdominal obesity and might better reflect accumulation of intra-abdominal fat. Obese diabetics had both insulin resistance and insulin secretory dysfunction [37]. Visceral fat in abdominal obesity is the main source of free fatty acids and inflammatory cytokines and could lead to insulin resistance and diabetes [36]. In our study, we found a joint effect of FHD and abdominal obesity on IFG. Consistently, studies from Canadian and Finnish populations have shown joint effects of family history and obesity on diabetes [24, 23].

Table 3 Additive interaction between the abdominal obesity and impaired fasting glucose by family history of diabetes among participants

Abdominal obesity	FHD	IFG	No IFG	OR (95 % CI)	RERI (%)	SI (%)
No	No	195	10,424	1		
	Yes	45	262	9.1 (6.4–12.8)		
Yes	No	318	3725	4.4 (3.6–4.2)		
	Yes	76	100	40.1 (28.8–61.5)	27.9 (15.4–40.3)	2.4 (1.1–3.7)

Adjusted for age, sex, region, marital status, education level, occupation, smoking, drinking, physical activity, sleep quality, and history of hypertension. *P* value represents significance of interaction from weighted logistic regression model

IFG impaired fasting glucose, *FHD* family history of diabetes, *RERI* relative excess risk due to interaction, *SI* the synergy index

A main strength in our study is that we used a validated self-rated questionnaire to assess sleep quality, which provided relatively accurate estimation of individual sleep quality. The large population-based representative sample size ensures the generalizability of our results. There are several potential limitations in our study. Firstly, as a cross-sectional design, we cannot determine causal-and-effect associations between sleep quality, FHD, obesity, and the development of IFG. Secondly, we could not control some important and well-known risk factors, such as snoring, which may be associated with the risk of diabetes [38]. Thirdly, we did not measure dietary intake related to diabetes which may have also influenced sleep patterns. Fourthly, we did not measure impaired glucose tolerance (IGT), another kind of prediabetes.

In summary, our study showed joint effects of poor sleep quality and family history of diabetes as well as family history of diabetes and abdominal obesity on prediabetes in a large representative Chinese adult population. Since family history cannot be modified, populations with a family history of diabetes should be a priority for early prevention, especially body weight management. Environments should be modified for promotion of physical activity, weight control, and sleep cycle [39]. As it seems no measures are currently applied to focus on sleep quality with both prediabetes and diabetes in China, prospective studies are warranted to elucidate the causal relationship between sleep quality and prediabetes and diabetes.

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

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ORIGINAL ARTICLE

Prevalence and clinical significance of potential drug-drug interactions in diabetic patients attended in a tertiary care outpatient center, Brazil

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Abstract The aim of this study is to investigate the prevalence of potential drug-drug interactions (PDDIs), as well as classifying them in relation to level of severity, scientific evidence, time of onset, and potential clinical impact in adult and older adult patients with diabetes mellitus 2 (DM2). This cross-sectional study was conducted in a tertiary care outpatient center. The consecutive sample was made up of 140 patients with DM2. The Anatomical-Therapeutic-Chemical Classification was used for classifying the classes of medications. The PDDIs were analyzed using the DRUG-REAX® system. The relationships between PDDI and the associated factors were ascertained using a multiple logistic regression model. The prevalence of total PDDI was 75 %, and the prevalence of major severity PDDI was 20.7 %. Simvastatin (30.8 %), captopril/enalapril (12.8 %), and oral anti-diabetics/insulin (12.8 %) were the medications which were most involved in the major PDDI, bringing relevant potential clinical impacts such as rhabdomyolysis, hyperkalemia, and important glycemic alterations. Polypharmacy was associated with PDDI (adjusted odds ratio = 10.46, 95 % confidence interval = 4.10–26.71). Diabetics were highly exposed to clinically significant PDDI. It is important that health professionals should be aware of the risks related to PDDI, so that measures may be implemented in order to assure safe care for the patient.

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Introduction

Chronic non-communicable diseases (NCDs) currently represent an important public health problem with high morbidity and mortality and significant economic repercussions. Although NCDs do not occur exclusively in older adults, it is anticipated that, with age, the individual will come to present some morbidity [1, 2]. Among these, one finds diabetes mellitus (DM), which, due to its chronic nature, requires long-term management. As a result, the treatment of DM aims to maintain good glycemic control, which generally prevents the appearance of the chronic complications which make up the principal causes of mortality, morbidity, and worsening of quality of life [3, 4].

As the disease progresses and with the presence of comorbidities such as dyslipidemia and systemic arterial hypertension (SAH), the patient may come to use complex antidiabetic treatments made up of three or more medications, as well as making use of other therapeutic agents for treating other comorbidities [5, 6]. Through this, the individual has greater exposure to the use of polypharmacy, that is, the use of five or more medications, contributing to the occurrence of drug interactions (DDIs) [7–9].

Drug interactions occur when two or more medications are used concomitantly and the actions of one medication (object, substrate) are altered by the presence of another (precipitant, interacting medication), causing an alteration of the clinical or pharmacological effect on the patient's response to the treatment [10, 11]. The present study considers the potential drug-drug interactions (PDDIs). This term refers to the possibility of a given medication altering the intensity of the

pharmacological effect of another medication used simultaneously by the patient [10–12].

Studies in different scenarios have indicated negative outcomes related to DDI, which can result in adverse events, a reduction or increase in the medications' therapeutic effects, an increase in the toxicity of medications, an increase in the health services' costs, failure of the treatment, and/or serious complications for the patient, including the risk of death [8, 9, 12–18].

One study undertaken in Nepal [19] with adult and older adult diabetic patients attended in tertiary healthcare identified a prevalence of PDDI of 52.5 %, of which 92.1 % were of moderate severity. The medications which contributed most to the risk of PDDI were those acting on the cardiovascular system (49.5 %), followed by oral antidiabetics (31.2 %). A study undertaken with diabetic and hypertensive older adults indicated a prevalence of 47.8 % of PDDI, with 93.2 % classified as moderate severity and 6.5 % as major. The medications which contributed most to PDDI in this scenario were acetylsalicylic acid (14.3 %), enalapril (12.6 %), glibenclamide (12.0 %), and digoxin (8.6 %) [15].

However, other studies directed towards evaluating the prevalence of PDDI, as well as its possible significant clinical implications in diabetic adult and older adult individuals, are scarce. In light of these considerations, this study aimed to investigate the prevalence of potential PDDIs, as well as classifying them in relation to level of severity, scientific evidence, time of onset, and potential clinical impact in adult and older adult patients with diabetes mellitus 2 (DM2).

Methods

Study design and setting

This cross-sectional study was conducted in an outpatient center specializing in DM, Arterial Hypertension and Obesity, at the Hospital de Clínicas, University of Campinas, Brazil. The service undertakes an average of 700 free attendances per year for adults and older adult patients, as it is part of the Unified Health System.

Sample selection and data collection

The consecutive sample was made up of 140 adult and older adult patients with DM2, receiving drug treatment with at least two medications, and who had been treated on an outpatient basis for a minimum of 12 months in the service. Data collection took place between May and October 2012. For extraction of the data, patient medical records were consulted, and an instrument was used which was made up of demographic-clinical variables and those related to the drug treatment.

Classification of the potential DDI

The present study considers the potential drug-drug interactions (PDDIs). This term refers to the possibility of a given medication altering the intensity of the pharmacological effect of another medication used simultaneously by the patient [10–12]. Only the PDDI related to major those that were quite severe were considered clinically significant due to the potential impact on the morbidity or mortality of the patients. The analysis of the PDDI was undertaken using the DRUG-REAX® system (Truven Health Products, 2015), which allows the identification of the PDDI according to severity, scientific evidence, time of onset and provides additional information such as potential clinical impact and clinical management [22].

The level of severity was categorized as follows: contraindicated, concomitant drug use is not recommended; major, interaction may be life-threatening and/or require medical intervention to reduce or prevent serious adverse effects; moderate, the interaction may result in aggravation of the patient's condition and/or require a change in the therapy; minor, the interaction would result in limited clinical effects and could include an increase in the frequency or severity of side effects but should generally not require any change in therapy; and unknown, interactions are unknown [22]. In terms of scientific evidence, the PDDIs were categorized as follows: excellent, controlled clinical studies have clearly established the existence of DDI; good, the documentation strongly suggests that there is an interaction, but no controlled clinical studies are available; fair, availability of documentation is poor, although pharmacological considerations exist regarding the interaction, or the documentation is good for a pharmacologically similar drug; and unknown, there is no evidence of such interactions [22]. For the time of onset, the PDDIs were classified as follows: rapid, onset expected within 24 h; delayed, onset not expected to occur within the first 24 h; and not specified, time not known [22].

Analysis of the data

The data collected were transferred to a Microsoft Excel 2010® Windows 8 spreadsheet, using double keying. The medications were classified by the Anatomical-Therapeutic-Chemical Classification—ATC, in level 1—main anatomical group [20]. The description of the qualitative variables was undertaken through the calculation of frequencies and percentages, and for the quantitative variables, measures of central tendency and dispersion were calculated. In order to study the association and the variables of sex, age range, number of drugs taken, body mass index (BMI) (normal, pre-obesity, and obesity), number of comorbidities, time since diagnosis, and HbA1c values with the variables of presence/absence of PDDI, simple logistic regression models were applied [21] and, subsequently, multiple models were constructed with

the stepwise criteria for selecting variables. The HbA1c values used in this study were based on a previous study [23], which demonstrated that HbA1c values between 7 and 8 % contribute to lower risks of mortality in diabetic patients. The results were presented through calculations of the raw and adjusted odds ratios. For all the analyses, a level of significance equal to 5 % was considered, and the SAS (Statistical Analysis System) statistical software, version 9.2, was used.

Results

Clinical-demographic profile

Over a 6-month period, 140 patients with a diagnosis of DM were included in this study. The distribution of these sociodemographic and clinical characteristics is presented in Table 1.

Therapeutic profile and potential drug interactions

The mean number of drugs used was 6.3 (SD 2.6). The majority of patients (79.3 %) were using five or more drugs. A total of 75 active substances were prescribed, with 364 pairs of PDDI being found: 39 (10.7 %) belonged to the group of major severity PDDI, 300 (82.4 %) belonged to the group of moderate severity PDDI, and 25 (6.9 %) to the group of minor PDDI. Contraindicated PDDIs were not found.

Among the 140 individuals, 105 were exposed to at least one PDDI, resulting in prevalence of 75.0 %. Among these patients, more than half (63.2 %) were exposed to between one and three PDDIs (mean of 2.6, SD 1.8). The prevalence of patients exposed to major PDDI was 20.7 % ($n = 29$), the case being that, in this group, 72.4 % were exposed to at least one major PDDI, 20.6 % to two major PDDIs, and 7 % to three major PDDIs. Table 2 presents the data referent to the 105 patients exposed to PDDI. In both the group of older adults and the group of adults, the moderate PDDIs were the most frequent (66.7 %), followed by the major PDDI (27.6 %).

Among the medications which contributed most to major severity PDDI, 50.0 % belonged to group C (cardiovascular system), followed by 17.8 % to group A (digestive system and metabolism) and 17.8 % to group N (nervous system). Simvastatin 30.8 %, captopril/enalapril 12.8 %, and oral antidiabetics/insulin 12.8 % were the drugs which were most involved in these events. In relation to the major PDDI, 86.9 % of the scientific evidence was classified as either excellent or good quality; 47.8 % was classified as delayed, that is, the onset was not expected to occur within the first 24 h (Table 3).

Statistically significant differences were not found in the multiple models between the variable presence/absence of PDDI with sex, age range, BMI, number of comorbidities, time since diagnosis, and HbA1c. In both univariate and multiple analyses, the number of drugs prescribed was associated with PDDI, with a growing risk among both patients who were not using five or more drugs and those who were doing so (OR = 10.46; CI 95 % 4.10–26.71) (Table 4).

Table 1 Demographic-clinical characteristics of patients with diabetes mellitus type 2, attended in a tertiary healthcare outpatient center

Demographic-clinical variables	Number	(%)
Sex		
Female	75	53.6
Male	65	46.4
Age in years		
Mean (SD)	60.5 (9.4)	–
Individuals <60 years	67	47.9
Individuals ≥60 years	73	52.1
BMI		
Mean (SD)	29.5 (6.1)	–
Comorbidities		
Systemic arterial hypertension	121	86.4
Dyslipidemia	93	66.4
Obesity	66	47.5
Peripheral vascular disease	38	27.3
Previous acute myocardial infarction	24	17.5
Angina	13	9.3
Cerebrovascular accident	06	4.3
HbA1C		
Mean (SD)	8.6 (1.9)	–
<7	33	23.6
≥7 and ≤8	31	22.1
>8 %	76	54.3
Fasting glycemia		
Mean (SD)	166.3 (69.3)	–

Discussion

The patients in the present investigation used a number of medications (6.3; SD 2.6) similar to that in other studies held in a tertiary healthcare outpatient center which included patients with DM2 in their samples [24–27].

Approximately 79 % of the patients made use of five or more medications. In the literature, the values for polypharmacy varied from 25.2 to 96.7 % [8, 15, 24, 25, 27, 28]. It is believed that this variation referent to the number of patients using five or more medications may be related to the level of care (primary or tertiary), to the associated morbidities, and to the study design.

In the present study, the prevalence of patients exposed to PDDI was 75 %. Rates of PDDI varying from 52.2 to 93.3 % have been described in patients receiving outpatient treatment in various specialties, including DM2 [19, 24, 25, 27].

Table 2 Distribution of patients with diabetes mellitus type 2 monitored in tertiary care, in relation to exposure to potential drug interactions, by severity

Severity	Number (%) of patients exposed to potential drug interactions[a]		
	Adults	Older adults	Total
Contraindicated	–	–	0 (0)
Major	11 (37.9)	18 (62.1)	29 (27.6)
Moderate	32 (45.7)	38 (54.3)	70 (66.7)
Minor	3 (50.0)	3 (50.0)	6 (5.7)
Total	46 (43.8)	59 (56.2)	105 (100.0)

[a] The patients exposed to more than one potential drug interaction were considered only once, that is, by the interaction with the greatest relevance

In this study, the prevalence of patients exposed to major severity PDDI was 20.7 %. This result is superior to the findings of a Mexican study which presented a prevalence of major PDDI of 3.8 %, in which only 29.5 % of the patients were diabetics [25]. This fact may be associated with the patients' differences in relation to the diagnoses and consequently, in relation to the drug treatment prescribed.

The prevalence of pairs of major severity PDDI was 10.7 % in the present study, this result falling within the values (3.67–17.6 %) present in other investigations with patients receiving outpatient treatment, which included DM2 [19, 24, 26, 27]. The major PDDI are considered clinically relevant, as it is important for health professionals to be aware of the risks related to the PDDI, so that measures may be implemented in order to ensure safe care for the patient.

The medications involved with the greatest frequency in major severity PDDI were simvastatin, captopril/enalapril, and oral antidiabetics/insulin, which is consistent with other studies which presented these combinations [9, 15]. More than half of the participants (58.6 %) had SAH and dyslipidemia,

Table 3 Frequency of pairs of clinically significant major severity potential drug interactions in prescriptions of patients with diabetes mellitus type 2 attended in a tertiary healthcare outpatient center

Drug A	Drug B	Frequency (%)	Potential clinical impact	Evidence	Time
Simvastatin	Amiodarone	10 (25.6)	↑ risk of rhabdomyolysis and myopathy	E	R
	Amlodipine			G	R
Captopril Enalapril	Spironolactone	5 (12.8)	Hyperkalemia	G	D
NPH insulin Insulin R Metformin Glibenclamide	Norfloxacin	4 (10.3)	Important glycemic alterations	E	R
Clopidogrel	Omeprazole	4 (10.3)	↓ clopidogrel efficacy and ↑ risk of thrombosis	E	R
	Amlodipine				NS
Simvastatin	Warfarin	2 (5.1)	↑ risk of rhabdomyolysis and of bleeding	E	D
Captopril	Losartan	2 (5.1)	Hypotension, syncope, kidney failure	E	NS
Amiodarone	Carvedilol Propranolol	2 (5.1)	Hypotension, bradycardia, and cardiac arrest	E	R
Digoxin	Amiodarone Spironolactone	2 (5.1)	Nausea, vomiting and cardiac arrhythmia	E G	D
Carbamazepine	Fluoxetine	2 (5.1)	↑ risk of toxicity of the carbamazepine	G	NS
Atenolol	Diltiazem	1 (2.6)	Hypotension, bradycardia, atrioventricular conduction disturbances	G	R
Atenolol	Clonidine	1 (2.6)	↑ risk of sinus bradycardia	F	NS
Amitriptyline	Fluoxetine	1 (2.6)	Prolongation of the QT interval, torsades de pointes, cardiac arrest	G	NS
Metformin	Topiramate	1 (2.6)	↑ risk of lactic acidosis	F	NS
Hydrochlorothiazide	Lithium	1 (2.6)	↑ of the concentration of the lithium (weakness, tremors, excessive thirst and confusion)	G	NS
Allopurinol	Enalapril	1 (2.6)	Hypersensitivity reactions	F	R

↑ increase, ↓ decrease, *F* fair, *G* good, *E* excellent, *R* rapid, *D* delayed, *NS* not specified

Table 4 Factors associated with the potential drug interactions in patients with diabetes mellitus type 2 attended in a tertiary healthcare outpatient center

Variable	PDDI				Raw odds ratio (C.I. 95 %)	*p* value	Adjusted odds ratio (C.I. 95 %)*	*p* value
	No		Yes					
	n	%	*n*	%				
Sex								
Male	14	21.54	51	78.46	1.00 (ref)	0.3797		
Female	21	28.00	54	72.00	0.71 (0.33; 1.54)			
Age range (years)								
<60	21	31.34	46	68.66	1.00 (ref)	0.0994		
≥60	14	19.18	59	80.82	1.92 (0.88; 4.19)			
BMI								
Normal	12	37.50	20	62.50	1.00 (ref)	0.1385		
Pre-obesity	12	25.00	36	75.00	1.75 (0.66; 4.07)			
Obesity	11	18.33	49	81.67	2.67 (1.00; 7.05)			
No. of drugs								
<5	19	65.52	10	34.48	1.00 (ref)	< 0.0001	1.00 (ref)	<0.0001*
≥5	16	14.41	95	85.59	11.28 (4.45; 28.62)		10.46 (4.10; 26.71)	
No. of comorbidities								
≤2	25	35.21	46	64.79	1.00 (ref)	0.0058		
>2	10	14.49	59	85.51	3.21 (1.40; 7.34)			
Time since diagnosis								
≤60 months	9	21.95	32	78.05	1.00 (ref)	0.5924		
>60 months	26	26.26	73	73.74	0.79 (0.33; 1.87)			
HbA1c (%)								
<7	7	21.2235	26	78.78	1.00 (ref)	0.6389		
≥7 and ≤8	7	22.58	24	77.42	0.82 (0.24; 2.80)			
>8	21	27.63	55	72.37	0.63 (0.23; 1.75)			

associated with DM2. This may explain the greater occurrence of PDDI with cardiovascular system drugs, as well as with medications for controlling dyslipidemia.

In general, the statins are used for preventing cardiac events and are well established for patients with dyslipidemia [29]; accordingly, simvastatin is a medication which is widely prescribed for the patient with DM2, given that dyslipidemia is a frequently associated comorbidity. Combined with amlodipine or amiodarone, there is an increase in the risk for myopathy and rhabdomyolysis; the risk of rhabdomyolysis and bleeding also increases with the use of warfarin [30–32]. In this way, these PDDIs represent a risk to health and consequently require interventions from the multi-professional team for preventing serious adverse effects. These patients must be monitored and guided in relation to signs and symptoms of the disease.

The risk for hyperkalemia occurred with the combined use of captopril/enalapril with spirinolactone in 12.8 % of the PDDI. This phenomenon is usually asymptomatic, and the greatest risk is the occurrence of arrhythmias. One study indicated that the combination of angiotensin-converting enzyme inhibitors with spironolactone gave rise to hyperkalemia, posing serious risks to the patients; 76 % of the patients presented electrocardiographic changes compatible with hyperkalemia (T tenting, QRS widening, or PR prolongation), with two patients dying in the emergency room [33].

One study revealed that the combination of these drugs was also associated with a significant increase in the risk of patients being transferred to the intensive care unit (ICU) or dying. The risk of death after 2 days from the detection of hyperkalemia was 5.3 times greater than in patients who were not exposed to PDDI, which led to this adverse event [34]. The combination, therefore, must be carefully evaluated with regard to the risk and benefit for each patient.

Other important combinations found in this study were for norfloxacin with insulin or oral antidiabetics (10.3 %). According to the literature, the main effect of combining these drugs is severe hypoglycemia [35, 36]. It is important to emphasize that the patient who maintains rigor in metabolic control already presents a risk for hypoglycemia and, associated with the combination of these drugs, the risks increase and may expose the patient to risks of death.

The combination of clopidogrel with omeprazole or amlodipine was also among the most common in this study (10.3 %). The USA's Food and Drug Administration (FDA) issued an alert regarding the interaction of clopidogrel with omeprazole [37]. Omeprazole reduces the antiplatelet effect of clopidogrel by approximately 50.0 %. However, it seems that omeprazole is rapidly eliminated, and the PDDI may be attenuated when the clopidogrel and the omeprazole are administered with an interval of 12 h. In some studies, the concomitant use of calcium channel blockers and clopidogrel was associated with a reduction of the action of the clopidogrel [38, 39]. In other studies, however, this hypothesis was not confirmed, and in these cases, there is no evidence that calcium channel blockers may reduce the efficacy of the treatment using clopidogrel [40, 41]. For this, it is necessary to undertake studies which better seek scientific evidence.

The use of five or more drugs was significantly associated with PDDI. Polypharmacy is a factor which is well documented in the literature as a factor associated with PDDI, independent of the disease investigated, country or place of care, and health treatment [8, 9, 12–18]. The polypharmacy recorded in this study is expected for this population, given that these individuals present an increased risk for cardiovascular diseases, such as SAH, dyslipidemias, and abnormalities related to coagulation. The higher the number of comorbidities, the greater the chances of co-administration of various drugs for the control of DM and its associated comorbidities.

The present study's results confirm the risk to the safety of patients with chronic diseases who are subjected to polypharmacy. The professional team needs to exercise continuous surveillance in relation to identifying signs/symptoms and possible alterations in laboratory examinations which result from PDDI and to review drug treatment so as to propose changes when possible. Furthermore, the professional must advise patients and their family members with the aim of reinforcing the early identification and treatment of these possible clinical implications. It falls to the health system to implement warning systems in the electronic prescriptions, with the aim of detecting and preventing prescriptions with problems, as well as providing databases on PDDI which allow PDDI to be tracked in real time. The use of warning systems for categorizing PDDI by severity, in certain care scenarios, has improved the acceptance of the clinical recommendations, such that specific medications should not be prescribed simultaneously [42].

Among this study's limitations, one finds the selection of the consecutive sample, which may prejudice its external validity. The PDDIs were established through the evaluation of the medical prescriptions of patients treated on an outpatient basis and were not compared with the actual clinical impact caused to the patient, which indicates a field for future investigations. On the other hand, this study, undertaken with diabetic patients, appears to be one of the first to investigate PDDI in this population, which contributes to shedding light on those PDDIs which are clinically significant, and provides data for assisting in developing warning systems for treatment of persons with diabetes, this being a group with greater vulnerability, due to the presence of comorbidities, the increase of possibilities of complications, and the use of complex polypharmacy.

Conclusion

Diabetic patients were exposed to clinically significant PDDI, the case being that polypharmacy increased the chances for PDDI. The most frequent potential clinical impacts were rhabdomyolysis, hyperkalemia, and important glycemic alterations. It is important for health professionals to know the risks related to the PDDI, so that measures may be implemented in order to ensure safe care for the patient. Changing the therapeutic scheme must be discussed within the multiprofessional team and undertaken where possible.

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

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ORIGINAL ARTICLE

Health suggestibility, optimism and sense of responsibility for health in diabetic patients

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Abstract The study examined the relationship between sense of responsibility for health, health suggestibility, and dispositional optimism in diabetic patients (n=110) with (n=56) and without (n=54) complications/accompanying diseases. The two groups of patients did not differ significantly in their sense of responsibility for heath, but health suggestibility was significantly higher and optimism was significantly lower in patients with complications. Health suggestibility and optimism had positive significant correlations with sense of responsibility for health in patients without complications, but in patients with complications, these correlations were not significant. However, the correlations between the two groups did not differ significantly suggesting lack of significant moderation effects due to complications. While it is understandable that suggestibility scores are higher and optimism lower in patients with complications, it is not easy to explain as to why the correlations were significant in patients without complications, but not in patients with complications. Further studies are warranted to draw any clinical implications of these results.

Keywords Diabetes · Dispositional optimism · Health sense of responsibility · Health suggestibility

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Introduction

Diabetes is characterized by chronic hyperglycemia and often accompanied by carbohydrate, protein, and fat metabolism disorders. It is caused by deficiency of insulin, which mainly results from autoimmune damage to the pancreatic beta cells [1, 2]. The World Health Organization (WHO) estimates that diabetes affects 135 million people around the world and predicts that its incidence will increase over the years, especially among young people [3].

Treatment of diabetes includes insulin therapy, proper diet, physical activity, self-control, and education about the disease. Properly selected treatments reduce the risk of complications and improve the quality of life of patients [1, 4]. In recent years, researchers have stressed the role of such psychological factors as patient's attitude towards the disease, adherence to medical recommendations, and patient–doctor relationship in the effectiveness of treatments [1, 5]. Research suggests that the patient–doctor relationship is characterized by numerous irregularities, which may adversely affect treatment outcomes [3–5]. Suchocka's [6] identification of 'sense of responsibility for health' as an important factor in treatment allowed for a new approach to diabetes therapy. The sense of responsibility for health construct is defined as self-perceptions relating to motivation and use of various behavioural strategies to keep good health [6]. Two aspects characterize sense of responsibility: active involvement and adequate behaviour. Whereas active involvement concerns cognitive and motivational aspects related to the need for undertaking appropriate actions to maintain good health, adequate behaviours concern actions taken to maintain health or make improvements. In this study, sense of health responsibility is conceptualized as a disposition, possibly shaped over many years, rather than temporary motivational and behavioural measures taken when medically required.

In examining the factors related to patients' sense of responsibility of health, we identified dispositional health suggestibility and optimism as its potential correlates. These factors have been examined infrequently in human health promotion studies and have not been generally considered as part of therapy in patients with diabetes; furthermore, their interrelationships have not been examined.

Health suggestibility, a construct developed by Jaworski and Adamus, is defined as a relatively stable disposition to yield to others' opinions. Health suggestibility is often examined within the context of interpersonal relationships. Research suggests health suggestibility is related to such demographic factors as age and sex and such psychological factors as level of intelligence, anxiety, self-esteem, and sense of control [7]. However, most studies on health suggestibility have pertained to healthy people. To the best of our knowledge, no studies have been conducted on the relationship of health suggestibility with other personality traits on individuals diagnosed with diabetes.

Research suggests that dispositional optimism is a personal resource that is related to physical and psychological health. Optimism may help facilitate the attainment of success in life, increase resistance to stress, and correlate with the inclination towards making behaviour changes favourable to better health [8, 9].

This exploratory study was designed to examine (1) if diabetic patients with and without complications differed with respect to their self-perceptions of health suggestibility, dispositional optimism, and sense of responsibility for health and (2) the magnitude and directions of correlations of health suggestibility and optimism with sense of responsibility for health in diabetic patients with and without complications.

Given that these variables have not been examined with diabetic patients, no predictions are being made as to the differences on these variables between the two groups. However, on logical grounds, we would not expect the two groups of patients to differ on sense of responsibility for their health given that diabetes is a chronic condition and most patients have to actively manage their disease. However, a question of interest is whether patients with complications show higher levels of suggestibility to health-related suggestions and lower levels of optimism. Added complications may make patients more suggestible to seeking alternative treatments or complying with prescribed medical regimen. Alternatively, having complications may make patients less optimistic about treatment outcomes. Such a finding might have clinical implications by targeting these two variables as needed to improve treatment outcomes.

As regards the correlations between health suggestibility and optimism in diabetic patients with and without complications, our interest was to see if having complications moderates the magnitude and direction of relationships. If suggestibility and optimism differ in the two groups, there is also a possibility that the correlations might also differ. If they do differ, then this finding may have clinical implications in terms of how to work with these variables for improving treatment outcomes.

Materials and methods

Participants were 110 (65 men and 45 women) patients with diabetes, ranging in age between 18 and 71 years (average age=36.60 years, SD=14.06). The inclusion criteria were (1) age above 18, (2) clinical diagnosis of diabetes (type 1 or type 2), (3) ongoing clinical treatment, (4) use of medical treatment supervised by a diabetologist, (5) use of dietetic counselling supervised by a dietician, and (6) completion of informed consent to participate in the study.

Based on information obtained from interviews, patients were divided into two groups: group 1 consisted of 56 diabetic patients without complications and accompanying diseases and group 2 had 54 diabetic patients with complications and/or comorbidities.

Three instruments were used in this study: Health Suggestibility Scale, Sense of Responsibility for Health Scale, and Life Orientation Test-Revised.

The Health Suggestibility Scale, developed by Jaworski and Adamus, consists of nine items for use with both healthy individuals and patients. The first five items are rated on a five-point scale ranging from 'almost always' (5) to 'never' (1), and the remaining four questions are rated on a five-point scale ranging from 'disagree' (1) to 'totally agree' (5). The total score, the sum of ratings on the nine items, was used in this study with higher scores reflecting higher suggestibility. Cronbach's alpha coefficients were reported at .65 in a pilot study by Jaworski and Adamus (unpublished data). Cronbach's alpha coefficient in this study for diabetic patients was found to be .72.

The Sense of Responsibility for Health Scale (HSRS), developed by Adamus, consists of 12 items rated on a five-point scale (1—hardly ever, 2—rarely, 3—sometimes, 4—often, 5—nearly always/very often). The scale yields a total score (HSRS-T) and two subscale scores: Active Involvement (HSRS-AI, 7 items), and Adequate Behaviour (HSRS-AB, 5 items). Higher scores reflect higher sense of responsibility for health. A pilot study (unpublished) found Cronbach's alpha coefficients for HSRS-AI, HSRS-AB, and HSRS-T at .73, .70, and .74, respectively. In this study, Cronbach's alpha coefficients with diabetic patients were .68, .67, and .75, respectively for the three scores.

The Life Orientation Test-Revised, developed by Scheier, Carver, and Bridges, was translated into Polish by R. Poprawa and Z. Juczyński. The test consists of 10 items, 6 of which are designed to measure dispositional optimism. The items are rated on five-point scales (0—not at all true of me, 1—somewhat untrue of me, 2—neither true nor untrue of me (neutral), 3—

somewhat true of me, 4—completely true of me). The total score derived from the six items was used in the study with higher scores reflecting higher levels of self-perceived optimism. Cronbach's alpha coefficient was found to be .76 in a pilot study (unpublished); in this study, it equalled .72 [10].

Additionally, data on patient's age, body weight, and body height were also gathered and body mass index (BMI) was calculated and interpreted in accordance with the recommendations of WHO. BMI assesses the risk of diseases associated with overweight and obesity (including ischemic heart disease and atherosclerosis).

Results

Demographic characteristics

Of the 110 patients, 88 (80 %) had type 1 diabetes and 22 (20 %) had type 2 diabetes. The patients were divided into two groups: group 1 consisted of diabetic patients without complications and group 2 consisted of patients with diabetic complications and/or accompanying diseases. The two groups did not differ significantly on age (t=−1.34; p=0.18; means (and SD) for group 1 and group 2 were 35.90 (11.60) and 39.2 (14.2), respectively).

Disease complications

In group 2, the number of patients reporting complications and diseases was as follows: 7 retinopathy, 6 polyneuropathy, 2 diabetic foot, 18 cardiovascular disease (e.g., hypertension, coronary artery disease and cardiac arrhythmias), 19 thyroid disease (e.g., hypothyroidism, Hashimoto's thyroiditis, Graves' diseases), 8 digestive system conditions (e.g., food allergy, irritable bowel syndrome, celiac disease, anaemia, ulcers), 12 osteoarticular system (e.g., connective tissue disease, the intervertebral discs, arthrosis, osteoporosis, connective tissue disease), 2 urinary system (e.g., urinary diseases), 4 respiratory system (e.g., bronchial asthma), and 7 others (e.g., endometriosis, Addison disease, and neurosis).

Differences on anthropometric parameters

The two groups of patients did not differ significantly on body weight (t=−1.45; p>.05) and body height (t=1.63; p>.05) (Table 1). The two groups, however, differed significantly (t=−2.82; p<0.01) on BMI; patients with uncomplicated diabetes had BMI in the normal range (mean=23.81 kg/m^2) and patients with complicated diabetes and/or accompanying diseases had higher BMI indicating overweight (mean= 26.39 kg/m^2) (Table 1).

Differences between groups on optimism, health suggestibility, and sense of health responsibility

A preliminary analysis using the Kolmogorov–Smirnov Z test suggested that the normal distribution assumption was met for all scales and subscales used in this study.

A multivariate analysis of variance (MANOVA) was performed to test differences between the two groups of diabetic patients on optimism, health suggestibility, and sense of responsibility for health total score. The analysis revealed an overall significant effect (Wilks' lambda λ=0.93; F(3, 106)=2.75; p<.05; Eta=.07). Thus, further univariate analyses were conducted on each of the three variables by means of t tests (two-tailed).

As expected, group 1 diabetic patients without complications had significantly higher (t=2.03, p<.05, with Cohen's d=.38, small effect size) dispositional optimism scores (mean=15.17, SD=3.94) than group 2 patients with complications and/or accompanying diseases (mean=13.59, SD=4.86).

Group 2 diabetic patients with complications scored significantly higher (t=−2.08, p<.05, with Cohen's d=.39, small effect size) on health suggestibility (mean=26.38, SD=3.65) than group 1 patients without complication (mean=25.00; SD=3.34). However, the two groups did not differ significantly on sense of responsibility for health total score. Also, a MANOVA on the two groups of patients did not differ significantly (F(2, 107)=2.32, p>.05) on the two sense of responsibility subscales (adequate behaviour and active involvement; see Table 2 for univariate t test results).

Correlations of optimism and health suggestibility with sense of health responsibility

In group 1 diabetic patients without complications, optimism had significant positive correlations with the sense of responsibility for health total score (r=0.34; p<.01) and its two subscales, adequate behaviour (r=0.37; p<.01) and active involvement (r=0.30; p<.05). However, in group 2 patients with complications, both dispositional optimism and health suggestibility had no significant correlations with health sense of responsibility (Table 3). Z tests for testing differences in independent correlations (two-tailed) between the two groups showed no significant differences on any of the correlations, suggesting lack of moderation effects due to complications.

Discussion

As expected, the two diabetes patient groups (with and without complications) did not significantly differ on the general level of sense of responsibility for health. This result is understandable given that both groups of patients were diabetic and they need to be conscientious to actively follow through their medical regimen to keep their disease in check.

Table 1 Groups' anthropometric parameters

Dependent variable	Group	Mean	SD	Std. error	95 % confidence interval		*t* value	*p* value	Cohen's *d*
					Lower bound	Upper bound			
Body weight (kg)	1	70.77	15.52	2.31	66.19	75.35	−1.45	0.15	−0.28
	2	75.54	18.98	2.36	70.87	80.20			
Body height (cm)	1	171.63	9.46	1.26	169.14	174.13	1.63	0.11	0.31
	2	168.70	9.39	1.28	166.16	171.25			
BMI (kg/m^2)	1	23.82	4.01	0.64	22.55	25.09	*−2.82*	*0.01*	*−0.53*
	2	26.40	5.48	0.65	25.11	27.69			

Group 1—diabetes without complications and accompanying diseases (n=56), group 2—diabetes with complications and/or accompanying diseases (n=54), SD—standard deviation, t value—value for independent groups, p value—type 1 error probability (two-tailed)

The two patient groups differed significantly on health suggestibility and dispositional optimism. Although it is tempting to conclude that patients with complications are more suggestible and less optimistic than patients without complications, the small effect sizes associated with these differences suggest caution in interpreting these results warranting further study. Furthermore, the differences are confounded with group membership—that is, there were simply more suggestible people in group 1 and fewer optimistic people in group 2 and the differences have no relationship with complications or not having complications. In any case, one might ask what might contribute to the differences between the two patient groups on health suggestibility and optimism, if in fact they exist? It is possible that patients with complications seek out alternative treatments and, consequently, are more likely to be open to suggestions, but tend to be less hopeful that something would work better—things didn't work before, how can we expect them to work now? The effect size associated with these differences was possibly small because the suggestibility and optimism were measured as trait (relatively stable) variables and not as state variables.

These results do not, however, reflect the importance of suggestibility and optimism to treatment outcomes, as no data were gathered on treatment outcomes. A future study should examine the possibility of improving treatment outcomes by having doctors address these factors when working with patients. Suggestibility and optimism are not necessarily positive traits—since high levels of both may lead to trying out quack treatments, leading to poor health outcomes or other complications. Some degree of suggestibility and optimism may be helpful to treatment outcomes, but these are matters for further investigation.

An interesting finding was that correlations of health suggestibility and optimism with sense of responsibility for health were significant in group 1 patients without complications, but not in group 2 with complications. The differences in correlations between the two groups were not significant, possibly because of small sample size in each group. If the differences are due to chance as our results suggest, then one might argue that health suggestibility and optimism correlate equally well with their sense of responsibility for health in all diabetic patients. If the differences in correlations were significant, then it would not be easy to explain as to what factors might

Table 2 Differences in patients with and without complications on selected personality characteristics

Dependent variable	Group	Mean	SD	Std. error	95 % confidence interval		*t* value	*p* value	Cohen's *d*
					Lower bound	Upper bound			
Dispositional optimism	1	15.32	3.94	0.60	14.14	16.51	*2.03*	*0.05*	*0.38*
	2	13.59	4.86	0.61	12.39	14.80			
Health suggestibility	1	25.00	3.35	0.47	24.07	25.93	*−2.08*	*0.04*	*−0.39*
	2	26.39	3.66	0.48	25.44	27.33			
Adequate behaviour	1	20.96	2.52	0.34	20.30	21.63	0.97	0.34	0.18
	2	20.50	2.52	0.34	19.82	21.18			
Active involvement	1	21.66	5.08	0.60	20.48	22.84	−1.22	0.22	−0.23
	2	22.70	3.73	0.61	21.50	23.91			
The general level of health sense of responsibility	1	42.63	6.83	0.82	41.01	44.24	−0.50	0.62	−0.09
	2	43.20	5.24	0.83	41.56	44.85			

Group 1—diabetes without complications and accompanying diseases (n=56), group 2—diabetes with complications and/or accompanying diseases (n=54), SD—standard deviation, t value—value for two independent groups, p value—type 1 error probability (two-tailed)

Table 3 Correlations of optimism and health suggestibility with sense of health responsibility

Analysed variables		Adequate behaviour	Active involvement	The general level of sense of responsibility for health
Group 1—diabetes without complications and accompanying diseases				
Dispositional optimism	*r*	*0.37*	*0.30*	*0.34*
	p	*0.01*	*0.02*	*0.01*
Health suggestibility	*r*	0.13	0.06	0.10
	p	0.16	0.33	0.24
Group 2—diabetes with complications and/or accompanying diseases				
Dispositional optimism	*r*	0.05	0.12	0.11
	p	0.36	0.20	0.22
Health suggestibility	*r*	-0.01	0.18	0.12
	p	0.46	0.10	0.19

r—Pearson's correlation coefficient, *p*—type 1 error probability (two-tailed)

have contributed to such results. Thus, further study is needed to see if the current results are replicated.

In summary, it should be noted that this study was of a correlational nature and thus no cause and effect relationships can be drawn as to the effects of complications on the variables or the relationships among the variables. Further research is warranted that includes treatment regimen compliance as a variable. It would also be helpful to understand by interviewing patients with complications as what might have contributed to their higher suggestibility and lowered optimism scores. In this study, suggestibility and optimism differences are confounded with group membership and measured as trait variables. A long-term study of patients before and after they develop complications may help provide useful information on changes in suggestibility, optimism, and sense of responsibility for health.

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ORIGINAL ARTICLE

Factors associated with mortality in children with diabetic ketoacidosis (DKA) in South India

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Abstract Mortality in diabetic ketoacidosis (DKA) among children has been reported to be 0.3–3 % in developed countries. Based on the limited data from developing countries, the mortality reported is as high as 13.4 %. A prospective study was conducted to identify the factors leading to high mortality in children with DKA in South India. This was a study of 118 episodes of DKA among children, admitted in a pediatric tertiary care center at Chennai. Clinical presentation, laboratory parameters at admission, parameters during treatment, and complications were considered as risk factors. All children were followed up till discharge from hospital or death. Univariate and multivariate analyses for risk factors were undertaken. Altered sensorium and higher osmolality at admission, delayed diagnosis, cerebral edema, shock, renal failure, and sepsis were the major risk factors associated with mortality in multivariate analysis. Cerebral edema was encountered in 23.7 %, shock in 12.7 %, sepsis in 11 %, and renal failure in 9.3 %. The overall mortality rate was 11 %. Delayed diagnosis may be the root cause for high mortality in children with DKA in developing countries. There is an urgent need to create awareness among physicians, teachers, and parents to avoid a delay in diagnosis and decrease the mortality in children with DKA. Higher incidence of cerebral edema, shock, renal failure, and sepsis are unique problems identified in this study. There is a need for further studies on fluid management of shock, strategies for management of renal failure in DKA, and use of antibiotics in DKA in developing countries.

Keywords DKA · Mortality · Renal failure · Shock · Sepsis · Cerebral edema · Risk factors

Introduction

Diabetic ketoacidosis (DKA) is one of the medical emergencies in children with diabetes mellitus (DM). Mortality rates in children with DKA from developed countries vary from 0.3 to 3 % [1–5]. Existing data from developing countries have shown mortality rates varying from 3.4 to 13.4 % [6–15]. Cerebral edema is the major contributing factor for death in DKA from developed countries. However, the data is different from developing countries. In addition to cerebral edema, sepsis, shock, and renal failure have been identified as contributory factors for mortality. Similar data from developing countries like India, Pakistan, and Bangladesh are very recent. There are no prospective studies from developing countries to address the factors associated with mortality in DKA among children. The root cause for existing high mortality in developing countries needs to be addressed. It is mandatory to identify the factors associated with increased mortality so that they can be addressed to effectively reduce death in DKA. The Institute of Child Health and Hospital for Children, Chennai, is a pediatric tertiary care referral center, which treats large numbers of children with DKA. Hence, this study was undertaken to identify the risk factors associated with mortality in children with DKA from South India.

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Methodology

This prospective study was conducted at the pediatric intensive care unit (PICU) of a tertiary referral center at Chennai, South India, between 2009 and 2013. All children aged less than 12 years and diagnosed to have DKA during the study period were included. The sample size was calculated based on the pilot data from the retrospective study undertaken at the same institute, with type 1 error at 5 %, power of 80 %, and estimated mortality of 12 %. The sample size based on this was arrived to be 117 episodes of DKA. Children with recurrent episodes of DKA needing admission were also included for analysis, as the risk factors were different for each episode. Children partially treated elsewhere and referred to our institute and whose initial details were not traceable were excluded. Study variables were socio demographic factors: age, gender, new onset DKA or DKA among the established diabetes, diabetic age, number of previous medical consults for this illness, initial diagnosis, delayed diagnosis, delay in treatment, precipitating factors for DKA among diabetic children, infections, poor compliance to therapy, and poor social support. Variables at admission were clinical features, hemodynamic status, sensorium, blood glucose, serum osmolality, blood gases, anion gap, severity of DKA, azotemia, and electrolytes. Fluid bolus given for resuscitation of shock was studied. Variables during therapy were serum osmolality at 6 h; serum pH at 6 h; duration of insulin infusion; duration of acidosis; dyselectrolytemia—hypokalemia, hyperkalemia, hyponatremia, and hypernatremia; recovery of acidosis; cerebral edema; shock; sepsis; infections; acute respiratory distress syndrome (ARDS); acute renal failure; rhabdomyolysis; and HBA1C levels. All children were treated at the PICU and were followed up to discharge from hospital with recovery or death.

Data were analyzed using Epi Info™ 7.1.1.0 and SPSS software. Proportions were calculated. Student's *t* test/Fisher's exact as appropriate in the case of parametric data and Mann-Whitney *U* test in case of non-parametric data were used. As a part of risk factor analysis, children who died were classified as group 1 and children who survived were classified as group 2. Comparison of study parameters between the two groups was undertaken and risk factors analyzed. $P<0.05$ was considered as significant. Variables found to be significant by univariate analysis were entered into multivariate analysis for significance. This study was approved by the institutional ethical board, ethical committee of Madras medical college, Chennai and informed written consent was obtained from the parents or caregivers of these children.

Case definitions used for the study are as follows: new onset DKA—children diagnosed to have diabetes for the first time and presenting with DKA; criteria for DKA, hyperglycemia—blood glucose ≥200 mg/dl; venous pH <7.3 or bicarbonate <15 mmol/l; ketonemia and/or ketonuria; diabetic age—duration of diabetes in completed years; number of pediatric consults—number of physician visits for this illness until the diagnosis of diabetic keto acidosis; initial diagnosis—diagnosis entertained by the first physician for this illness; delayed diagnosis—any child with DKA who was not diagnosed to be DKA at the time of the first health-care consult was considered as delayed diagnosis; missed diagnosis—any alternate diagnosis given by the treating physician for this episode of illness, prior to admission in the PICU was considered as missed diagnosis; delayed treatment was defined when the appropriate treatment for DKA was not commenced within 3 h of diagnosing DKA; precipitating factors for DKA among diabetic children were inadequate management during intercurrent illness and poor compliance to therapy; poor compliance to therapy was defined as missing one or more doses of insulin or inappropriate reduction of the prescribed insulin dose without indication or medical advice. Poor social support or unstable family circumstance was defined by the presence of any one of the following parameters—single parent or lack of both parents, unsupervised insulin self-injections, lack of blood glucose monitoring at home or unsupervised blood glucose monitoring at home, child not attending school for reasons other than hospitalization for a duration more than 1 month, and lack of regular follow-up at the diabetic clinic—defined as no follow-up visit for more than 12–16 weeks; hemodynamic status—the presence or absence of shock; shock was defined as tachycardia; and signs of poor end organ perfusion, as defined by poor peripheral pulses with normal central pulses, prolonged capillary refill (more than 3 s) or flash refill, altered sensorium, cool extremities and decreased urine output. Normotensive shock was considered if blood pressure was normal. Hypotensive shock was considered if systolic blood pressure was below the fifth percentile for age. Septic shock was considered with tachycardia and signs of poor end organ perfusion, as defined by poor peripheral pulses with normal central pulses, prolonged capillary refill or flash refill, altered sensorium, cool extremities, decreased urine output, with hypothermia or hyperthermia, tachypnea, leukocytosis, or leucopenia in the background of suspected or confirmed infection. Sensorium grading at admission using the AVPU scale, A—alert, P—responsive to pain, V—responsive to verbal stimuli, and U—unresponsive. Pain responsiveness and unresponsiveness were considered as altered sensorium . Blood glucose—bedside estimation using glucometers, was confirmed by laboratory estimation of blood glucose. Serum osmolality—calculated osmolality—2Na+Gl in mg/dl/18 expressed as mOsm/kg. Blood gases as measured by ABL80 machine at the PICU. Anion gap calculated as $Na-(Cl+HCO_3)$. Severity of DKA as: mild—venous pH <7.3 or bicarbonate <15 mmol/L; moderate—venous pH <7.2 or bicarbonate <10 mmol/L; and severe—venous pH <7.1 or bicarbonate <5 mmol/L. Azotemia was defined as blood urea more than 40 mg/ dl. Corrected sodium (actual sodium) was measured Na+1.6 ([glucose—100]/100) mg/dl. The duration of insulin infusion was the time between commencements of

insulin infusion and subcutaneous insulin. Recovery of acidosis was the time taken from onset of treatment of DKA to attain a pH of 7.36 and/or bicarbonate of 15 mEq/L. Hypokalemia is defined as serum K of <3.5 mEq/L, hyponatremia serum Na of <135 mEq/L, hyperkalemia serum K of >5.5 mEq/L, hypernatremia serum Na >150 mEq/L, and hypoglycemia blood glucose of <70 mg/dl. Criteria for cerebral edema are as follows: cerebral edema was diagnosed with one of the diagnostic criteria or two major criteria or one major and two minor criteria [5]. Diagnostic criteria are as follows: abnormal motor or verbal response to pain, decorticate or decerebrate posture, cranial nerve palsy (especially 3, 4, and 6), abnormal neurogenic respiratory pattern (e.g., Cheyne-Stokes respiration and apneusis). The major criteria are altered mental status/fluctuating level of consciousness, sustained heart rate deceleration (decline more than 20 bpm) not attributable to impaired intravascular volume or sleep state, and age inappropriate incontinence. The minor criteria are vomiting, headache, lethargy or being not easily aroused from sleep, diastolic pressure >90 mmHg, and age <5 years. Infections: the presence of fever in DKA was considered as infection to start antibiotics. This was categorized as sepsis, bronchopneumonia, urinary tract infection, skin and soft tissue infection, otitis media, and acute CNS infection based on clinical and/or radiological or other laboratory investigations. If there was no identifiable focus of infection, it was categorized as fever without a focus. Isolated mucosal candidiasis of the external genitalia or oral cavity was not considered as an infection predisposing to DKA. Sepsis was defined as follows: documented blood stream infection and/or two of the four systemic inflammatory response syndrome (SIRS) criteria . SIRS was defined as temperature more than 38 °C or less than 36 °C, tachycardia or bradycardia for age, tachypnea, and leucopenia or leukocytosis. ARDS: acute onset, bilateral CXR infiltrates, non-cardiac etiology, and P_aO_2/F_1O_2 ratio <200. Acute renal failure—as defined by pediatric modified RIFLE [16] criteria, is the estimated creatinine clearance decrease by 75 % or estimated creatinine clearance less than 35 ml/mt/1.73 m^2 or urine output less than 0.3 ml/kg/h for 24 h or anuria for 12 h. Children with azotemia at presentation whose values normalized at less than 6 h of fluid therapy were considered to be prerenal. Rhabdomyolysis was defined as raised CPK levels more than three times the upper limit of normal with or without myoglobinuria and renal failure. HBA1C levels ≤7.5 %—was considered good glycemic control >7.5 %—was considered poor glycemic control.

Results and analysis

During the study period, 120 episodes occurred among 102 children, of which two episodes among two children were excluded as their initial parameters were not available for analysis. The study included 118 episodes of DKA among 100 children. Ninety-two children had one episode, two children had two episodes each, four children had three episodes, and one child each had four and six episodes. Among these eight children with more than one episode, seven were girls. Age distribution revealed increasing numbers of children with increasing age. Male to female ratio was 1:1.7. Sixty-eight episodes (57.6 %) were among new onset diabetic children and 50 episodes (42.4 %) were among children with established diabetes. Sixteen percent of DKA among children with established diabetes and 64.7 % of new onset DKA had delay in diagnosis. Of the infants, 85.7 % had delayed diagnosis in comparison to 58 % among school-going children. The reasons for delay in the diagnosis were lack of parental awareness about diabetic symptoms, lack of awareness among physicians, and delay in transport to an appropriate center where a structured diabetic care team was available. The referral diagnosis in DKA children were UTI, acute febrile illness, bronchopneumonia, bronchiolitis, sepsis, myalgia, renal failure, septic shock, acute encephalopathy, acute abdomen, constipation, acute CNS infection, and pancreatitis. Among children with established diabetes single parents, lack of adequate blood glucose monitoring at home, unsupervised injections at home, and school dropouts were common. Preadmission therapy was hypotonic fluids, intravenous boluses for dehydration, bicarbonate therapy without indication, use of antiemetic drugs exclusively, continuing subcutaneous insulin in routine doses despite severe acidosis, and insulin boluses. Finger prick estimation of blood glucose was not done as a routine by the consulting physicians even in sick children. This study revealed only 11 children to have undergone a finger prick estimation of blood glucose during physician consultation.

History revealed polyuria, polydipsia (97 %), breathlessness (86 %), vomiting (80 %), altered sensorium (70 %), fever (56 %), dehydration (41 %), abdominal pain (35 %), and leucorrhea (8.4 %). Leucorrhea was encountered in 24 children on examination but was overlooked by parents or caregivers in majority of the children. At the emergency room, only 42 % were alert, 27 % were verbal responsive, 26 % were pain responsive, and 5 % were unresponsive. Of the children, 12.6 % were presented with shock at the emergency room. Of the episodes, 45.8 % were severe DKA, 30.5 % were moderate episodes, and 23.7 % were mild episodes. Clinical features at admission are summarized in Table 1.

Univariate analysis of the clinical features at presentation revealed the presence of altered sensorium (being pain responsive or unresponsive) and shock to be significant factors associated with mortality in DKA. Age, gender, and new-versus-known diabetic children did not reveal any statistically significant difference as a risk factor for mortality. However, delay in diagnosis was identified to be a statistically significant risk factor for mortality with a p value of 0.001 (11 of the 52 with delay versus 2 of the 66 without delay; odds ratio (OR) 8.5

Table 1 The univariate analysis of the clinical features

Clinical features	Non-survivors (13)	Survivors (105)	*P* (significance <0.05)
Polydipsia	12	94	0.585
Polyuria	12	98	0.61
Abdominal distension	2	12	0.65
Abdominal pain	5	36	0.762
Dehydration	9	41	0.07
White discharge	5	20	0.14
Weight loss	6	54	0.77
ALOC	12	71	0.05*
Shock	8	7	0.00001*
Breathlessness	11	91	0.55
Fever	10	51	0.076
Vomiting	12	78	0.296

*p value <0.05

(1.8–40.7). Biochemical parameters at admission are shown in Tables 2 and 3 and during therapy in Table 4.

Among the dyselectrolytemia encountered, hypernatremia (p=0.00) and declining trend of sodium (p=0.001) were significant among children who died in comparison to those who survived. Hyponatremia (p=0.54), hypokalemia (p=0.08), and hyperkalemia (p=0.001) did not reveal any significant difference. Among the other risk factors, sepsis (p=0.00), renal failure (p=0.00), shock (p=0.00), and cerebral edema (p=0.00) were found to be statistically significant among those who died of DKA. All the factors significant in univariate analysis were subjected for backward regression multivariate analysis, and the findings are summarized in Tables 5 and 6. Mean HBA1C among the two groups did not reveal any significant difference. Among the 13 children who died, the major problems encountered were cerebral edema in 12, shock at admission in 12, delayed diagnosis in 11, acute renal failure in 8, culture-proven sepsis in 8, and ARDS in 1 child. Cerebral edema was diagnosed as per clinical criteria and was diagnosed in the majority of children (26 out of the 28) within the first 6 h of therapy. The documented serious infections in children with DKA were UTI (14), culture-positive sepsis (13), skin and soft tissue infections (12), bronchopneumonia (5), and mucormycosis (2). Though fever was considered as infection to start antibiotics, not all children with fever had an identifiable focus of infection, and children without fever at presentation did have documented infections with DKA. Combinations of multiple problems were encountered children with DKA in this study.

Table 2 Profile of biochemical parameters at admission

Parameters	Median	Range
Glucose (mg/dl)	509.5	200–922
Osmolality (mOsm/kg)	301.5	271–363
Bicarbonate (mg/dl)	5.05	1–14
Initial pH	7.08	6.7–7.38
$PaCO_2$	15	5.3–58
Base deficit	−23.3	−6.6–36.8
Anion gap	27.8	17.5–39

Risk-factor-related mortality for renal failure is 72.7 % (8 out of 11), sepsis is 57 % (8 out of 14), shock is 53.3 % (8 out of 15), cerebral edema is 42.8 % (12 out of 28), and for delayed diagnosis, it is 21 % (11 out of 52). Summary of all the risk factors by univariate and multivariate analyses are shown in Table 7.

Discussion

Delayed diagnosis, altered sensorium in the form of pain responsive or unresponsive at admission and increased serum osmolality at admission, increased incidence of cerebral edema, sepsis, renal failure, shock are the major factors identified for the increased mortality in DKA. Some of these factors have already been reported to be risk factors for mortality in DKA. Zabeen et al. [15] reported cerebral edema in 7.5 % and renal failure in 3.7 %. Mortality was 13.4 %. The causes of death were cerebral edema, septicemia, and pneumonia. Madiha et al. [7] reported shock at presentation in 19.3 % and sepsis in 4.5 %. Cerebral edema was encountered in 6.8 %. The overall mortality was 3.4 %. Cerebral edema, sepsis, and ARDS were the causes of death in DKA. Jeyashree et al. [9] reported hypokalemia in 41 %, hypoglycemia in 15 %, cerebral edema in 13.2 %, and pulmonary edema in 3 %. Overall mortality was 13.2 %. Osmolality at admission was the only significant factor associated with mortality. Septic shock, cerebral edema, pulmonary edema, and hypokalemia with ventricular tachycardia were the causes of death.

Table 3 Univariate analysis of the biochemical variables at admission

Parameter	Non-survivors (13) median and range	Survivors (105) median and range	*H* statistic	*P*
Blood glucose (mg/dl)	600 (200–922)	500 (245–827)	2.11	0.145
Sodium (mEq/L)	140 (130–165)	136.1 (125–150)	6.00	0.01*
pH	6.9 (6.7–7.1)	7.1 (6.72–7.38)	15.38	0.00*
Potassium (mEq/L)	4.7 (1.5–6)	4.2 (2.7–7)	2.25	0.13
Bicarbonate (mg/dl)	3 (1–9)	5.5 (1.2–15)	6.57	0.01*
$PaCO_2$	11 (6.8–20)	16 (5.3–58)	9.88	0.00*
Anion gap	31 (28.4–39)	27 (17–39)	4.6	0.03*
Urea (mg/dl)	48 (18–134)	34 (15–120)	5.5	0.02*
Osmolality (mOsm/kg)	313 (293–363)	300 (277–329)	9.60	0.00*
Total count (cell/cumm)	15,000 (4500–34,000)	12,000 (1790–45,000)	2.4	0.16

*p value <0.05

Lokesh Kumar et al. [10] from India reported hypotensive shock in 48.1 % and cerebral edema in 26 %. Overall mortality was 9 %. Cerebral edema was the major cause of death. Kanwal SK et al. [11] published that the mortality was 12.7 %, with cerebral edema with or without renal failure and sepsis accounting for most of the deaths. They reported cerebral edema in 14.5 %, renal failure in 7.2 %, and infections in 16.3 %. Prasad et al. [12] reported mortality to be 12.5 %. The adverse outcome was reported as 17.5 %.

Altered sensorium at admission is probably due to severe dehydration, shock, severe acidosis, or cerebral edema at admission. Among the biochemical parameters, higher osmolality at presentation was significantly associated with death in DKA. This may be a consequence of severe dehydration at presentation following delay in diagnosis of DKA. The reported incidence of cerebral edema varies from 0.1 to 1 % in the developed countries. The case fatality rate varies from 20 to 90 % in different studies. Incidence of cerebral edema in this study was 23.7 %, and the case fatality rate was 42.8 %. The rate of occurrence of cerebral edema is much higher in this study. The risk-factor-related mortality in DKA in developed countries and developing countries is nearly the same. Hence, factors predisposing for such high occurrence of cerebral edema needs to be identified. This high incidence of cerebral edema is similar to the existing literature based on retrospective data from India.

Among the other risk factors, sepsis needs to be identified early and appropriate antibiotics be prescribed. Sepsis was encountered in 12 % of the children with a case fatality rate of 75 %. For the purpose of this study, only culture-proven cases have been considered as sepsis. Overall infections have been identified as risk factors for mortality in various studies in developing countries [7–10, 17]. Infections in DKA worsen the metabolic control of glucose due to insulin resistance and also leads to MODS resulting in poor outcome in DKA. It is difficult to identify children with sepsis in DKA by clinical examination at presentation. Fever in DKA signifies infection unless proved otherwise; however, it is difficult to identify the focus of infection in all children with fever. Also infections can be present without fever in DKA. The clinical signs and laboratory parameters of sepsis and severe dehydration overlap in children with DKA. Parameters like tachypnea, tachycardia, delayed capillary leak, shock, and hypotension are common for hypovolemia and sepsis in children with DKA. Similarly, leucocytosis in children with DKA can be a stress response rather than infection in DKA. Occurrence of infections is high in DKA, and sepsis is a significant risk factor for mortality in this study. Hence, it may be ideal to start antibiotics in DKA until infection has been ruled out among the children from developing countries.

Renal failure in DKA is associated with significant mortality in DKA. The incidence of renal failure in this study was

Table 4 Comparison of biochemical parameters during therapy

Parameter (median)	Non-survivors	Survivors	Chi-square/*H*	*P*
pH at 6 h	6.96	7.3	25.2	0.00*
Osmolality at 6 h (mOsm/kg)	310	290	20.6	0.00*
Anion gap at 6 h	31	20	18.1	0.00*
Duration of acidosis in hours	63	19	18.6	0.00*
Time to reach blood glucose <250 mg/dl h	12	6.75	4.09	0.04*

*p value <0.05

Table 5 The multivariate analysis of the risk factors for death at admission

Variables	SE	*P* value	Adjusted OR	95 % CI for OR	
				Lower	Upper
Shock	1.373	*0.003	57.862	3.927	852.578
Altered sensorium	1.262	*0.020	18.796	1.583	223.188
Delayed diagnosis	1.234	*0.040	12.595	1.122	141.396
Osmolality	.053	*0.018	1.133	1.021	1.258

*p value <0.05

9.3 %. Literature from developing countries have reported this as a complication in DKA varying from 3.7 to 11.5 %[11, 15, 18, 19]. The case fatality rate of renal failure in DKA is 72.7 %. Mortality in DKA with renal failure has been previously documented as 40 %[20]. Acute renal failure is secondary to sepsis or is a consequence of hypovolemia and shock resulting in acute tubular necrosis aggravated by delay in diagnosis. Standard protocols do not provide guidelines for acute renal failure in DKA as this was not identified as a major risk factor for mortality in developed countries. Restriction of fluids, use of bicarbonate therapy, avoiding potassium replacement, peritoneal dialysis, and smaller doses of insulin were the major strategies used for management for renal failure in DKA in this study.

Shock in DKA has not been reported as a major risk factor from developed countries. But studies from developing countries like India, Bangladesh, and Pakistan have documented shock as a risk factor in children with DKA [7–10]. In this study, shock was encountered in 15 children (12.8 %) and the shock-related fatality is 53.3 %. One must be vigilant to recognize shock in children with DKA as the management with vigorous fluid may potentiate the risk of cerebral edema. The presence of shock indicates severe hypovolemia with delayed presentation or associated sepsis. Increased fluid for resuscitation was not identified to be a significant risk factor for mortality in children with DKA in multivariate analysis. Whether too little or too much of fluid is a risk factor for mortality in DKA is controversial. The data from western literature on fluids in DKA cannot be extrapolated as sepsis and shock are peculiar problems in developing countries [18]. Children with DKA and shock in developing countries may need more fluids for resuscitation of shock. However, there is a need for further studies on fluid therapy for shock in DKA.

Table 6 The multivariate analysis of risk factors for death during therapy

Variables	SE	*P* value	OR	95 % CI for OR	
				Lower	Upper
Cerebral edema	1.387	0.004*	52.322	3.451	793.291
Sepsis	1.225	0.011*	22.173	2.009	244.684
Acute renal failure	1.066	0.025*	10.910	1.350	88.184

*p value <0.05

Table 7 Summary of risk factors for death in DKA by univariate and multivariate analyses

Factors at admission	Factors during therapy	Other factors
Delayed diagnosis[a]	Lower pH at 6 h	Cerebral edema[a]
Shock[a]	Duration of acidosis	Sepsis[a]
Altered sensorium[a]	High osmolality at 6 h	Shock needing inotropes
Fluids more than 40 ml/kg at ER	High anion gap at 6 h	Renal failure[a]
Hypernatremia	Duration of hyperglycemia	
High osmolality[a]		
Lower pH (severe DKA)	Hypernatremia	
High anion gap	Declining trend of sodium	
Low $PaCO_2$		
High urea creatinine		

[a] Significant by multivariate analysis

In this study group, 64.7 % of the new onset DKA had delay in the diagnosis. Delayed diagnosis of diabetes in children has been recently reported to be a risk factor for presentation of DKA by the International Society of Pediatric and Adolescent Diabetes (ISPAD) [21]. Delay in diagnosis of DM is the major cause of DKA at presentation, ranging from 16 to 51 % [5, 22–25]. However, there are no published studies identifying the role of delayed diagnosis of DKA on its outcome in children. Delay in the diagnosis may be the root cause for increased mortality in children with DKA in developing countries. Hence, emphasis needs to be given for earlier diagnosis of DKA by creating awareness programmes for the public and physicians. Display of posters with DKA signs in common places like schools and places where public gathering occurs may help to increase awareness. Such posters can be displayed at physician clinic, too. This has helped in the past to decrease the occurrence of DKA in children significantly based on the study at Parma in Italy and in Gosford and Sydney [26–29]. There was a significant reduction in the occurrence of DKA in both new onset and among children with established diabetes. There had been no reported case of DKA in the intervention area even after 8 years of completion of the intervention. This may be a useful intervention to prevent delayed diagnosis of DKA. However, there are reports of no benefit following such interventions in study by Lansdown et al. [30].

Since the majority of the factors for mortality are preadmission factors, less likely to be related to therapy, it may be

understood that emphasis should be laid on prevention of DKA by increasing the awareness about diabetes mellitus and DKA among the parents and physicians.

Conclusions

The conclusions derived from this study are the following:

- Occurrence of cerebral edema (23.7 %) is high and is still a major cause of death in DKA.
- Sepsis (11 %), shock (12.7 %), and renal failure (9.3 %) are other major factors associated with high mortality in DKA.
- Altered sensorium and increased osmolality at admission are other major risk factors for mortality in DKA.
- Treatment-related factors' contributing to mortality are minimal, and the majority of them are preadmission factors.
- Infusion of more than 30 ml/kg of normal saline for initial resuscitation of shock is not a risk factor for mortality by multivariate analysis.
- The root cause for mortality in DKA in children may be due to the delayed diagnosis (44 %).
- Finger prick estimation of blood glucose is underutilized in diagnosis of DKA in children.
- Avoiding delay in diagnosis is the only preventable cause identified.

Recommendations

Suggested recommendations for this study are as follows:

- There is an urgent need to increase the awareness among the public and physicians about DKA by hanging up of posters in public places, schools, and physician clinic which may be helpful to create awareness.
- Performing a finger prick capillary blood glucose in a sick child should be mandatory at all levels of care.
- High risk alert from labs for hyperglycemia and glycosuria in children may help early diagnosis.
- Children with DKA in developing countries may need antibiotics at admission until sepsis screening is negative.
- Children with DKA and shock from developing countries may need more fluids than conventional recommendation.
- There is an urgent need for studies on management strategies for renal failure and shock in DKA due to limited evidence.

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Conflict of interest None

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ORIGINAL ARTICLE

Association of sociodemographics, technology use and health literacy among type 2 diabetic individuals living in an Indian setting: an exploratory cross-sectional study

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Abstract Diabetes is a prevalent health problem in developing as well developed countries. Previous study advocates for diabetes self-management education (DSME) among diabetics. In this study, we have examined the association of sociodemographics and technology use with health literacy among type 2 diabetic individuals. This exploratory cross-sectional study was performed by enrolling a convenient sample of 100 type 2 diabetes mellitus (T2DM) patients. Individuals of age 18 years or above were enrolled during regular outpatient visit to the diabetic clinic of Saveetha Medical College in Chennai, a metropolitan city in southern state of India in August 2013. A modified version of previously validated questionnaires was used for gathering information on sociodemographic characteristics, technology use assessments, diabetes-related information, health literacy, and health information-seeking behavior. Results of the study showed that majority of the individuals had received some form of diabetes education from their doctor at the time of diagnosis. However, 56 % of the participants had difficulty (sometimes to always) in understanding the health information provided by the healthcare professional. Individuals who had access to computer and Internet at home or work required less support for reading instructions, pamphlets, or other written material from the doctor or pharmacy. Individuals having access to technology had higher health literacy as compared to individuals with no access. Technology can act as potential enabler for improving the health literacy. Future research is warranted to identify most cost-effective, feasible, and accessible technology medium for providing diabetes self-care management education.

Keywords Diabetes · Technology · Health literacy · Health information

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Introduction

Chronic diseases have surpassed infectious disease as leading cause of death and disability around the globe [1]. Chronic disease conditions place additional burden on healthcare system and families of patients [2]. Diabetes is one of the chronic diseases which is increasing worldwide and needs attention for its management [3]. It occurs when the pancreas is unable to synthesize insulin or the body is incapable to utilize the available insulin [4]. Impaired glucose tolerance and impaired fasting glycemia are risk categories for future development of diabetes and cardiovascular disease [5].

Global number of people with diabetes was 382 million in year 2013 and is estimated to reach 592 million by year 2035 [3]. World Health Organization (WHO) had projected that diabetes will be the seventh leading cause of death by 2030 [6]. More than 80 % of diabetes death occurs in low- and middle-income countries [6]. Diabetes caused 5.1 million deaths in year 2013 of which greatest numbers of diabetes

patients were in 40–59 years of age [3]. Global healthcare expenditure on diabetes in 2013 was at least US$548 billion which is 11 % of total healthcare expenditure on adults [3]. India is the second largest contributor to global diabetes burden after China; number of people with diabetes in India was 65.1 million in year 2013 and is projected to increase to 109 million by year 2035 [3]. India is facing an epidemic of diabetes, with high prevalence in urban settings [7]. In the past 30 years, diabetes has increased to 12–18 % in urban areas and 3–6 % in rural areas with significant regional variations [7]. These rates are 50–80 % higher than China [7]. A cross-sectional household study on adults and elderly age group, in rural Tamaka, Kolar, showed that only 50.8 % of the participants heard about diabetes and only 26.8 % of non-diabetics and 74.2 % of diabetics were aware of its complications [8]. Past study in Chennai has shown that 80.9 % of the participants knew about the condition known as diabetes and 48.2 % knew about its complications [9].

Diabetes self-management education (DSME) is a critical element of care for diabetic patients and is necessary to improve the patient's outcome [10]. A comparative study of portion control diet (PCD) and DSME-based intervention showed higher decline of HbA_{1c} in PCD (0.7 %) participants than DSME participants (0.4 %) [11]. A previous qualitative study results showed that there should be emphasis on nurse-based diabetes education [12]. Diabetes education and awareness program was launched in state of Gujarat, India, in June 2012, and its results showed higher proportion of female (52 %) beneficiaries [13]. Previous study had shown indirect effect of health literacy on diabetes self-care [14]. There is a need of understanding various perspectives and possible opportunities in building diabetes management education module to minimize the healthcare burden.

The aim of this study was to examine the association of sociodemographics and technology use with health literacy among individuals with type 2 diabetes.

Methods

An exploratory cross-sectional study was performed by enrolling a convenient sample of 100 type 2 diabetes mellitus (T2DM) patients. Individuals of age 18 years or above were enrolled during regular outpatient visit to the diabetic clinic of Saveetha Medical College in Chennai, a metropolitan city in southern state of India in August 2013. Those individuals with mental and physical challenges or not willing to participate were excluded. The study was approved by the ethics committee of the Foundation of Healthcare Technologies Society, New Delhi (IRB#FHTS/012/2013), and conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004).

Information on the following variables was gathered.

(a) Sociodemographic characteristics: Information was gathered about age (years), gender, educational status [grade 1–5, grade 6–8, grade 9–10, grade 11–12, graduate or above, and no education], marital status (single/married/divorce or separated/widow), annual household income, household location (rural/urban), type of family (joint, nuclear, broken, extended), family size, occupation status (semi-professional to professional, skilled worker, unskilled, unemployed), and work shift timings (morning, evening, night, alternate, day) [15].

(b) Technology use assessment: Information was also gathered to assess the individual's access to landline phones or mobile phones and availability of computer and Internet at home or work. Information gathered included the frequency of computer use.

(c) Diabetes-related information: Variable information included history of diabetes, medication, and insulin intake. Information was also gathered about individual's past history of diabetes education and existing sources of diabetes-related information.

(d) Health literacy: Health literacy was assessed by using modified version of short test of functional health literacy in adults (STOFHLA) [16]. The STOFHLA is a 36-item reading assessment tool which requires 7 min to administer [16]. The following modified five questions from the original tool were used in the study: (i) How often do you have problems learning about your medical conditions because of difficulty in understanding written information (e.g., books, magazine, and written prescription)? (ii) How often do you have difficulty understanding information from your healthcare provider (like a doctor, nurse, or health worker) (oral communication)? (iii) How often are the directions on medication bottles difficult to understand for you? (iv) How often you are unsure about how to take your medication correctly? and (v) How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy. Responses were obtained on a five-point Likert scale. Responses of all five questions were dichotomized into "sometimes to always" and "occasionally to never" [16].

(e) Health information-seeking behavior: Information was gathered using an 18-item open-ended questionnaire which included the following: (i) from where help is sought for solving healthcare problem, (ii) reason of seeking help, (iii) healthcare seeking in case of failed healthcare, (iv) help sought from traditional healers, (v) credibility of the diabetes information source, (vi) reason of seeking information about diabetes, (vii) any event which have prompted to seek further information, (viii) changes in pattern of information since the time of

diagnosis, (ix) reliance on Internet for information, (x) trust on Internet for seeking information, (xi) following of another source after searching information on Internet, (xii) feeling difficulty in decision-making with the current information, (xiii) approach for seeking information on other healthcare problems, (xiv) method of selecting current healthcare provider and ever changing of healthcare provider, (xv) reliance on current healthcare provider for diabetes education and the method used in conveying the information, (xvi) satisfaction with current healthcare provider, (xvii) situation of any inconsistency in information received from various sources, and (xviii) factors impacting in decision making of the treatment of diabetes [17].

Statistical analysis

Descriptive analysis was performed using univariate statistics to report means and standard deviations for the continuous variable and frequency distributions for the categorical variables. Student's *T* statistics and analysis of variance were performed to see any possible difference in continuous variables. Chi-square analysis and Fisher's exact test were performed to see the possible association between health literacy and availability of technology. Binary logistic regression was performed to see individual sociodemographic and technology use variable with each of the five health literacy questions. Content analysis of the open-ended data generated from health information-seeking behavior questionnaire was performed to identify the common themes that emerged after textual data were coded. All statistical analysis was performed using SPSS version 16.

Results

Sociodemographic characteristics

Results showed that more than half of the study participants were males (60 %) with an average age of 55 years (SD=12) (Table 1). Majority of them were married (94 %), lived in nuclear family structure (90 %) with an average size of family being five (SD=3). One third of the total participants was either graduate or postgraduate (30 %) and had annual household income of more than 300,000 INR (approx. US$5000). Median annual household income of the participants was 200,000 INR (approx. US$3333) ranging from 15,000–3,000,000 INR (approx. US$250–50,000).

Table 1 Sociodemographic characteristics of diabetes patients

Variables	Results (n=100)
Sociodemographics	
Age (years)	Mean=55 (SD=12.3)
Gender	
Male	60 %
Female	40 %
Marital status	
Married	94 %
Widow/widower	6 %
Type of family	
Extended	2 %
Joint	8 %
Nuclear	90 %
Household location or setting	
Rural	5 %
Urban	95 %
Family size	Mean=5 (SD=3)
2	11 %
3	15 %
4	30 %
5	22 %
≥6	22 %
Annual household income, INR[a]	Mean=355,285 (SD=459,309)
≤50,000	12 %
50,001–100,000	15 %
100,001–200,000	30 %
200,001–300,000	10 %
>300,000	31 %
Highest education level of participant	
No formal education	8 %
Primary (1st–5th Grade)	9 %
Middle (6th–8th Grade)	11 %
High school (9th–10th Grade)	18 %
Intermediate (11th–12th Grade) or equivalent	24 %
Graduate or postgraduate	30 %
Occupation[a]	
Skilled worker	51 %
Unskilled worker	13 %
Unemployed	35 %

INR Indian National Rupee

[a] Some responses may not add up to a hundred due to missing values in some of the variables

Technology assessment

More than half of the participants had landline phones (55 %), and majority of them had access to cell phones (96 %). More than half of them had computer at home (53 %), and 43 % of them had Internet at home. Of the working participants (n=65), 45 % had computer and Internet at workplace. Merely 40 % of them were familiar with the use of computers (Fig. 1).

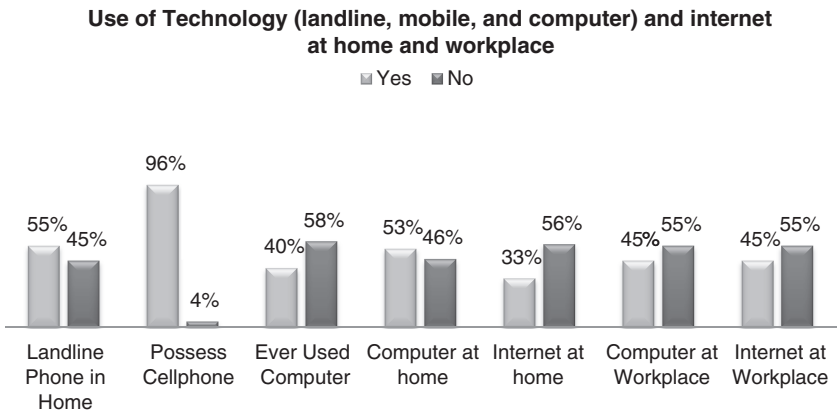

Fig. 1 Type of technology used for routine communication among the individuals having diabetes seeking treatment from the Diabetes Clinic in Saveetha Medical College, Saveetha University, Chennai, India (for computer and internet at workplace, *N*=65)

Diabetes-related information

More than half of the participants had a duration of diabetes of less than 5 years, majority of them were on oral medications (95 %) and about half of them were taking insulin (48 %) (Table 2), 45 % of them were taking both. Majority of them had received some form of diabetes education from the healthcare professional at the time of diagnosis (89 %), 15 % of them sought additional information regarding diabetes other than that provided by the doctor. The most preferred source of seeking diabetes-related information was traditional mass media (90 %) (Fig. 2).

Table 2 Diabetes education and current medication followed by the diabetes patients

Variables	Results (*n*=100) (%)
Diabetes was first diagnosed	
<1 year	16
1 year or more but <3 years	16
3 years or more but <5 years	25
5 years and more	43
Insulin use[a]	
No	49
Yes	48
Oral diabetes medicine intake	
Yes	95
No	5
Received initial diabetes education at the time of diagnosis[b]	
Doctor	89
Nurse	6
Dietician	3
Diabetes educator	6
Additional information regarding diabetes obtained from other than doctors' office[a]	
No	83
Yes	15

[a] Some responses may not add up to hundred due to missing values in some of the variables

[b] Responses are in multiple scales

Health literacy

Results showed that more than half of the participants (60 %) had encountered problems in understanding their medical condition, and this was primarily due to of difficulty in understanding the written information. Twenty-six percent of the participants were always uncomfortable in understanding information provided by the healthcare professionals. Twenty-five percent of the study participants always felt difficulty in understanding the directions on medicine bottle and were unsure about the correct method of medicine administration. Forty-three percent of the participants never needed help for reading instructions, pamphlets, or other reading material provided by the doctor or pharmacist (Table 3).

Health information-seeking behavior

Majority of the participants sought help of a doctor (90 %) for diabetes-related health ailments. However, only 13 % of the participants found health information credible when given by a doctor. Majority of them reported that attainment of better health and wellbeing prompted them for seeking health information (99 %). Eighty-nine percent expressed interest in seeking help about controlling their blood sugar levels. Majority of them reported change in pattern of health information since the time of diagnosis (74 %), showed more willingness for self information seeking. Trust and reliance on the Internet for seeking health information was seen in 74 % percent of the participants. Sixty-nine percent of them used "diabetes and its management" as keyword for searching diabetes-related health information. Only 20 % of them had reported different approach in seeking information and care for other health problems as compared to diabetes. Most of them were satisfied with the current healthcare providers (99 %) (Table 4).

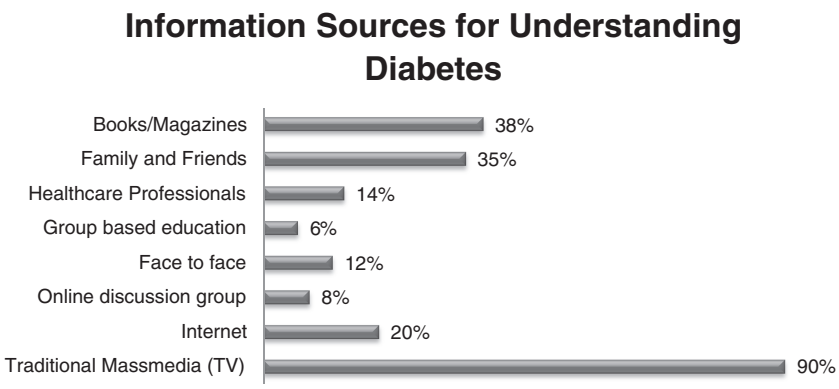

Fig. 2 Various sources of information to understand diabetes among the individuals having diabetes seeking treatment from the Diabetes Clinic in Saveetha Medical College, Saveetha University, Chennai, India

Association between sociodemographics and technology use and health literacy among T2DM individuals

Analysis was performed for five health-literacy-related issues including problems faced in understanding a medical condition because of difficulty in understanding written information, difficulty in understanding information from the healthcare provider, difficulty in understanding directions on medication bottles, uncertainty about the correct medicine intake, and need of help while reading instructions, pamphlets, or other written material from the doctor or pharmacy (Table 5).

(i) Understanding medical condition

There were an increased proportion of females compared to males (73 versus 52 %) who were facing problems in understanding a medical condition because of difficulty in understanding written information (p=.037). Individuals having more than high school education were less likely to face problem in understanding their medical condition (65 %; p<.0001). Similarly, individuals in skilled occupation (53 %; p=.039) had less chance of not able to understand their medical condition. Statistically significant difference was seen with annual income (p=.025). Variables such as age (p=.61) and family size (p=.59) did not differ significantly because of difficulty in understanding written information. There was a significant difference among individuals who had no landline phone as compared to individuals having a landline phone (85 versus 40 %; p<.0001) while understanding a medical condition because of difficulty in understanding written information. Similarly, individuals with no access to computer at home (83 %; p<.0001) or work (78 %; p<.0001) were facing greater problems in understanding a medical condition because of difficulty in understanding written information. Individuals with Internet access at home (65 %; p<.0001) or work (78 %; p<.0001) were facing less problems in understanding their medical conditions (Table 5). Regression analysis has shown that age (p=.49), gender (p=.50), family size (p=.15), education (p=.21), occupation (p=.61), AHI (p=.65), having landline phone (p=.07), computer at home (p=.79), computer at work (p=.79), ever use of computer (p=.17), Internet at home (p=.96), and Internet at work (p=.73) have not shown any statistically significant association.

(ii) Understanding information from the healthcare provider

Again there were increased proportion of females as compared to males (73 versus 45 %) who had difficulty in understanding the information provided by the healthcare provider (p=.007). Individuals with education level less than high school (89 %; p<.0001) had encountered less problems in understanding information from the healthcare provider. Unemployed (75 %; n=26) and unskilled workers (77 %; n=10) were facing higher degree of problems in understanding information provided by the healthcare provider (p=.001) as compared to skilled workers (37 %; n=19). Individuals who had less difficulty in understanding the information provided by the

Table 3 Problems in understanding health information by diabetes patients

Variable	Always (%)	Often (%)	Sometimes (%)	Occasionally (%)	Never (%)
Problems faced in understanding medical condition because of difficulty in understanding written information	25	5	30	4	36
Difficulty in understanding information from the healthcare provider	26	6	24	8	36
Difficulty in understanding directions on medicine bottles	25	4	28	5	38
Unsure about how to take the medication correctly	25	6	23	4	42
Need help while reading instructions, pamphlets, or other written material from your doctor or pharmacy	28	5	21	3	43

Table 4 Health information seeking behavior of diabetes patients

Variable	Results (n=100) (%)
Where do you seek help if you have health problems?	
Doctor	90
Hospital	1
Medical books	1
Diabetologist	2
None	6
Why do you seek help?	
Control blood sugar level	89
Due to symptoms	2
For cure	2
To get information and advice	5
On finding anything wrong	1
Routine checkup	1
If healthcare fails, where do you seek help?[a]	
Nowhere	89
Change physician/hospital	3
God	4
Spouse	1
Is help also searched from traditional healers? If yes from whom and reason for seeking help?	
No	99
Yes, from cousin for diet	1
What leads you believe that the source of information about diabetes is credible?	
When it is provided by the doctor	13
If it is in the magazine or internet	2
If it helps in reducing problems	1
Nothing	84
What prompts you to seek information about diabetes?	
Regular, for better health and wellbeing	99
Never	1
Have you ever heard or seen something about diabetes that made prompted you to seek out further information?	
Yes, on hearing latest news about it	4
No	96
Has how you obtain information about your diabetes changed over time? For instance, are you more willing to look up information on your own and to trust your own judgment?[a]	
Yes	74
No	25
Do you find yourself relying on the Internet for information?[a]	
Yes	74
No	25
Do you trust the Internet for information?	
Yes	74
No	26
Do you follow up with another source after you find information on the Internet? If you use the Internet, do you use a search engine. If so, what keywords or topics do you search for?	
Diabetes and its management	69
Complication of diabetes	1
Health	1
Magazine	1
No	28
With your diabetes have you ever felt that you could not obtain information that would help you make decisions about what to do?	
Yes, surf Internet to get solution	1
No	99
Consider other health care problems you have had or currently have. Do you approach obtaining information and care for the problem differently than you've approached your diabetes care?	
No	80
Yes	20
Consider the health care providers or provider you currently see to help you manage your diabetes. How did you choose this person or people? How did you "find" them? Have you ever changed care providers due to a choice, not something that was imposed upon you? What were those circumstances?	
None	92
Doctor	5
Friend	3
Do you rely heavily on your physician for your diabetes education? How and when do they convey information to you?	
Yes, during visit	30
No	70
Are you satisfied with how your diabetes care providers convey information to you about your diabetes? What do you like? Dislike?	
Yes	99
No	1
Have you ever been in a situation where what the sources were saying was inconsistent? How did you determine which one was more reliable?	
Yes, sometimes, reliability is based on trueness of information	2
No	98
External factors that have an impact on your choice to treat your diabetes?	
Doctor's advice	1
Work and family	2
None	97

[a] Some responses may not add up to a hundred due to missing values in some of the variables

healthcare provider had higher average income (M=515,113; SD=586,159) as compared to individuals with severe difficulty (M=225,055; SD=262,416) and it was found to be statistically significant (p=.002). Results showed that individuals who had landline phone at home compared to individuals with no landline phone at home (58 versus 27 %; p=.002), access to computer at home compared to no access to computers at home (68 versus 17%; p<.0001), access to computer at work compared to no access to computer at work (79 versus 36 %;

Table 5 Description of sociodemographic characteristics and technology use with health literacy among the diabetes patients

	Problems faced in understanding medical condition because of difficulty in understanding written information		Difficulty understanding information from your healthcare provider		Difficulty in understanding directions on medicine bottles		Unsure about how to take medication correctly		Need help while reading instructions, pamphlets, or other written material from your doctor or pharmacy	
	Sometimes to always	Occasionally to never	Sometimes to always	Occasionally to never	Sometimes to always	Occasionally to never	Sometimes to always	Occasionally to never	Sometimes to always	Occasionally to never
Age										
M (SD)	55 (13)	54 (12)	56 (13)	53 (11)	56 (13)	53 (11)	57 (12)	53 (12)	57 (13)	52 (11)
p value	0.61		0.17		0.14		0.1		0.06	
Gender										
Male	31 (52 %)	29 (48 %)	27 (45 %)	33 (55 %)	28 (47 %)	32 (53 %)	27 (45 %)	33 (55 %)	27 (45 %)	33 (55 %)
Female	29 (73 %)	11 (27 %)	29 (73 %)	11 (27 %)	29 (73 %)	11 (27 %)	27 (68 %)	13 (32 %)	27 (68 %)	13 (32 %)
p value	0.037*		0.007**		0.01**		0.02*		0.02*	
Family size										
M (SD)	5 (3)	5 (3)	5 (2)	5 (4)	5 (2)	5 (4)	5 (2)	5 (4)	5 (2)	5 (4)
p value	0.59		0.47		0.52		0.78		0.78	
Education										
≤High school	41 (89 %)	5 (11 %)	41 (89 %)	5 (11 %)	40 (87 %)	6 (13 %)	39 (85 %)	7 (15 %)	39 (85 %)	7 (15 %)
>High school	19 (35 %)	35 (65 %)	15 (28 %)	39 (72 %)	17 (31 %)	37 (69 %)	15 (28 %)	39 (72 %)	15 (28 %)	39 (72 %)
p value	<.0001**		<.0001**		<.0001**		<.0001**		<.0001**	
Occupation										
Skilled worker	24 (47 %)	27 (53 %)	19 (37 %)	32 (63 %)	23 (45 %)	28 (55 %)	20 (39 %)	31 (61 %)	21 (41 %)	30 (59 %)
Unskilled worker	9 (69 %)	4 (31 %)	10 (77 %)	3 (23 %)	8 (62 %)	5 (38 %)	9 (69 %)	4 (31 %)	8 (62 %)	5 (38 %)
Unemployed	26 (75 %)	9 (25 %)	26 (75 %)	9 (25 %)	25 (71 %)	10 (29 %)	24 (69 %)	11 (31 %)	24 (69 %)	11 (31 %)
p value	0.039*		0.001**		0.054*		0.015**		0.03*	
Landline phone at home										
Yes	22 (40 %)	33 (60 %)	23 (42 %)	32 (58 %)	24 (44 %)	31 (56 %)	22 (40 %)	33 (60 %)	23 (42 %)	32 (58 %)
No	38 (84 %)	7 (16 %)	33 (73 %)	12 (27 %)	33 (73 %)	12 (27 %)	32 (71 %)	13 (29 %)	31 (69 %)	14 (31 %)
p value	<.0001**		0.002**		0.003**		0.002**		0.007**	
Computer at home										
Yes	21 (40 %)	32 (60 %)	17 (32 %)	36 (68 %)	19 (36 %)	34 (64 %)	17 (32 %)	36 (68 %)	17 (32 %)	36 (68 %)
No	38 (83 %)	8 (17 %)	38 (83 %)	8 (17 %)	37 (80 %)	9 (20 %)	36 (78 %)	10 (22 %)	36 (78 %)	10 (22 %)
p value	<.0001**		<.0001**		<.0001**		<.0001**		<.0001**	
Computer at work[a]										
Yes	5 (17 %)	24 (83 %)	6 (21 %)	23 (79 %)	7 (24 %)	22 (76 %)	6 (21 %)	23 (79 %)	6 (21 %)	23 (79 %)
No	28 (78 %)	8 (22 %)	23 (64 %)	13 (36 %)	24 (67 %)	12 (33 %)	23 (64 %)	13 (36 %)	23 (64 %)	13 (36 %)
p value	<.0001**		<.0001**		.001**		<.0001**		<.0001**	
Internet at home										
Yes	15 (35 %)	28 (65 %)	14 (33 %)	29 (67 %)	17 (32 %)	26 (68 %)	15 (35 %)	28 (65 %)	15 (35 %)	28 (65 %)

Table 5 (continued)

	Problems faced in understanding medical condition because of difficulty in understanding written information		Difficulty understanding information from your healthcare provider		Difficulty in understanding directions on medicine bottles		Unsure about how to take medication correctly		Need help while reading instructions, pamphlets, or other written material from your doctor or pharmacy	
	Sometimes to always	Occasionally to never	Sometimes to always	Occasionally to never	Sometimes to always	Occasionally to never	Sometimes to always	Occasionally to never	Sometimes to always	Occasionally to never
No	42 (79 %)	11 (21 %)	39 (74 %)	14 (26 %)	38 (72 %)	15 (28 %)	37 (70 %)	16 (30 %)	37 (70 %)	16 (30 %)
p value	<.0001**		<.0001**		0.004**		0.001**		0.001**	
Internet at work[a]										
Yes	5 (17 %)	24 (83 %)	6 (21 %)	23 (79 %)	7 (24 %)	22 (76 %)	6 (21 %)	23 (79 %)	6 (21 %)	23 (79 %)
No	28 (78 %)	8 (22 %)	23 (64 %)	13 (36 %)	24 (67 %)	12 (33 %)	23 (64 %)	13 (36 %)	23 (64 %)	13 (36 %)
p value	<.0001**		<.0001**		.001**		<.0001**		<.0001**	

M mean, *SD* standard deviation

*$p<.05$; **$p<.01$

[a] $N=65$ (working participants)

$p<.0001$), access to Internet at home compared to no access of Internet at home (67 versus 26 %; $p<.0001$), and access to Internet at work compared to no access of Internet at work (79 versus 36 %; $p<.0001$) were facing less problems in understanding the information provided by the healthcare provider (Table 5). Regression analysis has shown that individuals having more than high school education ($p=.048$) and computer at home ($p=.023$) had lesser difficulty in understanding information given by the healthcare providers.

(iii) Understanding directions on medication bottles

Females (73 %; $p=.011$) faced greater difficulties in understanding the directions on medication bottles. Individuals having education more than high school (69 %; $p<.0001$) and involved in skilled occupation (55 %; $p=.05$) faced less difficulties in understanding direction on medication bottles. Individuals who had lower average income ($M=261,054$; SD=318,679) had significantly greater difficulty in understanding the information provided by the healthcare provider as compared to those with higher income ($M=475,813$; SD=574,591) ($p=.02$). Individuals with access to landline phone ($p=.003$), computer ($p<.0001$), and Internet ($p=.004$) at home had less problems in understanding directions on medication bottles. Similar results were seen for those individuals who had access to computers ($p=.001$) and Internet at work ($p=.001$) (Table 5). Regression analysis has shown that skilled workers ($p=.04$) and individuals having computer at home ($p=.009$) had less difficulties in understanding the directions on medication bottles.

(iv) Correct method of medicine intake

Results showed that females (68 %) were less confident about the correct method of medicine intake as compared to males (45 %) ($p=.02$). Individuals having education level more than high school (72 %; $p<.0001$) and involved in skilled occupation (61 %; $p=.015$) were more confident about the correct method of medicine intake. Higher average income ($M=485,222$; SD=565,810) was seen among individuals who were confident about the correct method ($p=.009$). Results showed that individuals with access to landline phone at home ($p=.002$), access to computer at home ($p<.0001$) or work ($p<.0001$), and access to Internet at home ($p=.001$) or work ($p<.0001$) were more confident in the correct method of medicine intake (Table 5). Regression analysis has shown that participants having computer ($p=.05$) and Internet at home ($p=.05$) were more confident for correct medicine intake.

(v) Need of help while reading instructions

Results showed greater need of help while reading instructions, pamphlets, or other written material from the doctor or

pharmacy among females (68 %) than males (45 %) (p=.02). Individuals having more than high school level of education (72 %; p<.0001) and involved in skilled occupation (59 %; p=.03) also required less help while reading instructions, pamphlets, or other written material from the doctor or pharmacy. Individuals requiring assistance for reading instructions, pamphlets, or other written material from the doctor or pharmacy had lower average annual income (M=248,264; SD=307,772), and it was found to be statistically significant (p=.012). Results showed that individuals having access to landline phone (p=.007), computer (p<0.0001), and Internet (p=0.01) at home and access to computer (p<.0001) and Internet (p<.0001) at work required minimal help while reading instructions, pamphlets, or other written material from the doctor or pharmacy (Table 5). Regression analysis has shown that age (p=.03) and computer at home (p=.02) have shown statistically significant association with need of help for reading instructions from the doctor or pharmacy.

Discussion

This study explored association between sociodemographics, technology use and health literacy of type 2 diabetic individuals living in an Indian setting. Results of the study showed that majority of the individuals were on oral medications and nearly half of them were taking insulin; 45 % took both medications and insulin to control their blood sugar levels.

Previous studies in Chennai have shown that 49.9 to 80.9 % of individuals knew about diabetes [9, 18]. Results of the study showed that majority of the individuals had received some form of diabetes education from their doctor at the time of diagnosis. However, the patients of chronic disease like diabetes need tailored guidance for self-care management. More than half of the individuals faced problems in understanding medical condition because of either difficulty in understanding written information or information provided by the healthcare provider or understanding directions on medication bottles. Individuals were unsure about the correct medicine intake and needed help while reading instructions or other written material from the doctor or pharmacy. Results showed gender disparity in the health literacy levels as that there was lesser proportion of health-literate females as compared to males. Individuals with higher education level and annual household income faced lesser difficulty in understanding health-related information. Previous study has shown that individuals with lower education had limited health literacy [19].

Traditional mass media like television was reported to be the most preferred source for obtaining health information. More than half of the study participants (74 %) trusted and relied on the Internet for seeking health information. More than half of the participants had landline phone in their households. Use of voice-assisted response services through landline phones for seeking health information may contribute to diabetes awareness or health literacy. Results showed that majority of the individuals had access to one or more types of technology for communication. Hence, role of technology to disseminate diabetes-related self-care management needs further exploration especially for individuals living in rural and remote areas. In another previous study, Internet-based menu planning led to a 5 % or more net weight reduction in older adults with diabetes [20].

Present study showed that individuals with computers and internet at home or work had lesser difficulty in understanding written information or in understanding the information provided by the healthcare provider, and understanding directions on medication bottles. These individuals were confident about the correct medicine intake and required lesser help while reading instructions, pamphlets, or other written material from the doctor or pharmacy.

Previous study had shown that individuals turn to folk sector in case of failed healthcare [17]. But results of our study showed that majority of the individuals do not go anywhere (89 %) and only few (4 %) perceived god as the reason for their poor health condition. Only one participant had sought help from traditional healer for diet regulation. Majority of the individuals were satisfied (99 %) with the way information was currently conveyed by their healthcare providers, but only 30 % percent relied heavily on them for healthcare information. Present study had several limitations including cross-section design, smaller sample size, and was limited to a single geographical location, so the results of the study cannot be generalized. Further, the study did not capture use of mobile network in the cell phone and use of smartphones as many applications related to health could be used via the smartphone.

Conclusions

Our study had shown that the individuals having access to computer at home had higher health literacy as compared to individuals with no access. Technology (information) can act as potential enabler to bridge the gap of health literacy by providing self-care management education of diabetes as an intervention. Future research is warranted to identify most cost-effective, feasible, and accessible technology medium for providing diabetes self-care management education.

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Compliance with ethical standards The study was approved by the ethics committee of the Foundation of Healthcare Technologies Society,

New Delhi (IRB#FHTS/012/2013), and conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004).

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

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ORIGINAL ARTICLE

Role of anti-GAD, anti-IA2 antibodies and C-peptide in differentiating latent autoimmune diabetes in adults from type 2 diabetes mellitus

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Abstract Latent autoimmune diabetes in adults (LADA) is a form of autoimmune diabetes affecting adult patients who do not require insulin at diagnosis, positive for circulating islet autoantibodies and characterized by slower beta cell destruction. The study was aimed to identify and characterize LADA patients from clinically diagnosed type 2 diabetes mellitus (DM). We estimated anti-glutamic acid decarboxylase (anti-GAD), anti-tyrosine phosphatase-like insulinoma antigen 2 (anti-IA2) antibodies, fasting connecting peptide (C-peptide) and other clinical and biochemical parameters in 297 clinically diagnosed type 2 DM patients. The diagnosis of LADA was made by the presence of at least one pancreatic autoantibody, and thereafter LADA groups were compared with those of autoantibody-negative type 2 DM groups. The prevalence of LADA was found to be 15.2 % among patients presumed to have type 2 DM. There was significant difference concerning age of patients ($p<0.001$), body mass index ($p<0.001$), serum levels of C-peptide ($p<0.001$), insulin ($p<0.001$), total cholesterol ($p<0.001$), triglycerides ($p=0.025$), high-density lipoprotein cholesterol (HDL-C; $p=0.004$), low-density lipoprotein cholesterol (LDL-C; $p=0.001$) as well as insulin resistance ($p<0.001$) between LADA group and type 2 DM patients. In conclusion, anti-GAD antibody and C-peptide level determination can be considered as confirmatory diagnostic markers for LADA, along with anti-IA2 assay, while other clinical and biochemical parameters can be useful for further characterizing LADA patients.

Keywords LADA · Type 2 DM · Anti-GAD antibody · Anti-IA2 antibody · C-peptide

Introduction

The total number of people with diabetes mellitus is increasing expressively in most of the developed and many developing countries, and the prevalence of diabetes for all age groups worldwide was projected to rise from 2.8 % in 2000 to 4.4 % in 2030 [1]. Type 2 diabetes mellitus (DM) is the commonest form of diabetes constituting about 90 % of the total diabetic population [2], and type 1 diabetes mellitus accounts for about 5–10 % [3]. Latent autoimmune diabetes in adults (LADA) is a form of autoimmune diabetes that affects adult patients who do not require insulin at diagnosis, positive for circulating pancreatic islet autoantibodies, and is associated with slower beta cell destruction [4, 5]. It was Zimmet who introduced the term 'Latent autoimmune diabetes of adults' [6]. LADA shares features of both type 1 DM (presence of circulating autoantibodies and low fasting connecting peptide (C-peptide)) and type 2 diabetes (adult age at onset and initial response to oral hypoglycaemic agents), so it is often misdiagnosed as type 2 DM [7]. Many studies reported that LADA also shares genetic features of both type 1 and type 2 diabetes [8, 9]. So LADA is considered as a distinct form of diabetes that lies somewhere between type 1 and type 2 diabetes [8] and therefore has also been denominated as type 1.5 diabetes [10, 11]. This particularly has led to both mistaken diagnosis and inappropriate therapeutic management. In an attempt to standardize the features of LADA, the Immunology of Diabetes Society had proposed the following criteria: patients should be at least 30 years of age,

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positive for at least one of the four antibodies to glutamic acid decarboxylase 65 (GAD 65), islet cell cytoplasm (ICA), tyrosine phosphatase-like insulinoma antigen 2 (IA-2), insulin (IAA), and not treated with insulin within the first 6 months after diagnosis [12].

Epidemiological studies suggest that LADA may account for about 2–12 % of all cases of diabetes [2, 11]. Despite its frequency, there are no universal recommendations regarding testing for pancreatic antibodies in adult onset diabetes. Evidence obtained from studies point out that preservation of beta cell function in patients with autoimmune diabetes results in better glycaemic control and fewer end organ complications like nephropathy and retinopathy. Though the exact mechanism for the apparent beneficial effects of insulin treatment is yet to be completely understood, it is thought that early diagnosis and administration of exogenous insulin would preserve the residual pancreatic beta cell function. The rationale behind this thought is by allowing beta cells to rest, to minimize possible insulitis at least by decreasing their metabolism and also by relieving hyperglycaemic stress. It is also suggested that active beta cells producing high amounts of insulin are more susceptible to immune destruction, and therefore rest for beta cells could preserve them longer [13, 14].

We therefore set out to determine the biochemical markers for early diagnosis of LADA and also an attempt to compare the clinical and biochemical characteristics of LADA subjects with type 2 DM. Antibodies that can be used as markers for the diagnosis of LADA are anti-glutamic acid decarboxylase (anti-GAD), anti-tyrosine phosphatase-like insulinoma antigen 2 (anti-IA2), anti-ICAs, anti-IAA and recent zinc transporter (ZnT8) autoantibodies. The most sensitive marker for the diagnosis of LADA is anti-GAD antibody [15]. A recent Italian study has demonstrated that autoantibody reactivity to IA-2 in LADA patients is much more common than so far reported, and this can be considered as a novel and sensitive diagnostic marker for the detection of islet autoimmunity in subjects with type 2 diabetes [16].

Materials and methods

Subjects

The study was conducted at Amrita Institute of Medical Sciences and Research Centre, Kochi, during the period of July 2013 to January 2014, and study subjects were selected from Endocrinology OPD. Two hundred and ninety-seven (297) subjects who satisfied the inclusion criteria were selected by systematic random sampling. Inclusion criteria were individuals with newly diagnosed (within 3 years) clinical type 2 DM [3] and aged 30–70 years with initial 6 months of insulin independence. Exclusion criteria were patients with type 1 DM, those who started insulin therapy within 6 months after diagnosis of diabetes and patients with a history of diabetic ketoacidosis. Patients who were pregnant, taking steroid medications, taking chemotherapy for malignancy, taking medications for hypertension and dyslipidemia, had chronic liver disease, with acute infection and other disorders that could affect glucose metabolism were also excluded.

Sample collection and preparation

Venous blood samples were obtained for anti-GAD and anti-IA2 antibodies, and overnight fasting venous blood were obtained for plasma glucose, lipid profile, C-peptide and insulin. Serum was separated by centrifugation within 1 h after blood collection and refrigerated at −20 °C until the tests were performed. Whole blood samples were used for testing glycated haemoglobin (HbA_{1c}) and plasma was used for testing glucose. Informed written consent was obtained from each individual.

Physical examination

The weight of each individual was measured using a weighing scale; the height was measured with a stadiometer and arterial blood pressure with sphygmomanometer. The body mass index (BMI) of each subject was calculated using the following formula: BMI = Weight (kg)/Height^2 (m^2).

Biochemical analyses

Serum level of anti-GAD and anti-IA2 antibodies were estimated by enzyme-linked immunosorbent assay method (ELISA) using Medizym anti-GAD and Medizym anti-IA2 kit, respectively, and readings were taken on ELISA microwell plate reader with optical filters at 450 and 620 nm. The Medizym anti-GAD and anti-IA2 are calibrated against the WHO reference preparation, National Institute of Biological Standards and Control (NIBSC) 97/550, and concentrations are therefore expressed in International Unit/millilitre (IU/mL). The cut-off value for anti-GAD and anti-IA2 antibodies are taken as 5 and 10 IU/mL according to the recommendations for the kit, and values above 5 and 10 IU/mL were taken as positive, respectively. C-peptide was estimated by direct ELISA method using EiAsy way diagnostic kit (Diagnostic Biochem Canada Inc., Canada), and readings were taken on ELISA microwell plate reader at 450 nm. Reference range of C-peptide followed in the present laboratory is 1.3–3.1 ng/mL. Fasting plasma glucose was estimated by enzymatic UV test (hexokinase method) on Beckman coulter-Olympus AU2700 Chemistry Analyser. Fasting lipid profile was estimated by enzymatic colour test on Beckman coulter-Olympus AU2700 Chemistry Analyser. HbA_{1c} was estimated in whole blood by ion exchange high-performance liquid chromatography using Bio-Rad Variant II HbA_{1c} analyser. Fasting insulin was estimated by chemiluminescent microparticle immunoassay (CMIA) method on Abbott

Architect i2000 (Abbott Diagnostic, USA) analyser. Insulin resistance was calculated using homeostasis model assessment (HOMA-IR) formula [17], HOMA-IR=(Fasting glucose in mg/dL×Fasting insulin in μU/mL)/405.

Statistical analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences software (SPSS)—version 20.0. All quantitative data were expressed as mean±standard deviation (SD) while categorical variables were expressed as percentages. Continuous variables were compared using independent two-sample *t* test, and categorical variables were compared using chi-square test. A two-tailed *p* value less than 0.05 was considered statistically significant.

Results

According to currently accepted criteria for diagnosis of LADA proposed by Immunology of Diabetes Society [12], we identified 45 patients (15.2 %) as LADA out of 297 clinically diagnosed type 2 DM. At least one type of serum autoantibody (anti-GAD or anti-IA2) was detected in 45/297 subjects (15.2 %). Only one kind of autoantibody was detected in 40/297 subjects (13.5 %). The coexistence of two autoantibodies (anti-GAD and anti-IA2) was noted in 5/297 subjects (1.7 %). None of the autoantibodies was found in 252/297 subjects (84.8 %) who were classified as classic type 2 DM. Figure 1 illustrates the prevalence of pancreatic autoantibodies among study subjects. Among LADA subjects, 37/45 (82.2 %) showed positivity to anti-GAD antibodies and 13/45 (28.9 %) showed positivity to anti-IA2 antibodies. Table 1 lists the clinical characteristics of LADA group.

Comparison of LADA groups with type 2 DM

Mean age at diagnosis was different in LADA patients (44.1±8.2) compared to type 2 DM (55±7.5), and the difference was statistically significant ($p<0.001$). There was no significant difference in gender distribution between two groups as males

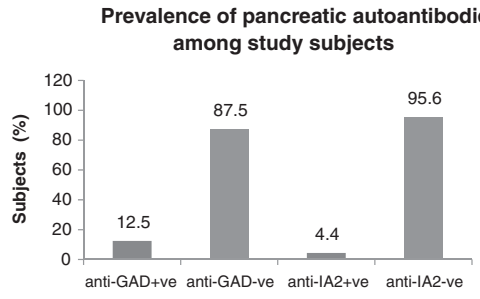

Fig. 1 Prevalence of pancreatic autoantibodies among study subjects

Table 1 Clinical characteristics of LADA group

No.	Clinical characteristics	Value
1.	Number of patients, n (%)	45 (15.2 %)
2.	Gender (*n*)	
	-Male	27
	-Female	18
3.	Age at diagnosis (years) (mean±SD)	44.1±8.2
4.	Distribution of patients according to age groups, *n* (%)	
	- 30–40 years	15 (33.3 %)
	- 41–50 years	23 (51.1 %)
	- 51–60 years	5 (11.1 %)
	- 61–70 years	2 (4.5 %)
5.	BMI (kg/m^2) (mean±SD)	24.1±4.5
6.	Distribution of patients according to BMI groups, *n* (%)	
	-Normal weight (BMI <25)	28 (62.2 %)
	-Overweight (BMI 25.1–30.0)	12 (26.7 %)
	-Obese (BMI >30)	5 (11.1 %)
7.	Fasting plasma glucose (mg/dL) (mean±SD)	175.7±20.0
8.	Fasting C-peptide (ng/mL) (mean±SD)	1.2±0.5
9.	Fasting insulin (μU/mL) (mean±SD)	9.9±2.1
10.	Distribution of patients by the presence of autoantibodies, *n* (%)	
	-Anti-GAD +ve	37 (82.2 %)
	-Anti-IA2 +ve	13 (28.9 %)
	-At least one antibody	45 (100 %)
	-Coexistence of antibodies	5 (11.1 %)

Values are expressed as mean±standard deviation or number (%)

BMI body mass index, *Anti-GAD* anti-glutamic acid decarboxylase, *Anti-IA2* anti-insulinoma antigen 2

are affected more in both groups. Mean BMI values were different between the two groups (LADA 24.1±4.5 kg/m^2 versus type 2 DM 28.8±5.1 kg/m^2) and were statistically significant ($p<0.001$). Mean systolic blood pressure was significantly lower in LADA patients (128±8.3 mmHg) compared to those with type 2 DM (132±8.8 mmHg), $p=0.003$, but no significant difference of diastolic blood pressure between LADA patients (82.5±5.9 mm/Hg) and type 2 DM (83±6.0 mm/Hg) with $p=0.594$. Personal history of autoimmune diseases especially autoimmune thyroid disease was noted in 15 (33.3 %) subjects with LADA when compared with 16 (6.3 %) subjects with type 2 DM, and it was statistically significant ($p<0.001$). Family history of autoimmune diseases was also common in subjects with LADA 12 (26.7 %) when compared to type 2 DM 14 (5.6 %), and it was statistically significant ($p<0.001$). Table 2 depicts comparative analysis of clinical characteristics of LADA with type 2 DM.

Mean fasting C-peptide was significantly lower in LADA patients (1.2±0.5 ng/mL) compared to those with type 2 DM (2.7±0.9 ng/mL), $p<0.001$. Mean fasting insulin levels was significantly lower in LADA patients (9.9±2.1 μU/mL) compared to those with type 2 DM (15.9±3.9 μU/mL), $p<0.001$.

Table 2 Comparative analysis of clinical characteristics of LADA with type 2 DM

No.	Clinical characteristics	LADA	Type 2 DM	*p* value
1.	Number of patients, *n* (%)	45 (15.2 %)	252 (84.8 %)	–
2.	Gender, *n* (%)			
	-Male	27 (60 %)	138 (54.8 %)	0.63
	-Female	18 (40 %)	114 (45.2 %)	
3.	Age at diagnosis (years) (mean±SD)	44.1±8.2	55±7.5	<0.001
4.	BMI (kg/m^2) (mean±SD)	24.1±4.5	28.8±5.1	<0.001
5.	Distribution of patients according to BMI groups, *n* (%)			
	-Normal weight (BMI <25)	28 (62.2 %)	53 (21 %)	<0.001
	-Overweight (BMI 25.1–30.0)	12 (26.7 %)	108 (42.9 %)	0.042
	-Obese (BMI >30)	5 (11.1 %)	91 (36.1 %)	0.001
6.	Systolic blood pressure (mmHg) (mean±SD)	128±8.3	132±8.8	0.003
7.	Diastolic blood pressure (mmHg) (mean±SD)	82.5±5.9	83±6.0	0.594
8.	Personal history of autoimmune disease, *n* (%) (especially autoimmune thyroid disease)	15 (33.3 %)	16 (6.3 %)	<0.001
9.	Family history of autoimmune disease, *n* (%)	12 (26.7 %)	14 (5.6 %)	<0.001

Values are expressed as mean±standard deviation or number (%)

BMI body mass index

HOMA-IR was significantly lower in LADA patients (4.3±1.0) compared to those with type 2 DM (7.0±1.8), $p<0.001$. There was no significant difference between mean fasting plasma glucose of LADA patients (175.7±20.0 mg/dL) and type 2 DM (178.2±18.3 mg/dL), $p=0.412$. Also there was no significant difference between mean HbA_{1c} of LADA patients (8.2±0.8) and type 2 DM (8.1±0.9), $p=0.643$. Mean total cholesterol was significantly lower in LADA patients (193.3±23.8 mg/dL) compared to those with type 2 DM (208.4±26.5 mg/dL), $p<0.001$. Mean triglyceride level was significantly lower in LADA patients (145.9±18.9 mg/dL) compared to those with type 2 DM (151.9±16.2 mg/dL), $p=0.025$. Mean low-density lipoprotein cholesterol (LDL-C) was significantly lower in LADA patients (102.1±11.5 mg/dL) compared to those with type 2 DM (110.1±14.3 mg/dL), $p<0.001$. Mean high-density lipoprotein cholesterol (HDL-C) in LADA patients (42.2±5.5 mg/dL) was significantly higher than that in type 2 DM (39.7±5.2 m/dL) with $p=0.004$. Table 3 depicts comparative analysis of biochemical parameters of LADA with type 2 DM.

Discussion

According to LADA characteristics previously described, we identified 45 patients as LADA out of 297 clinically

Table 3 Comparative analysis of biochemical parameters of LADA with type 2 DM

No.	Parameters	LADA (*n*=45) (mean±SD)	Type 2 DM (*n*=252) (mean±SD)	*p* value
1.	Fasting plasma glucose (mg/dL)	175.7±20.0	178.2±18.3	0.412
2.	HbA_{1c} (%)	8.2±0.8	8.1±0.9	0.643
3.	Total cholesterol (mg/dL)	193.3±23.8	208.4±26.5	<0.001
4.	Triglycerides (mg/dL)	145.9±18.9	151.9±16.2	0.025
5.	HDL-C (mg/dL)	42.2±5.5	39.7±5.2	0.004
6.	LDL-C (mg/dL)	102.1±11.5	110.1±14.3	<0.001
7.	Fasting insulin (μU/mL)	9.9±2.1	15.9±3.9	<0.001
8.	Fasting C-peptide (ng/mL)	1.2±0.5	2.7±0.9	<0.001
9.	HOMA-IR	4.3±1.0	7.0±1.8	<0.001

Values are expressed as mean±standard deviation

HDL-C high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HbA1c* glycated haemoglobin, *HOMA-IR* homeostasis model assessment for insulin resistance

diagnosed type 2 DM giving a prevalence of 15.2 %. Various studies all over the world reported a prevalence of 5.1 % [18], 9.2 % [19] and 13.5 % [20] among type 2 diabetic patients. However, the prevalence of LADA group rose to 25 % among type 2 diabetic patients less than 35 years of age [21]. A wide range of disparity in the prevalence of LADA within a country or across countries may depend on clinical characteristics of the patient, antibody assay methods, norms for diagnosis and genetic predisposition. Among the study subjects, 12.5 % showed positivity to anti-GAD antibodies and 4.4 % showed positivity to anti-IA2 antibodies which gives the indication that anti-GAD antibody is the commonest autoantibody in these patients. At diagnosis, both anti-GAD and ICA were stronger predictors of insulin requirement, but anti-GAD antibodies appeared to have better sensitivity as predictors than ICA [22]. Conversely, ICA disappears with increasing disease interval, while all patients with anti-GAD positivity at diagnosis remain positive indefinitely. Hence, anti-GAD measurements can be carried out years after diagnosis with preserved sensitivity. Testing for other autoantibodies should also be carried out as some of these patients may be IA2 or IAA positive. In the present study, we included IA2 antibody along with anti-GAD, and anti-IA2 assay enhanced the diagnostic prevalence of LADA from 12.5 to 15.2 %. Kanungo A et al. [23] and Tiberti C et al. [16] pointed out the emerging importance of anti-IA2 antibody in their studies.

A lower mean age of diagnosis was found in LADA group when compared to classic type 2 DM, and this is in agreement with a study done by Genovese S et al. [24]. The prevalence of LADA was more in males than in females in the present study and was comparable with type 2 diabetes patients. BMI values of patients with type 2 diabetes showed that most of the patients were in overweight and obese category, but majority of LADA patients were of normal weight group. Mette K. Andersen et al. [25] and Maria A. Radtke et al. [26] reported that BMI of LADA patients were significantly lower than those of the corresponding type 2 diabetic group. Leslie RD et al. [27] in their study reported that majority of LADA patients were usually thin or of normal weight group, while few studies also reported mean BMI of LADA patients in the overweight or obese categories [28, 29]. The present study showed significant difference in mean systolic blood pressure between LADA and type 2 DM patients, but no significant difference in the mean diastolic blood pressure between two groups. Study done by Hosszufalusi N et al. [30] reported the low prevalence of hypertension in LADA patients when compared to type 2 DM patients. Of the LADA patients in the present study, 33.3 % gave personal history of autoimmune thyroid disease, which is in accordance with earlier reports which found out the increased incidence of organ-specific autoimmune disorders especially the thyroid gland [31]. Jin et al. [32] also reported high frequency of thyroid peroxidase (TPO) antibodies in LADA patients compared with type 2 DM. Of the LADA group, 26.7 % gave a family history of autoimmune disease which is in agreement with Spiros Fourlanos et al. [33] study 'A clinical screening tool identifies autoimmune diabetes in adults' which reported that family or personal history of DR3- and/or DR4-related autoimmune diseases was more common in LADA, and the most common associated autoimmune disease in patients with LADA was thyroid autoimmune disease.

We observed that LADA patients had lower mean C-peptide levels compared with type 2 diabetes groups. Arikan E et al. [34] also reported similar findings. C-peptide is secreted at equimolar concentration with insulin and is not degraded as rapidly as insulin, so estimation of C-peptide levels would be a valuable test to quantify insulin secretion and therefore to evaluate beta cell function in LADA patients. Bell DS et al. [35], in their studies, had highlighted on the potential role of C-peptide as a screening tool for early detection of LADA patients, keeping more expensive antibody testing for high suspect cases. When mean fasting insulin levels along with the insulin resistance (HOMA-IR) were compared between the two groups, it was significantly lower in the LADA group when compared to classic type 2 DM patients. Britten A C et al. [36] in their study found out that insulin resistance were much lower in LADA as compared to type 2 DM. But some studies put forward that LADA patients share insulin resistant with type 2 DM patients [37]. In the present study, we found out that there is no statistical difference in mean fasting plasma glucose and HbA_{1c}% between LADA and type 2 DM patients. Estimation of serum cholesterol revealed that LADA patients had significantly lower mean cholesterol value when compared with type 2 diabetes, which was found to be in accordance with existing data [5, 38]. The ADOPT study revealed that LADA patients had a higher level of serum HDL-C, lower serum triglyceride levels and a lower prevalence of metabolic syndrome than patients with negative anti-GAD [29]. The present study also showed a lower mean value of serum triglyceride and LDL-C and a higher mean value of HDL-C in LADA patients.

In summary, patients classified as LADA presented the following features: At least one autoantibody present in all patients, mean age at diagnosis, mean BMI, mean C-peptide, mean insulin, mean HOMA-IR, mean cholesterol, triglycerides and LDL-C were significantly lower where personal and family history of autoimmune disease especially autoimmune thyroid disease and HDL-C were significantly higher than in type 2 DM patients. Many of our findings were similar with the study done by Fourlanos et al. [33] which point out that five clinical features were more frequent in LADA compared with type 2 DM at diagnosis: (1) age of onset <50 years, (2) acute symptoms (polydipsia/polyuria/unintentional weight loss), (3) body mass index <25 kg/m^2, (4) personal history of autoimmune disease and (5) family history of autoimmune disease.

Study limitations

As a limitation, in the present study, we estimated only fasting C-peptide value of study subjects and took this as baseline value. We did not estimate the stimulated C-peptide values which could further determine the actual beta cell capacity of LADA patients. We also did not evaluate the periodic C-peptide of study subjects, which estimate the prognostic value of C-peptide.

Conclusion

LADA patients comprise an important segment of the diabetic population, and though its prevalence being around 10 %, it often gets misdiagnosed. Therefore, early identification of LADA is a must to start an optimum treatment with insulin for these patients, possibly to preserve the remaining pancreatic beta cell function. From the present study, it appears that C-peptide level determination can be considered as an initial screening tool, while anti-GAD antibody along with anti-IA2 assay can be used as confirmatory diagnostic markers for identifying LADA patients from type 2 DM, whereas other clinical and biochemical parameters are useful for further characterizing LADA patients.

Compliance with ethical standards

Consent to participate Informed written consent was obtained from each individual.

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ORIGINAL ARTICLE

Self-care practices and barriers to compliance among patients with diabetes in a community in rural Bangladesh

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Abstract Diabetes is an emerging health threat in Bangladesh. The study objectives were to evaluate self-management practices among a population with diabetes in rural Bangladesh and to identify barriers to complying with prescriptions for diet, physical activity and drug use. In this cross-sectional study, 220 patients with diabetes were recruited from logs of diabetes clinics in Mirzapur, Bangladesh. Participants were asked about self-care practices and health complications and comorbidities associated with diabetes. Participants were also asked about treatments costs, barriers to diabetes treatment and socio-demographic characteristics. Almost half of the participants (49 %) were taking oral hypoglycemic agents (OHA), and 47 % were taking a combination of OHA and insulin; however, 30 % of those using insulin were not confident in their ability to self-administer the medication. The majority of participants (86 %) had complications that they attributed to diabetes, including vision impairments, poor wound healing and dizziness. The median monthly cost of diabetes maintenance was 725 taka (~US$9), approximately 8 % of the median monthly income. Common barriers to treatment included the high cost of medication, access and proximity to services, and feeling unwell as a result of prescribed treatments. Although the vast majority of participants managed their diabetes using OHA and insulin, there were common barriers that prevented patients with diabetes from complying with doctor's recommendations for diabetes management. Given the high incidence of self-reported diabetic complications among this population, addressing these barriers may improve self-care practices and overall quality of life among those with diabetes in rural areas in Bangladesh.

Keywords Diabetes mellitus · Diabetes complications · Self-care · Cost of illness · Bangladesh

Introduction

Diabetes is ranked ninth in the world as a leading cause of death [1]. Although previously regarded as a condition predominantly affecting high-income countries, the burden of diabetes has now transitioned to many low- and middle-income countries, with particularly high rates among Asian populations [2]. In Bangladesh, diabetes is considered an emerging health threat, with an estimated overall prevalence of 7 % among the general population ranging from 5 % in rural areas to 10 % in urban areas, which has almost doubled over the past decades [3]. The prevalence of those 'at risk' of diabetes with impaired fasting glucose or impaired glucose tolerance is also high, estimated at 7 and 8 %, respectively [3].

Proper management can decrease the risk of diabetes-associated complications and comorbidities, with implications for both the economical and psychological burden of the condition and overall quality of life [4]. Self-care practices are essential to increase the likelihood of maintaining appropriate blood glucose, lipid levels and insulin sensitivity, in order to

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control or reduce the likelihood of developing complications associated with diabetes, including neuropathy, nephropathy, retinopathy and cardiovascular disease [5, 6]. The extent to which patients with diabetes are able to follow this advice in Bangladesh is not well described in the literature. In a study sampling Asian countries including Bangladesh, overall glycemic control was 'poor' in more than half of the study sample, and poor glycemic control was associated with increased microvascular complications [7]. Additional research found that approximately 90 % of patients with diabetes in urban clinics did not test their blood sugar levels regularly [8].

The objectives of the present study were to evaluate the self-care practices and frequency and type of clinical management among a population of individuals with diabetes in rural Bangladesh and to identify potential barriers in adhering to prescribed recommendations for diet, physical activity and drug use.

Methods

Sample description

Participants were recruited from the Mirzapur sub-district in the Tangail district of Bangladesh, located approximately 60 km north-west of the capital city Dhaka. All participants were members of a previously established pool of individuals (N = 255,000) from the Demographic Surveillance System (DSS), maintained by the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b). Data collection took place in March, 2013.

Study patients were identified through registers of all patients with diabetes who had attended the Kumudini Hospital outpatient clinic or the clinic of the Diabetic Association of Bangladesh (DAB) in Mirzapur in 2012. This list was then cross-referenced with DSS participants, to obtain contact information for these individuals. Participants were recruited via telephone or in-person home visits by research staff from icddr,b. Interviews were conducted at Kumudini Women's Medical College and Hospital, a tertiary-level hospital serving the Mirzapur sub-district and adjacent sub-districts.

Participants were considered eligible for the study if they were over 18 years of age, had been diagnosed with diabetes by a physician and were enrolled in the DSS. Pregnant or lactating women and seriously ill or bed-ridden individuals were excluded.

A total of 309 individuals were identified from registers, and the final sample size was 220. The recruitment has been described in detail in Fig. 1. According to response rate no. 1 of the American Association for Public Opinion Research, there was a response rate of 72.6 % [9].

Study protocol

Interviews were approximately 1 h in length and were conducted in Bengali by local, trained field research assistants from icddr,b. Interviews were conducted in an office on the hospital grounds, and information was recorded using a pen and paper. Take-home medical records from the DAB clinic were available for all participants and were reviewed by a medical doctor (co-author SA). During recruitment, participants were requested to bring their recent available medical records. Ethics approval was provided by the University of Waterloo Office of Research Ethics and the Research Review Committee and Ethical Review Committee of icddr,b.

Measures

Information on individual and household demographics was collected. Measures of socioeconomic status included monthly household income and information on personal assets to assess wealth quintiles (homestead land, cultivable land, household assets, livestock assets, as well as building materials of the house).

Self-care practices

Participants were asked if they had type 1 or type 2 diabetes, and medical records were checked to identify diagnosis of diabetes type. A series of questions examined when participants were diagnosed with diabetes, what treatments they were currently receiving or had received in the past for diabetes, and if they had ever been prescribed various behavioural treatments or used any traditional remedies to control diabetes. Ownership of a glucometer and frequency of testing blood sugar or urine at home were also examined. Recent medical records provided by patients were reviewed to collect data on recently performed diagnostic tests for diabetes, when available.

Health-related measures

Participants were asked to self-report if they had been diagnosed with a number of common comorbidities (heart disease, stroke, hypertension, hypercholesterolemia, cancer, kidney disease, depression, and an open-ended response for other comorbidities) and had experienced a number of health effects known to be complications of diabetes (dizziness/fainting/glucose shock, blindness or vision problems, foot problems/ulcers, swelling/edema, kidney problems, heart problems, stroke, poor wound healing, amputation of limbs, and an open-ended response for other complications). Weight was measured with light clothing and shoes removed, to the

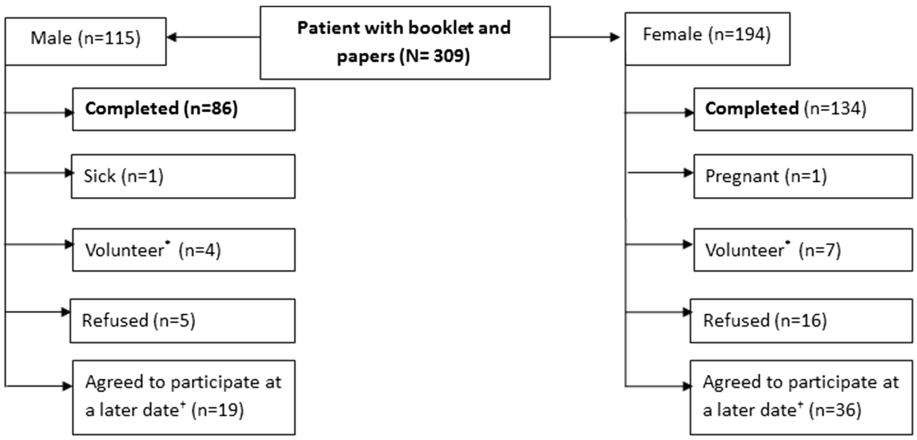

Fig. 1 Sample recruitment flow chart. *Asterisk* indicates that the participant was not contacted by the study staff, but heard of the study through word of mouth and asked to participate. The *cross* indicates that the participant agreed to be contacted at a later date, and the study was completed before re-contact occurred

*Volunteer = participant was not contacted by the study staff, but heard of the study through word of mouth and asked to participate.
† Agreed to participate at a later date = participant agreed to be contacted at a later date, and the study was completed before re-contact occurred.

nearest 100 g using a digital scale (TANITA, HD-308). Height was measured with shoes removed, standing straight with heels together using locally produced wooden height scales with 0.1 cm precision. Body mass index (BMI) was categorized using the World Health Organization cut-offs (underweight, BMI <18.5 kg/m^2; normal, 18.5–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; obese ≥30.0 kg/m^2) and further categorized into a binary measure of BMI < 25.0 kg/m^2 and BMI of 25.0 kg/m^2 or greater [10]. Waist circumference (WC) was measured at a level midway between the lower rib margin and iliac crest in the midaxillary line, taking the measurement at the end of expiration while the participant was standing. Hip circumference (HC) was measured at the widest part of the hip across both greater trochanters. 'Central obesity' was defined using the International Diabetes Foundation (IDF) cut-off points for South Asian populations (>90 cm WC for men, >80 cm for women) and waist-to-hip ratio (WHR) cut-off points of 0.90 for men and 0.85 for women [11].

Adherence and barriers to compliance

Treatment-seeking behaviours and self-reported compliance to physician advice were also assessed. Participants were asked if they had visited a health clinic in the previous month; open-ended questions about barriers to clinic use; how often they are able to follow their doctor's recommendations for drugs and insulin, diet, and physical activity; and open-ended questions regarding what barriers they face in following these recommendations.

Cost of illness

An estimated cost of illness over the previous 30 days was also adapted from the DSS survey [12]. Participants were asked to estimate their out-of-pocket expenses in the past 30 days for the following: pharmacy expenses/drugs (including insulin, oral medication, glucose strips, etc); traditional healer/village doctor; visit to a license practitioner/private doctor; visit to the DAB clinic (excluding lab and diagnostic fees); medicine bought at a shop/market; hospital admission fees (excluding lab and diagnostic fees); lab and diagnostic fees; food and diet during clinic or hospital visits; transportation to and from the clinic/hospital; food during the clinic/hospital visits; and any other fees relating to management or care for their diabetes or related complications.

Analysis

Descriptive statistics were used to describe sample attributes. When distributions of variables were skewed, median and ranges were provided. Statistically significant differences in proportions were determined using chi-square tests. Analyses were conducted using SPSS v. 22 (Armonk, NY), and results were considered statistically significant at $p < 0.05$.

Results

Sample characteristics can be found in Table 1. The sample was composed of more women than men (61 vs. 39 %).

The average age of diagnosis of diabetes was 43.4 years (SD = 11.5 years), and the average duration of diabetes was 5.9 years (SD = 5.2 years). Of the sample, 1 % reported that they had type 1 diabetes, 11 % reported that they had type 2 diabetes and 88 % did not know which type of diabetes they had and that information was not available in the medical records. Overall, 86 % (n = 189) of participants reported at least

Table 1 Sample characteristics

	Overall (n = 220)	Male (n = 86)	Female (n = 134)	X^2 or t test	p value
Age, mean (SD)	49.3 years (11.9)	52.6 years (13.1)	47.2 years (10.6)	3.3	0.005
Religion, % (n)					
Muslim	80 (177)	70 (60)	87 (117)	10.3	<0.001
Hindu/other	20 (43)	30 (26)	13 (17)		
Education, % (n)					
Illiterate/no education	31 (67)	14 (12)	41 (55)	51.2	<0.001
Primary school (1–5 years)	27 (59)	16 (14)	34 (45)		
Secondary school (6–12 years)	28 (62)	38 (33)	22 (29)		
Graduate or more	14 (32)	31 (27)	4 (5)		
Occupation, % (n)					
Homemaker	56 (123)	0 (0)	92 (123)	184.9	<0.001
Business	16 (36)	41 (35)	1 (1)		
Retired	7 (15)	16 (14)	1 (1)		
Office non-executive	6 (14)	11 (9)	4 (5)		
Farmer	5 (11)	13 (11)	0 (0)		
Other	10 (21)	20 (17)	3 (4)		
Income (median) (BD taka) (US$)	(~$139)	(~$181)	(~$139)		
Number of people in household, % (n)					
4 or less	51 (111)	49 (42)	52 (69)	0.15	0.7
5 or more	49 (109)	51 (44)	49 (65)		
BMI, % (n)					
BMI <18.5	6 (13)	11 (9)	3 (4)	8.3	0.04
BMI 18.5–24.9	64 (140)	63 (54)	64 (86)		
BMI 25.0–29.9	28 (62)	27 (23)	29 (39)		
BMI 30+	2 (5)	0 (0)	4 (5)		
WHR, mean (SD)	92.1 (0.078)	94.9 (0.076)	90.3 (0.073)	4.5	0.001
At risk, % (n)[a]	81 (178)	80 (69)	81 (109)	0.042	0.838
Waist circumference, mean (SD)	86.0 cm (9.4)	88.2 cm (9.0)	84.7 cm (9.4)	2.7	0.53
At risk, % (n)[b]	59 (130)	47 (40)	67 (90)	9.2	0.002

[a] Waist–hip ratio greater than 90 for men and 85 for women

[b] Waist circumference greater than 90 cm for male and 80 cm for women

one health effect known to be a complication of diabetes. A breakdown of self-reported complications and comorbidities can be found in Table 2. The most commonly reported health effect was vision impairments such as blurring, dim vision or blindness (66 %), followed by poor wound healing (29 %) and dizziness (28 %). Sexual dysfunction was reported among 13 % of men (5 % of the entire sample). In examining comorbidities, hypertension was most commonly self-reported in 45 % of participants, followed by heart disease and depression (19 and 16 %, respectively).

See Table 1 for full details on anthropometric measures. Of the entire sample, 30 % were 'overweight' or 'obese' with a BMI of 25 kg/m^2 or greater; the average BMI was 23.6 kg/m^2 (SD 3.3). The average WHR was 94.9 (SD 0.076) among men and 90.3 among women (SD 0.073). For men, 80 % had a WHR greater than 0.90 and for women 81 % had a WHR greater than 0.85, the respective cut-offs indicating central obesity for this population.

Self-care and diabetes management

The most commonly prescribed treatment was the use of both insulin and oral hypoglycaemic agents (OHA) (49 %), followed by use of OHA only (47 %), only insulin therapy (4 %) and no treatment prescribed (0.5 %). Of the 53 % of the sample that had been prescribed insulin for their diabetes (n = 116), only 64 % (n = 74) expressed that they felt confident that they could properly administer insulin. Among the OHA that patients were taking, metformin hydrochloride was the most commonly prescribed, followed by gliclazide and pioglitazone, either alone or as combination therapy. Of the entire sample, few participants were using alternative methods of treatment such as visiting a traditional healer (10 %) or using traditional remedies (6 %) to treat their diabetes. Overall, 90 % had been prescribed a special diet for their diabetes and 89 % had been prescribed physical activity, while 36 % had been advised to lose weight.

Table 2 Prevalence of self-reported complications and comorbidities

	Number	Percentage
Complications		
Vision impairments	145	66
Poor wound healing	63	29
Dizziness/glucose shock	61	28
Foot problems	42	19
Swelling/edema in legs	42	19
Sexual dysfunction	11	5
Kidney problems	8	4
Other complications	37	17
Comorbidities		
Hypertension	99	45
Heart disease	41	19
Depression	35	16
Hypercholesterolemia	33	15
Stroke	24	11
Kidney disease	7	3

Multiple responses were permitted for complications and comorbidities

Overall, 11 % of the sample owned glucometers, for whom the median glucose self-monitoring frequency was 12 times per year, ranging from 4 to 156 times; 2 % of the sample reported testing their urine at home at least once in the previous year.

Medical records were reviewed from all but one participant to examine medical tests each patient had undergone. The most commonly available test result was blood glucose measures 2 h post-breakfast, available from 86 % of participants, followed by 63 % with records for fasting plasma glucose, 19 % with records for random glucose tests and 13 % with records for serum creatinine levels. Measures of HbA1c were only available from 3 % of patients. Other measures were available for less than 10 % of the sample.

Clinic visits and barriers to visiting clinics

Participants visited the diabetes clinic on average six times per year. The average trip to the nearest clinic for diabetes treatment was approximately 1 h (63 min), by walking in combination with various forms of public and private transport. The most commonly reported barriers to visiting a clinic were the high cost of tests and fees for clinic visits (28 %), being too busy or having to work during the hours the clinic was open (14 %), and distance from home or transportation problems in accessing the clinic (12 %). Other common barriers included not being able to visit the clinic alone and having no one to take them, as well as being too ill or unwell to visit.

Barriers to diabetes management

Participants were asked how often they are able to follow a doctors' advice for insulin or OHA treatment, diet and physical activity and what were things that made it difficult to follow those instructions. More than half (58 %) of the sample reported that they are always able to follow instructions from their doctor for insulin or medication, while 21 % could usually follow instructions and 21 % could sometimes or never follow the instructions. For prescribed medication, the most commonly cited barriers were cost of the drugs or treatment (18 %), the participants felt unwell after the prescribed behaviour (11 %), being too busy (7 %) and forgetting to take medication (6 %).

Of the entire sample, 39 % always followed the nutrition advice from their doctor, while 24 % usually followed this advice and 44 % sometimes or never followed that advice. Barriers to following advice for diet were that they did not like the diet or were still hungry after they ate the prescribed amount (26 %), they were too busy to prepare the appropriate meals (19 %), it was too expensive (14 %) and it made the participants feel unwell (10 %). For physical activity, 53 % of the sample reported that they always followed doctor's advice, 20 % usually followed this advice and 25 % sometimes or never followed recommendations for physical activity. Common barriers to meeting physical activity recommendations included being too busy or not having time (26 %), other health problems (18 %) and physical activity makes them feel unwell (12 %).

Cost of illness

Participants were asked about various costs associated with their illness in the previous 30 days. The median cost of participants was 725 taka (Tk—Bangladesh currency) (slightly less than US$10), ranging from no costs (among 26 participants) to a maximum of 16,200 Tk (slightly more than US$200) among only one participant. The most significant contributor to expenses was the cost of drugs and pharmaceuticals to manage diabetes, followed by the cost of lab and diagnostic fees while visiting clinics and then the cost of transportation to and from the clinic. Indirect costs of illness due to losses in earnings were apparent in 5 % of the sample, with a median of 1190 Tk (approximately US$15) for those participants.

Discussion

Self-management using OHA and insulin was very high. However, a third of participants reported that they were not confident in their ability to administer insulin adequately. The lack of this type of skill may contribute to non-compliance with doctor's recommendations for drug or insulin treatment

and may lead to poor glycaemic control. Few participants (<1 %) were prescribed only behavioural interventions, significantly less than a previous study of Asian countries including Bangladesh [7]. Given the cost barriers to some drug interventions, behavioural interventions may be an area that warrants further attention and greater emphasis in the rural Bangladeshi context.

The self-reported prevalence of complications among the study population was high, suggesting that blood glucose control may be poor among this population. This is consistent with recent research suggesting that awareness, treatment and control of diabetes among Bangladeshi adults is low [13]. The prevalence of vision complications was overwhelmingly high. There may be other contributors to these high rates, and this deserves further investigation. In this study, the prevalence of depression among patients with diabetes was 16 %, slightly lower than a previous study examining the prevalence of depression in a rural Bangladeshi population with diabetes [14]. The present study only accounted for self-reported depression as compared to a diagnosis of depression, which may lead to differences in these outcomes. Interestingly, the reported prevalence of sexual dysfunction was fairly high among men, even when this condition was not particularly probed by interviewers. Additionally, not all participants were gender-matched with interviewers, which may have led to decreased reporting among male participants and actual rates may be higher than this study reveals. The psychological effects of diabetes may significantly influence quality of life among this sample, and the prevalence and impact of both depression and sexual dysfunction deserve further study.

There were several barriers that were consistent across the various types of self-care. Not surprisingly, cost was the main barrier to accessing medication, similar to another study on barriers to diabetes management access in a low-income country [15]. This is also demonstrated in the cost-of-illness assessment, in which the median cost of illness per month was equivalent to 8 % of the median monthly income for families. However, the proportion of those who reported that cost was a barrier to accessing insulin was lower in this study than previous research in Bangladesh, perhaps due to our sampling frame, which included patients who access a clinic for diabetes treatment and who may have improved socioeconomic status [16]. Cost barriers may also contribute to fewer clinic visits and decreased access to tests, which can lead to decreased monitoring of diabetes management among those who do not test glycaemic levels at home. For example, HbA1c is the gold standard for diagnosing and monitoring diabetes according to the WHO and is recommended every 2 to 6 months in standard care by the IDF; however, it had only been measured in 3 % of participants in this study [17]. The high cost of the test (approximately 700 Tk or US$9 at the time of the study—personal communications) is likely a barrier to using this assessment method. These results are aligned with previous research which has highlighted the increasing financial hardship due to non-communicable disease in Bangladesh, with implications for coping strategies for health-care-related expenses [18].

Another significant barrier was lack of time to purchase and prepare healthy food and participate in physical activity. Increasing accessibility to healthy food and promoting physical activity that is easily accessible, such as brisk walking, may improve these behaviours and may be a mechanism to improve blood sugar levels beyond medicinal interventions.

Strengths and limitations

There were several limitations to the study, including the use of self-report data of complications and comorbidities of diabetes and the collection of clinical data from diabetic records. Additionally, the study only collected information from those who attended a diabetes clinic in the previous year, who may have better health behaviours or improved socioeconomic status than those who did not attend the clinic. Therefore, the current findings may be more favourable than the general population with diabetes, and the results may be less generalizable to the overall population living with diabetes in rural Bangladesh. The sample contained more women than men; however, this is consistent with some studies of the prevalence of diabetes among women and men in Bangladesh [19]. Strengths of the study include high response rates and the examination of diabetes medical records to identify services accessed.

Conclusions

Individuals with diabetes in rural areas of low-income countries face unique challenges to adhere to lifestyle and clinical requirements in order to follow prescribed self-care practices. Improving access to clinics and testing, increasing patient knowledge and confidence surrounding techniques to manage blood sugar levels and decreasing the cost of treatment may improve compliance and decrease complications and comorbidities among this population. Additional education or counselling sessions, through clinics or community health workers, may help to improve self-efficacy around self-care practices, with implications for glycaemic control and incidence of complications among this rural population [20].

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Compliance with ethical standards

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

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.

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ORIGINAL ARTICLE

Assessment of multimedia-supported intervention in Muslim diabetic patients treated with insulin

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Abstract This study aimed to evaluate the effect on diabetic care of an educational DVD in Jawi, the primary spoken language of Muslims in the study area, and pharmacist intervention among Muslim patients with diabetes treated with insulin. Type 2 diabetes Muslim patients on insulin treatment and poor glycemic control ($N=143$) in one hospital in southern Thailand were recruited to participate in a 6-month-period pre- and post-intervention study. For the intervention, the pharmacist provided the patients with education using a DVD and then asked them to show how to use insulin injection. Afterward, the pharmacist would correct the techniques for patients individually. At 6 months after intervention, significant reductions in glycated hemoglobin (HbA_{1c}) (8.31 ± 1.40 to 7.19 ± 1.15 %, $P<0.001$), fasting blood glucose (FBG) (195.06 ± 86.14 to 115.81 ± 11.48 mg/dL, $P<0.001$), systolic blood pressure (130.62 to 126.57 mmHg, $P=0.004$), triglycerides (183.36 ± 90.48 to 182.31 ± 90.68 mg/dL, $P<0.001$), and total cholesterol (199.57 ± 68.77 to 194.97 ± 64.77 mg/dL, $P=0.006$) were detected in patients who received the intervention. Increased low-density lipoprotein cholesterol (LDL-C) level ($P=0.028$) but no significant change in high-density lipoprotein cholesterol (HDL-C) were found ($P=0.900$). Moreover, medication adherence, diabetes knowledge, and skill in using insulin injection improved at the end of the study ($P<0.001$). In conclusion, the combination of language-specific educational DVD and pharmacist intervention appears to improve the short-term outcomes of diabetes care in Muslim patients on correctional insulin therapy.

Keywords Multimedia · DVD · Pharmacist · Intervention · Muslim · Diabetes

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Introduction

Diabetes mellitus presents an important public health problem worldwide. The global prevalence of diabetes is fast growing, affecting 347 million people in 2014. The growth mainly occurs in developing countries (69 %), resulting from the rise in overweight, obesity, and physical inactivity [1–3].

Diabetes has become a primary cause of morbidity and mortality from microvascular and macrovascular complications [4]. Cardiovascular disease is the leading cause of death in 50 % of people with diabetes [1]. However, good glycemic control is related to reduced risk of the complications [5–7]. The goal of glycated hemoglobin (HbA_{1c}) of <7 % is recommended [8]. Approximately 90 % of individuals with diabetes worldwide are type 2 [1]. In the treatment of type 2 diabetes, patients may receive insulin therapy if they are newly diagnosed as having diabetes with obvious symptoms and/or hyperglycemia or are nonresponsive to noninsulin antidiabetic agents at maximum dose within 3–6 months of treatment [8].

Nonetheless, many patients receiving insulin treatment have poor glycemic control [9]. Factors associated with poor glycemic control include inadequate knowledge and non-

adherence to treatment [10, 11]. Additionally, skill deficits about the insulin injection technique were also associated with not achieving the glycemic goal [10].

Although the exact prevalence of diabetes in the entire Muslim population has not been reported, a study in India found that the prevalence of such a condition was 16.6 % in Muslims [12]. Diabetes has been recognized as the biggest cardiovascular risk factor in the Muslim world, accounting for 80 % of cardiovascular cases [13]. Dietary habits may play a crucial role. Muslim diabetic patients with poor glycemic control should receive educational intervention to improve the clinical outcomes. Muslims in some regions are a minority and use specific languages, such as Persian or Jawi, in their daily life. Most of them cannot communicate with official languages spoken by the majority in the regions, including their health professionals. About 78 % of the Muslim population in Thailand reside in the south of the country [14] and use Jawi as a spoken language especially in the deep south. Only 21.4 % of patients with diabetes in this region were reported to achieve the goal of treatment [15]. The language barrier may be one of the explanations for poor glycemic control. Therefore, the appropriate intervention is important in this group of patients.

Evidence also suggests that interactive multimedia is effective for health education [16–18]. Numerous studies have demonstrated the potentials of pharmacists in diabetic care [19–21]. This study employed multimedia in the Jawi language to educate Muslim patients on the awareness of diabetes, self-management, and insulin use, combined with pharmacist intervention. We hypothesized that this educational DVD together with pharmacist intervention would improve the outcomes of diabetic care among Muslim patients on insulin treatment. The objective of this study was to investigate the effects of educational DVD in Jawi together with pharmacist intervention on the outcomes of diabetic care in Muslim diabetes patients on insulin therapy.

Method

Study design and setting

A pre- and post-intervention study was performed with a 6-month patient follow-up. This study was conducted in one hospital located in Yala province in the deep south of Thailand using convenience sampling. In the four provinces located in the deep south of the country, the proportion of Muslim residents ranges from 32 to 87 %. At the time of the study, 77 % of residents in Yala were Muslims and their native language was Jawi. The prevalence of people with diabetes in this province was around 7 %. Of these, only 21.3 % had adequate glycemic control—lower than other provinces in this area [14, 15, 22].

In Yala, 47.5 % of the population had less than secondary level of education. Approximately, half had occupation in agriculture and the average income per person per year was about 2200 euro (1 euro = 41 baht). The major ethnicity was Malayu Thais, followed by Thais and Chinese Thais. The majority of religion was Islam (77 %), followed by Buddhism (23 %) and Christianity (<1 %). By contrast, the religious mix in the whole country comprised Buddhism (94 %), followed by Islam (5 %) and Christianity (1 %) [14].

The study site was a secondary hospital with no residency program for clinical training of health care professionals. Seven general practitioners were on duty for caring for patients with acute or chronic diseases. In severe cases, the patients would be referred to tertiary hospitals.

Usual care pre-intervention

Patients with diabetes received usual medical care with a physician every 2–3 months. At each follow-up visit, blood pressure, body weight, and information about patient health problems were reported by nurses. In addition, fasting blood glucose (FBG) was measured by laboratory staff. HbA_{1c} and lipid profile (i.e., low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, and total cholesterol) were monitored on an annual basis. Next, the patient visited a physician and afterward received the prescribed medications from a pharmacist. The pharmacist checked the accuracy of the medications and drug-related problems and then advised the patient about the drug use (name, dose, and possible precautions/warnings).

When a patient had above 7 % of HbA_{1c} or 126 mg/dL of FBG, the pharmacist delivered a brief diabetes recommendation focusing on drug utilization and self-care.

For those who received the prescription with insulin for the first time, a pharmacist instructed patients on how to perform the injection. Next, the patient had to show the steps of injection technique and corrections were made by the pharmacist.

Patient recruitment

Study patients were recruited from the outpatient diabetes clinic at the hospital site. Eligibility criteria were at least 18 years of age, Muslim patient, being diagnosed with type 2 diabetes, receiving insulin treatment, and having HbA_{1c} level >7 %. Exclusion criteria were inability to use insulin injection by him/herself, pregnancy, and breastfeeding.

To determine sample size, calculation was based on data of Huang et al. showing a standard deviation (SD) of 1.43 % and 1.00 % of HbA_{1c} [18], difference of 0.5 % in HbA_{1c}, type I error of 0.05, and a power of 80 %. A sample of 96 patients was required.

All diabetic patients who met the inclusion criteria and did not meet the exclusion criteria were asked to enroll in the

study. The sampling method used in this study was convenience sampling.

Educational DVD production

The aim of the 12-min educational DVD was to increase knowledge on diabetes, self-management, and insulin injection technique. Contents of the DVD comprised two components: (i) slides with illustrations and verbal narrations and (ii) a video. The first component was approximately 5 min in length, covering an introduction to diabetes, symptoms, complications, and self-care. The video in another component explained the steps of insulin injection. The first version of DVD was in Thai, the official language spoken by the majority of Thai people. The content validity of the first version was verified by two lecturers in clinical pharmacy from the Faculty of Pharmaceutical Sciences, one physician, and two pharmacists who practiced in the diabetes clinic of the hospital. After revision, the text was assessed by three Muslim diabetes patients for clarity. The revised text was then pre-tested in another three Muslim patients. All Muslim patients in the testing were able to communicate in the Thai language.

To obtain a Jawi version of the DVD multimedia, the Thai version was independently translated into Jawi by two bilingual Muslims, one a teacher of Islam studies and the other a hospital officer, and a consensus reached. Then, back translation from Jawi into Thai version was independently performed by another bilingual Muslim who was another teacher in Islam studies. All translators were fluent in both Thai and Jawi and understood Islamic culture. Subsequently, the Jawi version was piloted with three Muslims who did not speak Thai.

Study procedures

The research pharmacist informed the eligible patients of the study objectives and procedures verbally in Jawi and also gave the written information sheet to patients and their relatives. Those who agreed to participate in the study were asked to sign the informed consent. In addition, the participants were asked to bring all vials of insulin to the pharmacist at every hospital visit during the study for measuring insulin adherence. Medication adherence was determined by the insulin used by the patients multiplied by 100 and divided by the total volume of insulin dispensed.

At the first visit, patient baselines were measured, including HbA_{1c}, FBG, blood pressure, lipid profile, body mass index (BMI), adherence to insulin therapy, knowledge on diabetes, and skill in insulin injection. Subsequently, the patients received education via DVD multimedia in the hospital. Following the DVD intervention, the researcher pharmacist asked each patient to demonstrate how he/she used insulin injection, and then corrected the identified wrong steps or techniques individually. The demonstration and correction were repeated until the patient correctly used insulin. Furthermore, the researcher would give recommendations if the patients had problems about the prescribed pharmacotherapy or self-management. In the next three visits two months apart, they also received educational intervention via DVD and were assessed for their ability to use insulin correctly. At the last visit, HbA_{1c}, FBG, blood pressure, lipid profile, BMI, insulin adherence, knowledge on diabetes, and skill in insulin injection were assessed again.

Outcome measurement

The primary outcome was the change in HbA_{1c} value, measured at baseline and at 6 months after intervention. The secondary measures included the changes in FBG, blood pressure, lipid profile, BMI, insulin adherence, diabetes knowledge, and skill in using insulin. The patient knowledge about diabetes was assessed with a questionnaire developed by Wongwiwatthananukit and Lohavisavapanich [23] with permission from the researchers.

Statistical analysis

Categorical data at baseline and at the end of the study were compared using McNemar chi-square test. Comparisons of continuous data were analyzed with paired *t* test. A *P* value of <0.05 indicated statistical significance. Analyses were conducted with SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

The distribution of the primary outcome of the study (HbA_{1c} value) was tested by examining the quartile-quartile plot. Nearly all data lay on the standard normal distribution line indicating their normal distribution.

Results

Initially, the study recruited 153 Muslim patients on insulin treatment. Of these, ten dropped out: three died, four left the city, and three permanently moved and received care from other hospitals.

Characteristics of 143 patients who completed the study are presented in Table 1. The majority were female (62.2 %), had lower than secondary school education (66.4 %), and worked in the agricultural sector (65.0 %). The mean (+SD) age was 54.57 ± 10.51 years and mean (+SD) duration of diabetes 6.20 ± 3.34 years. Table 2 shows that after 6 months of educational DVD and pharmacist intervention, significant decreases were detected in HbA_{1c}, FBG, systolic blood pressure (SBP), triglycerides, and total cholesterol as compared to baseline ($P < 0.05$). Conversely, a significant increase was observed in LDL-C ($P = 0.028$). Diastolic blood pressure (DBP), HDL-C, and BMI showed no significant improvements

Table 1 Characteristics of patients ($N = 143$)

	N (%)
Gender	
Female	89 (62.2)
Male	54 (37.8)
Age range (years)	
<30	1 (0.7)
30–39	13 (9.0)
40–49	32 (22.4)
50–59	58 (40.6)
60–69	31 (21.7)
70–79	8 (5.6)
Age (mean ± SD)	54.57 ± 10.51
Education	
<Secondary school	95 (66.4)
≥Secondary school	48 (33.6)
Occupation	
Agriculture worker	93 (65.0)
Housewife	17 (11.9)
Merchant	14 (9.8)
Unskilled worker	11 (7.7)
Others[a]	8 (5.6)
Current smoking	54 (37.8)
Current alcohol drinking	1 (0.7)
Duration of diabetes (years)	6.20 ± 3.34
Other underlying disease	
Hypertension	126 (88.1)
Dyslipidemia	123 (86.0)
Cardiovascular disease	9 (6.3)
Presence of complications	
Neuropathy	19 (13.3)
Chronic kidney disease	15 (10.5)
Foot ulcer	5 (3.5)

[a] Such as government officer and unemployed

($P > 0.05$). As shown in Table 3, insulin adherence, knowledge on diabetes, and skill in correct insulin injection were significantly enhanced at the end of the study ($P < 0.001$).

Discussion

This study demonstrated that improvement of glycemic control, blood pressure, medication adherence, and knowledge among Muslim patients treated with insulin can be achieved with educational DVD and pharmacist intervention.

The finding on HbA_{1c} reduction after intervention is consistent with that of Jarab et al. who reported a 0.8 % decrease in HbA_{1c} in type 2 diabetes patients following education from a clinical pharmacist with weekly telephone follow-up, whereas those in the control group with usual care had an increase of 0.1 % of HbA_{1c} from baseline ($P = 0.019$) [21]. Al Mazroui et al. indicated a 1.6 % reduction in HbA_{1c} in patients with type 2 diabetes participating in a pharmaceutical care program relative to a 0.1 % reduction in control group patients ($P < 0.001$) [24]. However, pharmacist interventions in these studies were rather intensive, such as education delivery by pharmacists with regular follow-up calls or comprehensive pharmaceutical care program. These interventions may be applicable in the settings where pharmacist manpower is sufficient. On the contrary, the pharmacist intervention in the present study focused on counseling, multimedia education with the major role of pharmacists emphasizing the assessment, and correction of skill in using insulin, the crucial and prone-to-error component in diabetes control. Our intervention may be appropriate in the pharmacies with a heavy workload. The DVD multimedia had played an important role in improving patient knowledge. The educational DVD significantly enhanced awareness of Muslim patients on diabetes, disease management, and self-care ($P < 0.001$). Previous studies also found that the DVD was effective as an educational instrument to increase patient awareness [16–18]. The DVD multimedia is able to present words, illustrations, animations,

Table 2 Comparison of clinical parameters at pre-DVD and 6-month post-DVD with pharmacist intervention ($N = 143$) (mean ± SD)

	Pre-DVD	6-month post-DVD	Mean difference (95 % CI)	*P* value
HbA_{1c} (%)	8.31 ± 1.40	7.19 ± 1.15	−1.12 (−1.40, −0.84)	<0.001
FBG (mg/dL)	195.06 ± 86.14	115.81 ± 11.48	−79.24 (−93.48, −65.01)	<0.001
Systolic blood pressure (mmHg)	130.62 ± 22.16	126.57 ± 10.82	−4.05 (−6.82, −1.28)	0.004
Diastolic blood pressure (mmHg)	77.55 ± 10.63	78.46 ± 9.81	0.91 (−0.05, 1.87)	0.063
LDL-C (mg/dL)	122.12 ± 40.66	124.19 ± 39.89	2.07 (0.23, 3.91)	0.028
HDL-C (mg/dL)	37.01 ± 7.86	37.00 ± 7.78	−0.01 (−0.12, 0.10)	0.900
Triglyceride (mg/dL)	183.36 ± 90.48	182.31 ± 90.68	−1.06 (−1.47, −0.64)	<0.001
Total cholesterol (mg/dL)	199.57 ± 68.77	194.97 ± 64.77	−4.60 (−7.88, −1.32)	0.006
BMI (kg/m^2)	25.93 ± 6.41	25.83 ± 6.25	−0.10 (−0.23, 0.04)	0.167

Table 3 Comparisons of medication adherence, knowledge on diabetes mellitus, and skill in insulin use at pre-DVD and 6-month post-DVD with pharmacist intervention ($N = 143$) (mean ± SD)

	Score range	Pre-DVD	6-month post-DVD	Mean difference (95 % CI)	*P* value
Insulin adherence		66.83 ± 13.64	81.23 ± 7.01	14.40 (11.47, 17.33)	<0.001
Knowledge on diabetes and management					
Disease	0–5	2.68 ± 0.93	4.13 ± 0.73	1.45 (1.26, 1.65)	<0.001
Symptoms	0–1	0.66 ± 0.47	0.83 ± 0.38	0.17 (0.08, 0.26)	<0.001
Complications	0–4	0.73 ± 0.98	2.87 ± 0.79	2.14 (1.96, 2.32)	<0.001
Food	0–3	0.90 ± 0.47	1.49 ± 0.60	0.59 (0.48, 0.71)	<0.001
Self-care	0–5	0.82 ± 0.74	3.22 ± 0.94	2.39 (2.19, 2.60)	<0.001
Drug use	0–3	0.86 ± 0.65	2.87 ± 0.42	2.01 (1.89, 2.13)	<0.001
Total score	0–21	6.66 ± 2.17	15.42 ± 1.80	8.75 (8.32, 9.19)	<0.001
Skill in using insulin injection	0–12	8.37 ± 1.59	11.84 ± 0.50	3.47 (3.20, 3.74)	<0.001

and video facilitating the learning and understanding of the presented materials. There are many explanations for the effectiveness of the DVD in enhancing patient knowledge. First, the DVD content contained relevant knowledge which was needed by diabetes patients. Second, the media was created in Jawi, the spoken language of Muslims in the study area. These characteristics made it easy for Muslims to understand. Third, the educational DVD attracted patient interest by using color pictures, audio, and video. Higher levels of diabetes knowledge have been reported to be related to better glycemic control [25]. Beyond knowledge improvement, multimedia was also helpful in improving self-care behaviors [26, 27]. The increased awareness on diabetes of the patients may lead to lifestyle modification and, consequently, improved glycemic control.

Cardiovascular disease (CVD) is a leading cause of death in patients with diabetes. Although diabetes itself is a risk factor of CVD complications, its co-pathologies (e.g., hypertension and dyslipidemia) also increase the risk [6, 8]. The American Diabetes Association recommends health professionals to advise lifestyle changes to diabetic patients with blood pressure >120/80 mmHg [8]. In this study, blood pressure of the patients declined from 131/78 mmHg at baseline to 127/78 mmHg at 6 months after educational DVD and pharmacist intervention ($P = 0.004$ for SBP). Although the difference in DBP was not significant ($P = 0.063$), these values both at baseline and at the end of the study met the treatment goal. On lipid profile, a study by Phumipamorn et al. found that LDL-C reduction in Muslim diabetics who received a diabetic pamphlet and one-on-one education with the pharmacist was greater than those in a control group (−15.0 vs. +9.1, $P = 0.002$) [28]. Conversely, Muslim patients in the current study had an increased level of LDL-C after DVD and pharmacist education. This could be explained by the fact that the focus of the DVD content was not predominantly on self-care behaviors of patients with dyslipidemia but on diabetes. As a result, the patients may be less concerned with lipid control than glucose control. Further study should develop more intensive education on the importance of lipid management such as dietary control, physical activity, and weight control if overweight [8].

It has been proven that low levels of HDL-C, below 40 mg/dL, increase the risk of cardiovascular morbidity and mortality [29]. Several studies investigated the impact of strategies on HDL-C improvement such as pharmacist or video education [18, 26, 28]. Unfortunately, these interventions did not result in an increase in HDL-C levels. It is possible that intervention should be provided over a longer period or be more intensive. Evidence suggests that lifestyle changes such as exercise and weight control raise HDL-C levels [29, 30].

Potential barriers to appropriate insulin use were insufficient knowledge among patients, their negative perceptions of treatment, and their low level of confidence in their ability to use injection [11, 31]. To achieve the effectiveness of treatment, identification and resolution of barriers are important for health providers. In this study, DVD multimedia primarily successfully educated the patients on the knowledge about diabetes and management. Furthermore, the pharmacist assisted the patients to overcome the obstacles by giving advice for those who needed help and re-educated them on how to correctly use insulin injection. Demonstrations of using insulin by patients and supportive feedback from the pharmacist may improve patients' confidence when taking the drug. At baseline, 14.7 % of Muslim patients reported that they were afraid to use insulin; nevertheless, at the end of the study, only 4.7 % had that negative perception (data not shown in the results). Positive attitudes among those with DVD and pharmacist intervention may lead to increased levels of medication adherence. It has been shown that patients having more diabetes knowledge or greater self-confidence are more likely to comply with the treatment [25, 31, 32]. Medication adherence predicts glycemic control [33]. Additionally, DVD multimedia reduced the burden of pharmacists in educating patients. It has been reported that excess workload of health providers reduced the quality of patient care [34].

To our knowledge, this is the first study to use DVD multimedia as an education resource for diabetes patients who are unable to communicate with their health professionals because of the language barrier. The current study has some limitations. First, the DVD education was developed for only diabetic Muslims who used the Jawi language and were treated with insulin therapy. This may limit the generalizability of the findings. However, this study provided a strategy for patient intervention that was associated with a positive impact on clinical outcomes of patients with chronic diseases. Second, this research was conducted in one study site and this may restrict the representation of, and generalization to, other hospitals. Third, we invited all patients with diabetes and treated with insulin to participate in the study using convenience sampling. Hence, our sample may or may not represent the population. Fourth, there was no control group in this study because of the limited number of eligible patients in the study site. Moreover, the benefits of the intervention were foreseeable when compared to the usual pharmacy care at the study site where patient exposure to pharmacy education was very limited. Therefore, a randomized controlled trial was not employed as the study design. However, evidence of this effectiveness warrants further evaluation by randomized controlled studies. Fifth, this study was a pre-post study rather than an experimental study. Accordingly, the observed effects of the intervention may be confounded by many factors such as pre-test effects and experimental reactants. Future studies should include a comparable control group in the experimental study design. Sixth, the adherence measurement was focused on only insulin. However, adherence to other antidiabetic and non-antidiabetic medications and other aspects of self-care is also necessary and should be evaluated in further research. Finally, the present study had a follow-up of 6 months; therefore, the effect of the intervention reported here reflects only short-term impact. Additional research should evaluate the impact of this strategy in a longer period such as 12 months.

Conclusion

Language-appropriate DVD and pharmacist education resulted in significant improvement in clinical outcomes, particularly glycemic control, medication adherence, knowledge about diabetes, and techniques in injecting insulin among Muslim patients. The appropriate DVD multimedia could augment pharmacist intervention to enhance favorable outcomes among Muslim diabetics. The multimedia should be integrated into diabetes care especially for Muslim patients.

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Contribution of authors Woranuch Saengcharoen (PhD): concepts, study design, literature search, data analysis, and manuscript preparation. Rita Musleemanukul (MPharm): data acquisition and data analysis. Sanguan Lerkiatbundit (PhD): statistical analysis, manuscript editing, and manuscript review

Compliance with ethical standards The research protocol was approved by the Research Ethics Committee, Faculty of Pharmaceutical Sciences, Prince of Songkla University (PSU, 598/174) and Thai Clinical Trials Registry Committee (TCTR20140812001). Informed consent was obtained from all individual participants included in the study.

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.

Conflict of interest Miss Rita Musleemanukul is a pharmacist at the study site. However, the other authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Evaluation of foot care and self-efficacy in patients with diabetes in Turkey: an interventional study

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Abstract Ulceration of the feet, which can result in loss of limbs and even death, is one of the major health problems for people with diabetes mellitus. The aim of this study was to evaluate the impact of foot care education on patient awareness of the importance of foot care, their foot care-related behavior and sense of self efficacy in being able to take care of their own feet in Turkey. The study was a randomized controlled study. Ninety patients with diabetes mellitus were followed. Cases were stratified by the presence and absence of education on foot care. Foot care education relevant to the needs of the study group was developed on the basis of Bandura's social learning theory. The diabetic foot care self efficacy scale (DFCSES), the foot self-care behavior scale (FSCBS), and the diabetic foot knowledge subscale (DFKS) were used to evaluate, at 3-month intervals, the knowledge patients had about foot care before and after receiving the education. The scores for DFCSES, FSCBS, and DFKS of the experimental group increased during follow-up in the study group receiving foot care education while the scores of the cases in control group did not change. Education is a major tool for improvement in awareness of foot care in cases with diabetes mellitus. Self-efficacy levels of individuals regarding foot care should be evaluated, and accordingly, individual strategies should be developed to provide efficient foot care.

Keywords Diabetic foot · Education · Nursing practical · Self-efficacy

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Introduction

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Ongoing patient self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications [1]. The International Diabetes Federation (IDF) estimates that there were 381.8 million people with diabetes in 2013 [2]. According to the results of the Turkish Diabetes Epidemiology (TURDEP-II) study, the incidence of diabetes in adults in Turkey affects 13.7 % of the adult population and is continually rising. Commensurate with this increase, micro- and macrovascular complications associated with diabetes are also growing and are becoming a burden on the country's economy [3].

One of the major health problems associated with diabetes mellitus is foot ulceration. It is estimated to affect 15 to 25 % of people with diabetes at some time in their lives [4]. Foot ulcers lead to physical disability and loss of quality of life. Because of its high morbidity and mortality, diabetic foot is a worldwide economic burden [5]. Diabetes-related foot problems increase rates of admission to acute and community health services [6, 7]. Forty to 70 % of lower extremity amputations are attributed to diabetes. While there are no data in Turkey directly linking diabetes with the foot, it is estimated that at least half a million diabetics have diabetes-related foot ulcers [8].

In 1989, the European Declaration of St. Vincent aimed to reduce amputations caused by diabetes mellitus by 50 % [9]. International guidelines have stressed the importance of reducing the incidence of foot ulceration. In addition to metabolic control and screening for this problem, education to encourage foot self-examination and improve foot care knowledge was recommended [1, 10]. Thus, the best and

cheapest treatment is prevention. Regular monitoring and preventive behavior, achieved through the training of diabetics, is crucial [11].

Patient education is an important element of diabetes care, with demonstrated benefits for knowledge, skills, and self-care behaviors [12]. Foot self-care has a significant impact on prevention of foot complications in diabetes [4]. By enhancing their awareness and knowledge, educating patients with diabetes about foot self-care prevents ulcer-related complications [4, 13]. However, people with diabetes often do not practice the kind of foot care required to maintain healthy feet. Patients' sense of self-efficacy predicts behavior in many areas of health [14]. Therefore, when foot self-care education is introduced, the knowledge, self-efficacy, and behavior of diabetic patients with respect to foot self-care improve and the incidence of foot ulceration and lower extremity amputation declines [5, 13–15].

Self-efficacy is a component of Bandura's social cognitive theory, which is a social learning theory. Bandura's social cognitive theory advocates the use of demonstration in diabetic foot care instruction. Demonstrating foot care can increase self-efficacy in foot care behaviors by providing both an active mastery and vicarious experience. According to Bandura (1989), people learn through observation due to the effects of imitation [16, 17]. The modeling effect, which includes the acquisition of novel responses, can be applied to the learning of foot care behaviors when nurses show foot care and patients return with a foot care demonstration. Furthermore, verbal persuasion by healthcare professionals can also influence foot care behaviors [18].

Previous studies have demonstrated that training patients with diabetes can enhance foot care practices. Studies found that while patients had received instruction in foot care, they did not apply what they had learned. The social cognitive theory has been useful in explaining this lack of practice [19]. Hurley evaluated self-efficacy in patients with diabetes and emphasized the importance of self-efficacy in foot care practices [20].

Most studies in Turkey on diabetic foot care have been done to determine general status. Research shows that diabetics have enormous problems with their feet and that the reason for this is inadequate foot care. It has been suggested that foot care education programs for these patients would be beneficial [21–23]. However, there have been no studies of planned education programs designed to meet the foot care needs of diabetic patients in Turkey. In addition, studies have been void of valid scales for assessing foot care and behaviors.

The aim of this study was to evaluate the impact of educational intervention in diabetic patients by comparing studies done in Turkey and in other countries. The intervention included activities emphasizing self-efficacy, which entailed having patients practice foot self-care strategies [16]. We expected improved foot care behavior and, consequently, a decrease in foot complications.

Material and methods

Study design

The current study is a randomized controlled intervention study. The study was carried out in the Diabetes Department of Cerrahpasa Medical Faculty, Istanbul University in Turkey.

Subjects

The study comprised individuals who had received a diagnosis of diabetes at least 1 year prior to the study, were 40 years or older, and voluntarily agreed to participate in the study. Individuals with severe retinopathy, hearing loss, or psychiatric diagnoses were excluded from the study.

We used power analysis techniques in calculating the sample size. The study population included a total of 90 individuals, 45 experimental and 45 control subjects (α 95 %, power 80 %). Simple randomization method was used to form the experimental and control groups. A list of the names of the 90 subjects was drawn up. Then, subjects with odd numbers on the list were put into the experimental group while those with even numbers were put into the control group.

The chi-square test was used to test differences in categorical parameters between the two groups; no significant difference was found ($p > .05$). Thus, it was proven that individuals selected for the experimental and control groups were split homogeneously in terms of individual characteristics before the intervention (0 month) (Table 1).

Practices

Diabetic foot care self-efficacy scale (DFCSES) for sense of self-efficacy, Foot self-care behavior scale (FSCBS) for foot care behavior, and Diabetic foot knowledge subscale (DFKS) for foot care knowledge were used for the all subjects enrolled in the study [18, 24, 25].

Practices for the experimental group After the initial evaluation, foot care education was provided by researcher to each patient in the experimental group. An educational booklet designed to raise the self-efficacy of patients regarding foot care was prepared by the researcher and given to the patients. Education was provided on a one-to-one basis, with each education session taking approximately 30–45 min. Education was performed by using mixed learning methods consisting of lecture, question-answer, demonstration, and practice.

Education Booklet included information on: (i) the healthy foot, (ii) diabetic foot complications, (iii) how diabetes affects

Table 1 Baseline characteristics of participants after randomization ($N = 90$)

Variables	Experimental group ($n = 45$)		Control group ($n = 45$)		χ-square	p value
	n	Percentage	n	Percentage		
Gender						
Female	21	(46.7)	31	(68.9)	$\chi = 4.55$	$p = .05$
Male	24	(53.3)	14	(31.1)		
Marital status						
Married	37	82.2	34	75.6	$\chi = 0.60$	$p = .43$
Single	8	17.8	11	24.4		
Education level						
Literacy	2	4.4	7	8.9	$\chi = 4.09$	$p = .25$
Primary school	24	53.3	17	37.8		
Secondary school	14	31.1	15	33.3		
High school/univers.	5	11.1	6	13.3		
Diabetes type						
Type 1	6	13.3	5	11.1	$\chi = 0.10$	$p = .74$
Type 2	39	86.7	40	88.9		
Treatment type						
Diet	1	2.2	2	4.4	$\chi = 1.09$	$p = .77$
Insulin	8	17.8	11	24.4		
Oral hypoglycemic	11	24.4	9	20.0		
Insulin, oral medications	25	55.6	23	51.1		
Compliance to diabetes						
Good	22	48.9	24	53.3	$\chi = 0.93$	$p = .62$
Fair	16	35.6	17	37.8		
Poor	7	15.6	4	8.9		
A1C ≥7.0 (%)	34	75.6	30	66.7	$\chi = 0.865$	$p = .486$
BMI >24.9 (kg/m^2)	40	88.9	40	88.9	$\chi = 0.000$	$p = 1.000$
	Experimental group		Control group		p value	
	n	$X \pm$ SD	n	$X \pm$ SD		
Age	45	60.2 ± 9.9	45	61.0 ± 9.6	.683	
Diabetes duration (years)	45	13.3 ± 10.0	45	13.0 ± 8.1	.884	

your feet, (iv) frequently occurring foot problems, (v) surveillance of early foot problems, (vi) how to check your feet and problems to look for, (vii) nail and skin care, (viii) how to choose a shoe and footwear, (ix) preventing foot injuries, and (x) regular check-ups.

The educational program included scales.

Practices for the control group Education and follow-ups of the control group continued in the outpatient environment. The researcher did not attempt to intervene in the control group. Both the control and the experimental group were given appointments for the first, third, and sixth months. Measurements were taken at these appointments only for the control group. Neither the educational program nor the educational booklet was given. Standard care of the control group was provided by nurses. Standard care included routine laboratory follow-ups.

Data collection

Data collection tools prepared by the researcher were applied to all patients enrolled in the study. The "Diabetic Foot Evaluation Form," which contains assessments of dermatologic, vascular, neurologic, and musculoskeletal systems of the lower extremities, was filled out for each participant (http://www.tdhd.org/dhd_kitap/12blm.pdf, pg138-139) [26, 27]. Based on the findings of physical examination, risk assessment was done by using the "Best Practice Guideline Shaping the Future of Nursing; Reducing Foot Complications for People with Diabetes" (Appendix C–D) [28].

The DFCSES instrument (9 items) was developed by Quarles. The self-efficacy items are addressed using an interval scale ranging from 0 to 10, with 0 indicating "feeling not capable" and 10 being "feeling the most capable" (Appendix A) [18]. The Turkish version of the tool was found to have a high level ($\alpha = .86$) of internal consistency [29].

The Foot Self Care Observation Guide (16 items), which developed by Borges, was adapted by the researcher to create the Turkish-version Foot Self-Care Behavior Scale (FSCBS;15 items). Upon the advice of experts, the questions pertaining to the selection of socks were merged as "13. *Socks are clean, cotton and soft.*" [25]. Patients were asked to choose the most suitable response ["never," "rarely," "sometimes," "often," and "always"] to each question (Appendix B). The Cronbach's alpha internal consistency of the scale was .83 [30].

Foot self-care knowledge was measured using a foot self-care subscale (DFKQ; 5 items) from the DKQ-24, which was developed by Garcia et al. [24]. Potential response choices for the DFKQ were (1)"Yes," (2) "No," (3) "I don't know." Items were scored as correct or incorrect, and the correct items were summed to attain a total score (Appendix E). The five-item foot self-care subscale had a Cronbach's alpha of .58.

The required permission was obtained from the authors of the three scales to use them in the research. All of the scales were translated into Turkish and adapted to Turkish society by use of a pilot study conducted by the researcher [29, 30]. In the pilot study, the scales were translated into Turkish (the scale was translated into Turkish using the translation back-translation technique by two independent specialists, and then, the Turkish version of the scale created through common decision of both specialists was translated back into English by another specialist). The equivalence between the original and the back-translated versions of the scale was reviewed and some minor corrections were made, and the content validity index scores were calculated at appropriate values, which indicated satisfactory agreement among the experts (four academician nurses, three diabetologists).

The post-randomization data collection instruments were obtained by using face-to-face interview in the experimental and control groups. A total of four visits, including before the intervention, and at the first, third, and sixth months of the study, were planned for both groups. At each visit, data collection forms were filled out, foot assessments were made by the researcher, metabolic parameters were recorded and ankle-brachial indexes were obtained with vascular hand Doppler USG. After the pre-test evaluations, booklets containing the demonstration method and foot care education were given to the experimental group. Appointments for the first, third, and sixth months were given to both groups after the first interview. Patients' foot care behaviors, self-efficacies, and foot care practices were assessed again at these appointments. At this evaluation appointment, patients' foot care behaviors, self-efficacies, and metabolic control parameters, together with foot care practices, were assessed.

Statistical analysis

Descriptive statistics and chi-square were used to assess the demographic and disease-related characteristics of participants. Student's *t* test was used to compare the experimental and control groups in terms of mean age and duration of diabetes. Total scores for each DFCSES, FSCBS, and DFKQ measure were obtained. Repeated measure analysis was used to compare these scores at the initial, first, third, and sixth months.

Ethical issues

Istanbul University Cerrahpasa Medical Faculty ethics committee approved the study protocol (Voucher no: 21355 22.07.2008), and all participants read and signed an informed consent form. No patient was forced or obliged to participate in this study.

Results

Patients with diabetes participating in our study had many nail and skin problems, and few of them wore special diabetic shoes (6.7 % in the experimental group and 2.2 % in the control group). Fifty percent of the cases in both groups were at high risk for diabetic foot (Table 2).

The results of analyses to determine time-based foot care self-efficacy, foot care behaviors and foot care knowledge, and their averages in the control and experimental groups of the individuals with diabetes are presented as tables and graphs (Table 3, Figs. 1, 2, and 3).

In the experimental group, the pre-intervention foot care self-efficacy rose from 56.96 to 75.20 % by the end of the sixth month. In contrast, it did not change after the initial intervention at any of the follow-ups (Table 3, Fig. 1). The difference in the time-dependent changes in DFCSES value

Table 2 The result of loss of sensation, ankle-brachial index (ABI), deformity, footwear, and diabetic foot risk assessment in each group

	Experimental group		Control group	
	n	Percentage	*n*	Percentage
Neuropathy testing (Semmes-Weinstein 5.07 monofilament)				
Presence loss of sensation	26	57.8	22	48.9
ABI evaluated				
Normal range	34	75.6	34	75.6
Foot deformity	16	35.6	14	31.1
Footwear				
Standard shoes	42	93.3	44	97.8
Diabetic shoes	3	6.7	1	2.2
Diabetic foot risk assessment				
Lower-risk foot	23	51.1	20	44.4
Higher-risk foot	22	48.9	25	55.6

Table 3 The results of the RM_ANOVA for foot care self-efficacy, behavior, and knowledge

	Groups	(T0) Before initiative	T1 (First month)	T2 (Third month)	T3 (Sixth month)	F(df, n)	p value
Foot care self-efficacy	Experimental	56.96 ± 18.04	74.38 ± 13.24	75.62 ± 11.43	75.20 ± 12.10	$F(3, 264) = 55.53$	$p < .0001$
	Control	63.13 ± 14.87	63.93 ± 14.66	62.96 ± 15.12	63.18 ± 15.26		
Foot care behavior	Experimental	49.02 ± 10.25	60.84 ± 7.99	62.09 ± 7.38	62.07 ± 7.76	$F(3, 264) = 106.55$	$p < .0001$
	Control	54.31 ± 10.21	54.31 ± 10.11	54.31 ± 10.43	54.27 ± 10.62		
Foot knowledge	Experimental	3.44 ± 1.20	4.73 ± 0.69	4.93 ± 0.25	4.93 ± 0.25	$F(3, 264) = 32.63$	$p < .0001$
	Control	3.60 ± 1.18	3.64 ± 1.19	3.78 ± 1.20	3.82 ± 1.23		

for the experimental group was significant while it was not in the control group [$F(3, 264) = 55.53$, $p = .0001$]. At the end of the sixth month, the average value of DFCSES for the experimental group increased 32.02 % while the average change in the control group went up by only 0.07 % (Table 3, Fig. 1).

The initial score of "Foot Self-Care Behavior Scale" (FSCBS) in the experimental group was 49.02 ± 10.25, and increased until the third month while it remained stable at the sixth month. The pre-intervention FSCBS score of the control group was 54.31 ± 10.21 and remained similar at all follow-ups (Table 3, Fig. 2). The experimental group's time-dependent change in the value of FSCBS was significant, but it was not for the control group [$F(3, 264) = 106.55$, $p = .0001$]. The average FSCBS change between initiative and last tests in the experimental group was +26.6 % while the average change in the control group was −0.07 %.

The pre-intervention DFKS score of the experimental group increased until the third month and remain similar at the sixth month. On the other hand, no significant change was detected in the control group [$F(3, 264) = 32.63$, $p = .0001$] (Table 3, Fig. 3). The average DFKS change between initiative and last tests in the experimental group was +32.22 % while the average change in the control group was +5.75 %.

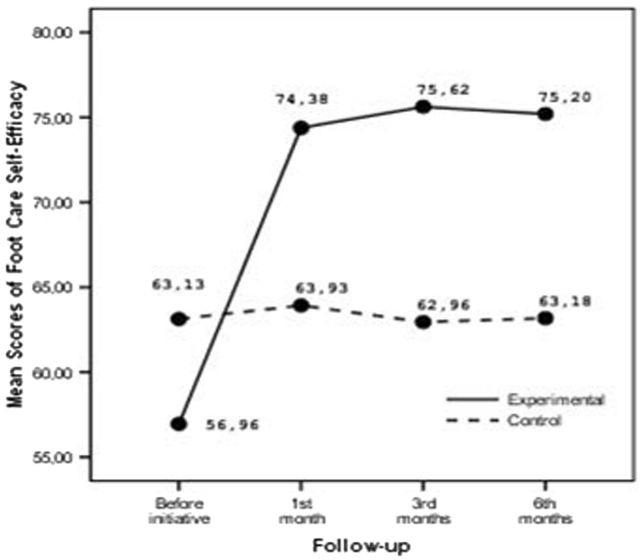

Fig. 1 The results of follow-up for foot care self-efficacy in each group

Discussion

Self-efficacy is the individual's belief that he is able to successfully fulfill a desired behavior. The stronger this belief, the more effort the individual makes to achieve the goal [31]. Individuals having high self-efficacy were observed to be more successful in fulfilling the desired behavior [32]. In order to instill positive health behaviors in patients, improvement of self-efficacy in the individuals is recommended. However, improvement or development of self-efficacy does not occur quickly [33]. In the current study, the foot care self-efficacy of the individuals with diabetes after diabetic foot care education was higher than those of the individuals not receiving the education.

In Kartal's study, where the effectiveness of education upon the management of diabetes was evaluated, the self-efficacy of the patients who received education was higher than those of the control group [34]. In a 3-month monitoring study done on patients with type-2 diabetes by Gleeson-Kreig (2006), the average scores of the experimental group increased while no increase was seen in the control group [33]. Foot care knowledge,

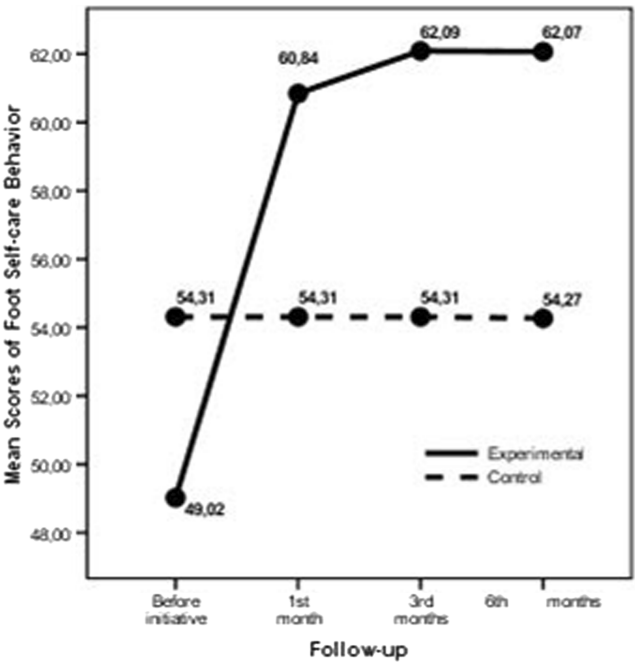

Fig. 2 The results of follow-up for foot self-care behavior in each group

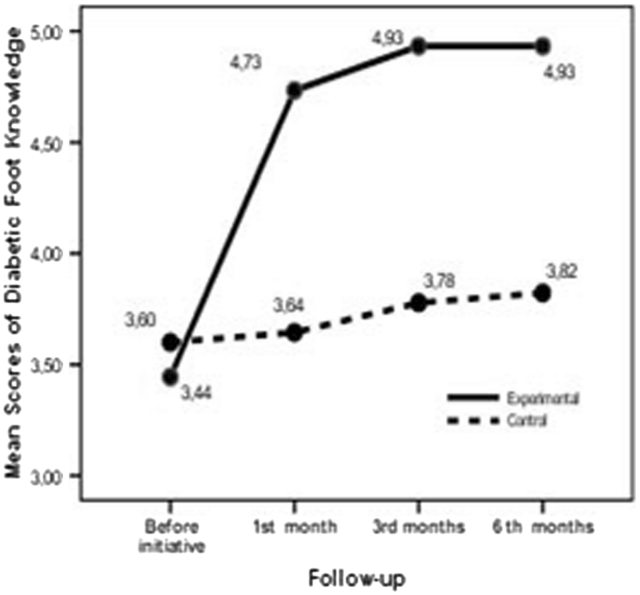

Fig. 3 The results of follow-up for diabetic foot knowledge in each group

self-efficacy, and foot care behaviors of both of the groups were assessed before the education, and the assessments were conducted again at the sixth and 12th weeks after education in Corbett's study [35]. As a result of the study, a significant increase in the score was obtained in foot care knowledge, self-efficacy, and applications in the experimental group while no significant change was seen in the control group.

Due to the fact that special treatment options specific to diabetic foot wounds are limited, foot care education and prevention in particular are of the utmost importance [36]. Education and regular checkups in the patients with diabetes lead to improvement in patient self-care and glycemic control, and the resultant sense of well-being encouraged patients' adaptation to the community [18, 21, 37, 38].

Although foot care education is generally given within general diabetes education, previous studies have shown that many patients with diabetes do not take care of their feet, so their foot problems continue [18]. Valk et al. (2002) reported in their study that patient education increased information related to diabetic foot and attitudes toward feet protection of the patients with high risk and thus decreased the frequencies of foot ulcers and amputation [39]. Previous studies have also shown that educational programs affect foot self-examination behavior positively [40].

In line with the literature, the present study found that a steady increment in the average scores of FSCBS of the experimental group, over time, led to patients provided with education thinking they could improve their foot care behavior.

Better foot care knowledge increases foot care practices [38]. In the study by Kruger and Guthrie, the foot knowledge and practices scores of the group receiving education increased after 6 months [41]. Dorresteijn found that by providing diabetic foot care education, foot care knowledge and self-care behavior developed in a short term [5]. In a study done by Plummer and Albert (1995) to improve foot care knowledge and practice in diabetics, persons receiving routine diabetic care instruction did not sufficiently learn about foot care and were unsuccessful in putting it into practice [42]. In our study, foot care practices increased in the experimental group receiving education as a result of follow-ups. The control group was monitored routinely, and no difference in the patients' knowledge and practices was observed during these follow-ups. As in the literature, in the present study, planned education program and foot care knowledge scores increased in the experimental group.

Meta-analyses of the outcome of diabetes education demonstrate that it is difficult to change behavior through education and that the continuity of such education is crucial. Assessments performed show that there may be regress in the behaviors achieved through education after the sixth month. In addition, it has been reported that it is necessary to periodically repeat education and to do so using additional, creative ideas. In our study, the greatest change in behavior in diabetics occurred in the first and third months, with very little change observed in the sixth month. The results of our study support those found in the literature [12, 43–46].

When the average DFCSES, FSCBS, and DFKQ scores are assessed according to the classification of the groups according to diabetic foot risk, only the patients in the experimental group at high risk for diabetic foot had meaningfully high average DFCSES scores. It has been reported in the literature that life-threatening situations had an impact on patients' perception of severity and resulted in the individual engaging in preventive health behavior [34]. This situation explains the elevation in self-efficacy scores in high-risk patients.

International foot care guidelines [47] state that education has a crucial role to play in preventing foot problems in diabetic patients, who are at great risk for such problems. Therefore, we believe that foot care education would function as a primary means of prevention if, at the very least, a patient receives instruction shortly after being diagnosed with diabetes and then again at their annual foot screening examinations.

It was observed in our study that positive foot care habits were developed in patients in the experimental group through foot care education and examination. During the 6-month follow-up, there were no new problems associated with diabetic foot.

Limitations of the research

Among the limitations of the research are small sampling size and short observation period (6 months). In addition, one-on-one training is effective but time consuming, thus making it difficult to conduct daily in crowded clinics. To overcome this drawback, the effectiveness of foot care self-efficacy perceptions could be evaluated by conducting training on larger groups.

Conclusion

Although there is no direct evidence that the incidence of ulcers and amputations decreases only through education, without any additional preventive measures, foot care behaviors are important in the prevention of diabetic foot. Nurses should provide health education to improve health-related habits and behaviors of individuals. All of the education should aim to increase self-efficacy levels and be continuous so as to translate knowledge into behavior. Individuals' self-efficacy levels should be evaluated at each visit, and appropriate individual strategies facilitating learning should be developed to ensure compliance with foot care and to increase education attainment.

Future research should evaluate a large sample of patients with diabetes and long-term evaluation of the foot self-care educational intervention effects over a 1-year period.

Relevance to clinical practice Nurses should be actively involved in foot care programs in persons with diabetes. These programs should be adjusted to prevent or decrease diabetic foot ulcers in high-risk patients. This information should be used in clinical practice when designing education for patients with diabetes.

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Compliance with ethical standards Istanbul University Cerrahpasa Medical Faculty ethics committee approved the study protocol (Voucher no: 21355 22.07.2008), and all participants read and signed an informed consent form. No patient was forced or obliged to participate in this study.

Appendix A Diabetic Foot Care Self Efficacy Scale (DFCSES)

Instructions: Below is a list of situations related to how you feel or behave concerning foot care. Mark the scale that follows to indicate how capable you feel you are regarding the specified situtations. A score of "O" means "I do not feel capable at all," while a score of "10" means "I feel most capable."

1. How capable do you feel in managing your foot are?

   0 1 2 3 4 5 6 7 8 9 10

2. How capable do you feel in your ability to check your feet for redness or sores ?
   0 1 2 3 4 5 6 7 8 9 10
3. How capable do you feel that you could find a reddened area on your foot if one developed?

   0 1 2 3 4 5 6 7 8 9 10

4. How capable do you feel in knowing what to do should you find a reddened area or sore on your foot/toe?
   0 1 2 3 4 5 6 7 8 9 10

5. How capable do you feel about selecting properly fitting shoes?

   0 1 2 3 4 5 6 7 8 9 10

6. How capable do you feel about wearing socks correctly?
   0 1 2 3 4 5 6 7 8 9 10

7. How capable do you feel about checking the inside of your shoes for foreign objects before putting on your shoes?

   0 1 2 3 4 5 6 7 8 9 10

8. How capable do you feel about having the proper temperature for bath water?

   0 1 2 3 4 5 6 7 8 9 10

9. How capable do you feel about requesting that your doctor check your feet at every visit?

   0 1 2 3 4 5 6 7 8 9 10

Appendix B

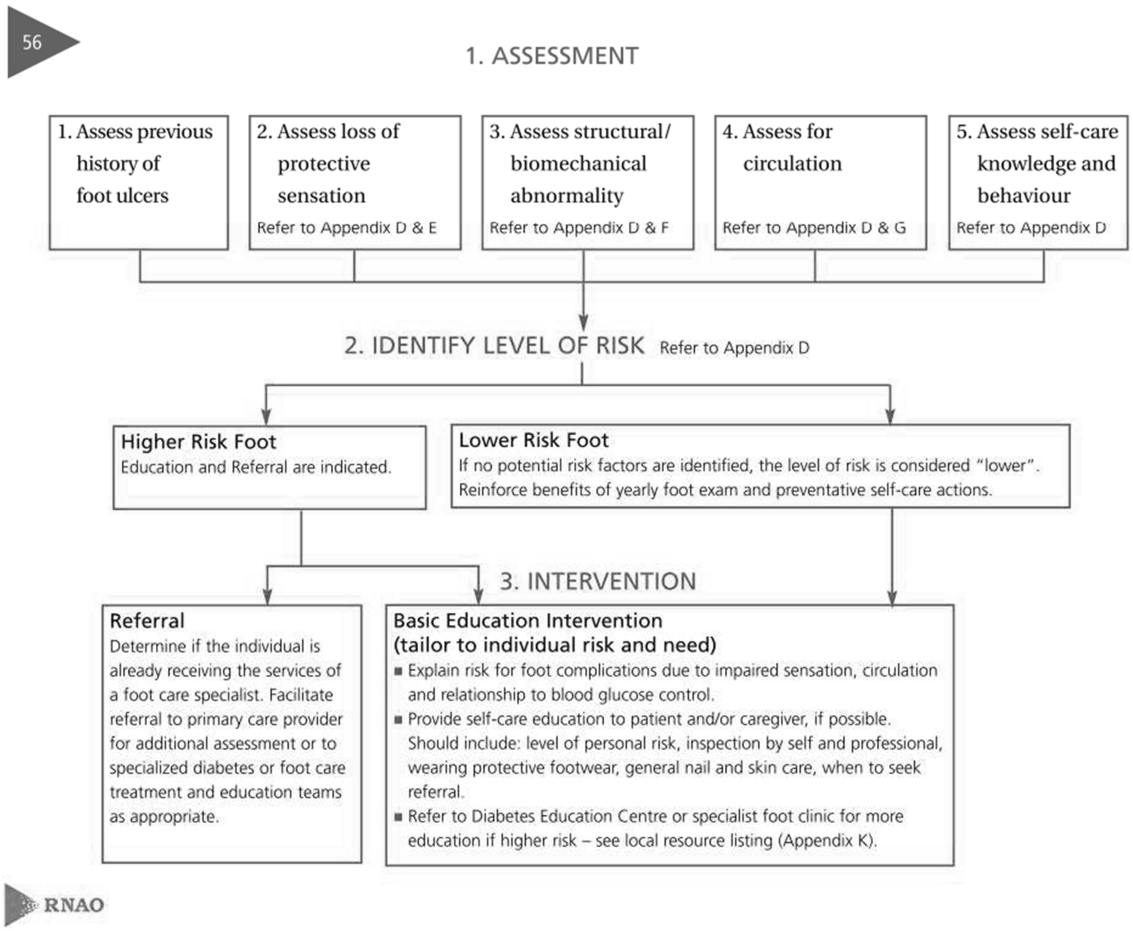
Table 4 Foot Self-Care Behavior Scale(FSCBS)

	always (5)	often (4)	sometimes (3)	rarely (2)	never (1)
Foot care items					
1. Checks temperature of water					
2. Dries between toes after washing					
3. Use moisturizing lotion for my feet					
4. Does not apply lotion between toes					
5. Cuts toenails "straight"					
6. Checks toenails in terms of thickening, ingrowth and length					
7. Checks between toes for denudation, fungus and rash due to humidity					
8. Checks feet sole for callus, rash, blister and wound					
9. Checks inside the shoes for foreign matters like nail, dust or stone.					
10. Does not walk barefoot. (e.g.,: at home, outdoor or on the beach)					
11. Wears shoes whose width, length and heels are appropriate and that grasp the foot as a whole.					
12. Wears shoes with soft leather and smooth internal surface.					
13. Socks are clean, cotton and soft					
14. Socks fit well—not tight or loose					
15. Does not use sharp instruments on feet (i.e., razor, scissors, etc.)					

Appendix C: Risk Assessment Algorithm Foot Care Risk Reduction Guideline

For all persons with diabetes over age 15 years (excluding women with gestational diabetes). Consider when best initiated for the individual, given priority within current issues and appropriateness of education on this issue at this time.

Assessment of the five factors strongly correlated with risk of the foot ulcer/amputation should be performed at least annually.



Appendix D: Diabetes Foot Assessment/Risk Screening Guide

Use this guide to assess presence of potentials risk factors for future foot ulceration and amputation. Examine both feet and inquire about client self-care practices.

Risk Factors	Yes	No
1. Foot ulcer (a wound that took > 2 weeks to heal) now or in the past.		
2. Loss of sensation at any one site (determined after testing the 4 sites: great toe, first, third, and fifth metatarsal heads using the 10 gram/5.07 monofilament).		
3. Callus present on soles of feet or toes or abnormal foot shape (e.g., claw or hammer toes, bunion, obvious bony prominence, Charcot's foot or joint).		
4. Pedal pulses (dorsalis pedis or posterior tibial) not palpable by nurse and positive history of lower limb pain on exertion that is relieved with rest.		
5. Client unable to see the bottom of feet and/or unable to reach the bottom of feet and does not have someone who has been taught to perform appropriate foot care/inspection.		
6. Poor fitting footwear (shoes too narrow or short, no toe protection, rough or worn interior, uneven wear on sole or heel).		
7. Client **has not** received foot care education before.		
8. Client **does not** check condition of feet most days, e.g., ask "How do you know if you have a reddened area or other problem with your feet?" or "How often do you check your feet?".		
9. Client **does not** report foot problems to health care provider, e.g., ask, "What would you do if you found a blister on your foot?".		
10. Client **does not** take steps to reduce risk of injury, e.g., ask if client walks bare foot in/outdoors, checks for foreign objects in shoes before wearing them, checks water temperature before entering a bath, etc.		

"Lower Risk"	"Higher Risk"
If client answers NO to any items 1-4, they are at "lower risk".	If the client answers YES to any items 1-4, they are at "higher risk".

If the client answers YES to any items 5-10, this indicates a self-care knowledge deficit and opportunity to enhance self-care knowledge and behaviour.

Adapted with permission of: Sharon Brez, RN, BScN, MA(Ed), CDE, Advanced Practice Nurse Endocrinology and Metabolism, The Ottawa Hospital, Ottawa, Ontario.

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Appendix E

Table 5 Diabetes Knowledge Questionnaire-24 (DKQ-24)-Diabetes Foot Knowledge Questionnaire

	Yes	No	I don't know
1. Diabetes often cause poor circulation.	√		
2. Cuts and abrasions on diabetes heal more slowly	√		
3. Diabetics should take extra care when cutting their toenails	√		
4. A person with diabetes should cleanse a cut with iodine and alcohol		√	
5. Diabetes can cause loss of feeling in my hands, finger and feet	√		
Total score	**0–5**		

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ORIGINAL ARTICLE

Association of age at menarche with metabolic syndrome and components of metabolic syndrome in premenopausal women, Korea National Health and nutrition examination survey VI

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Abstract A combination of genetic and environmental factors determines age of menarche. In Korea, there has been a trend for a younger age of menarche as the country has undergone industrialization and adopted a westernized diet. Previous studies have indicated that the incidence of obesity and metabolic syndrome, as well as cardiovascular mortality, is higher in women who undergo menarche at a younger age. This study was conducted to examine the relationship between age of menarche and metabolic syndrome in premenopausal women in Korea. Data for 1464 women were collected from the Sixth Korea National Health and Nutrition Examination Survey (KNHANES VI). The modified NCEP-ATP III criteria were used to define metabolic syndrome. Considering the unit of data extraction (investigation district), stratification variables, and weighted value, a complex sample design extraction method was applied for statistical analysis. After dividing the subjects by age of menarche, the risk of metabolic syndrome was assessed using multiple logistic regression analysis adjusting for age, smoking, drinking, exercise, education level, household income, and marital status. When the subjects were grouped by age of menarche (<12, 12–13, 14–15, and >16 years), a statistically significant increase in the average age of the group was observed (23.8 ± 0.8, 29.6 ± 0.4, 35.8 ± 0.4, and 39.8 ± 0.7, respectively; $p < 0.001$). The adjusted odds ratio (95 % CI) for metabolic syndrome was 3.84 (1.52–9.70) in women who reached menarche at <12 years compared to those who reached menarche at >16 years. Age of menarche is associated with the risk of metabolic syndrome in premenopausal women in Korea.

Keywords Menarche · Metabolic syndrome · Obesity · Premenopausal women

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Introduction

Menarche is defined as the first menstrual period, reflecting the onset of puberty, and a major trait of secondary sexual characteristics in women. After menarche, women establish a regular menstrual cycle and have the capacity to reproduce.

Age of menarche is determined by interactions between various genetic and environmental factors. Menarche is associated with stimuli involved in the gonadotropin releasing hormone system of the hypothalamus and accumulation of body fat related to blood leptin [1]. Age of menarche can vary depending on race and ethnicity and can also be affected by nutritional state, physical activity level, and socioeconomic factors, such as residence, income, and education level. It has a particularly strong association with nutritional state, and although the exact nature of the association is unclear, age of menarche is associated with the accumulation of adipose tissue following a high-calorie diet. Hence, onset of puberty is slow in adolescents with nutritional deficiency, whereas the age of menarche decreases when nutritional intake is sufficient [2, 3]. As Korea has undergone industrialization, and sedentary lifestyles and westernized diets have been widely adopted, it has shown a trend for earlier menarche, as seen in western society [4, 5].

Both eastern and western cross-sectional studies have reported associations of an early age of menarche with body mass index (BMI), obesity, glucose intolerance, and type II diabetes in adults, and further studies have shown increases in

cardiovascular mortality and morbidity [6–12]. A study based on the Korea National Health and Nutrition Examination Survey (KNHANES) 2007–2009 reported that an early age of menarche is associated with the onset of type II diabetes in young and middle-aged women in Korea [13]. Metabolic syndrome, a risk factor for cardiovascular disease and type II diabetes, is a combination of metabolic abnormalities including abdominal obesity, insulin resistance, dyslipidemia, and hypertension. The prevalence of metabolic syndrome is increasing worldwide with obesity at the source, with consequential increases observed for chronic diseases associated with metabolic syndrome [14, 15]. The prevalence of metabolic syndrome and associated chronic diseases is also rising in Korea. The prevalence of metabolic syndrome in Korea, as announced by the Ministry of Health and Welfare based on data from KNHANES 2007–2010, was 28.8 % in adults aged >30 years, with a rate of 31.9 % in men and 25.6 % in women. According to a study by Lim et al. in 2011, which was based on KNHANES data from 1998, 2001, 2005, and 2007, the prevalence of metabolic syndrome was 22.2, 26.9, 27.8, and 31.5 % each year, respectively, showing an increasing trend [16]. Although the role of menarche in the incidence of metabolic syndrome is not yet clear, numerous cross-sectional studies and meta-analyses have indicated that an early age of menarche and the incidence of metabolic syndrome are associated. In response to the trend of a younger age of menarche in Korea, this study was conducted to examine its association with an increased risk of metabolic syndrome and its components in premenopausal women in Korea.

Materials and methods

Study subjects

This study was conducted using data from the first year of KNHANES VI, which is the most recent survey conducted over the course of 3 years between 2013 and 2015. The number of sample households in the first year (2013) was 3182, and the number of participants was 8018. Of these, a total of 1464 premenopausal women were selected for inclusion in this study, excluding those who did not provide information on their menopausal state or age of menarche. The details of this study and the KNHANES methodology have been approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention.

Anthropometric measurements and blood tests

Basic data were collected in KNHANES VI using a standardized questionnaire. Body weight (kg) and height (m) were measured while the subjects wore light clothes and no shoes, and BMI was calculated based on these results. Weight was determined to the nearest 0.1 kg on a medical balance (GL-6000-20, CAS, Seoul, Korea). Height was measured to the nearest 0.1 cm with a wall-mounted stadiometer (Seca 220, Seca, Hamburg, Germany). Blood pressure was calculated from an average of two systolic and diastolic pressures that were measured with the subject in a sitting position after a ≥10-min rest and with a 5-min interval between measurements. Blood samples were taken following a >8-h fast. Blood samples were centrifuged, refrigerated at the examination site, and transferred in ice boxes to a central laboratory in Seoul on the same day. Plasma glucose, total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were measured using an autoanalyzer (Hitachi Automatic Analyzer 7600, Tokyo, Japan).

Age of menarche

Age of menarche was defined as the age when the first menstrual cycle was experienced and was investigated using a self-administered structured questionnaire. The question was open-ended asking, "When did you start your first menstrual cycle?", and the answer was in the form of age in years. When subjects reported their age at menarche as, for example, 12.00 to 12.99 years, then age at menarche was designated as 12 years.

Definition of metabolic syndrome

The diagnostic standard for metabolic syndrome proposed by NCEP-ATP III (2006) was used as a basis, in conjunction with the modified standard of NCEP-ATP III for abdominal obesity recommended by the World Health Organization West Pacific Region. Metabolic syndrome was diagnosed when three or more of the following five criteria were met. i) Abdominal obesity: waist circumference ≥ 80 cm; ii) hypertension: ≥130/85 mmHg or hypertension medication; iii) hypertriglyceridemia: ≥150 mg/dL or medication; iv) hyperglycemia: fasting glucose ≥100 mg/dL or medication; and v) low HDL cholesterol: <50 mg/dL.

Covariates

Smoking history was classified as non-smoking (never smoked or smoked <100 cigarettes in entire life) and smoking (smoked >100 cigarettes). Alcohol drinking was classified as non-drinking (drinks less than once a month) and drinking (drinks more than once a month) based on drinking behavior in the past year. Exercise was divided into three groups: "more than four times a week," "one to three times a week," and "do not exercise at all," based on >10 min of moderate-level physical activity that makes one tired or short of breath per day. As a factor of socioeconomic status, household income was divided into four groups. Education level was divided into four

groups: "elementary school," "middle school," "high school, " and "college or above." Marital status was classified as married and not married.

Statistical analysis

Data were analyzed taking into account the unit of data extraction (investigation district), stratification variables, and the weighted value of the first year from KNHANES VI (2013), and a complex sample design extraction method was applied for statistical analysis. The chi-square test was used to analyze the smoking, drinking, and exercise status and the general characteristics (marital status, education level, household income) of the subjects. Variance analysis was performed using the general linear model of the complex sample design to analyze age, intake of dietary energy, and BMI. Age of menarche was divided into four groups, and multiple logistic regression analysis was used to evaluate the association with metabolic syndrome and its components. IBM SPSS version 19.0 (IBM Co., Armonk, NY, USA) was used for the analysis, and the significance level was defined as $p < 0.05$.

Results

General characteristics

The average age of the study subjects (mean ± standard error) when grouped by age of menarche (<12, 12–13, 14–15, and >16 years) was 23.8 ± 0.8, 29.6 ± 0.4, 35.8 ± 0.4, and 39.8 ± 0.7, respectively, showing a statistically significant increase in average age according to age of menarche ($p < 0.001$). A statistically significant association with age of menarche was also observed for education level and marital status ($p < 0.001$) However, BMI, daily energy intake, smoking, drinking, exercise, and household income were not associated with age of menarche (Table 1).

Association between age of menarche and the components of metabolic syndrome

When the association between age of menarche and the five components of metabolic syndrome was analyzed, hyperglycemia and hypertension were significantly associated with late age of menarche (both $p = 0.004$). Abdominal obesity, hypertriglyceridemia, and low HDL cholesterol were not significantly associated with age of menarche (Table 2).

Odds ratio of metabolic syndrome and its components according to age of menarche

The odds ratio (95 % CI) of developing metabolic syndrome after adjusting for covariates (age, smoking, drinking, exercise, education level, household income, marital status) was 3.84 (1.52–9.70) in women with an age of menarche <12 years compared to women with an age of menarche >16 years. When only adjusted for age, the risk of metabolic syndrome was 2.36 (1.08–5.13) in women with an age of menarche <12 years compared to those with an age of menarche >16 years. However, the crude odds ratio (95 % CI) for metabolic syndrome was 0.54 (0.30–0.97) for women with an age of menarche 12–13 years compared to those with an age of menarche >16 years.

For the components of metabolic syndrome, the adjusted odds ratios (95 % CI) for abdominal obesity and hypertension were 4.24 (2.28–7.88) and 2.52 (1.15–5.51), respectively, in women with an age of menarche <12 years compared to those with an age of menarche >16 years. However, no significant associations were observed with hyperglycemia, hypertriglyceridemia, and low HDL cholesterol (Table 3).

Discussion

This study in premenopausal women in Korea showed that, after adjusting for covariates, the risk of metabolic syndrome was higher in women whose age of menarche was <12 years compared to those whose age of menarche was >16 years. When only adjusted for age, the risk of metabolic syndrome was significantly higher in women whose age of menarche was <12 years compared to those whose age of menarche was >16 years. When the adjusted odds ratio for each component of metabolic syndrome was analyzed according to the age of menarche, abdominal obesity and hypertension were higher in the early menarche group. Our results show that the average age of the early menarche group was significantly younger than the other groups, reflecting the trend of a younger age of menarche in Korea. According to a study based on KNHANES, the age of menarche in adolescents is gradually decreasing in Korea; the average age of menarche was 16.90 ± 1.25 for women born between 1920 and 1925, whereas it was 13.79 ± 1.37 for women born between 1980 and 1985 [4]. In our study, the average age of women with an age of menarche <12 years was 23.8 ± 0.8 compared to 29.6 ± 0.4 in women with an age of menarche of 12–13 years. Because the average age was higher in the latter group, the percentage of married women was also significantly higher. Since the frequency of smoking and drinking is relatively low in women in Korea, a significant association with these factors was not observed. When adjusted for covariates, the risk of metabolic syndrome was different according to age of menarche. However, the risks associated with the individual components of metabolic syndrome were not significant. Since the early menarche group mainly consisted of young subjects, with an average age in the early 1920s, it could be interpreted that the metabolic abnormalities, such as impaired glucose

Table 1 General characteristics by age at menarche

	Age at menarche (years)				
	<12	12–13	14–15	≥16	*P* value[a]
Age (years)	23.8 ± 0.8	29.6 ± 0.4	35.8 ± 0.4	39.8 ± 0.7	<0.001
BMI (kg/m2)	22.6 ± 0.3	22.1 ± 0.1	22.0 ± 0.1	22.4 ± 0.2	0.259
Energy intake (g/day)	1789.4±58.2	1859.2±35.8	1850.6±43.5	1820.6±87.4	0.763
Smoking					
None	86.4 (3.8)	89.0 (1.5)	89.7 (1.4)	84.9 (2.6)	0.357
Smoker	13.6 (3.8)	11.0 (1.5)	10.3 (1.4)	15.1 (2.6)	
Alcohol drinking					
None	40.7 (5.0)	41.1 (2.3)	44.3 (2.7)	37.9 (3.3)	0.512
Yes	8.9 (5.0)	39.1 (2.3)	37.8 (2.7)	14.2 (3.3)	
Exercise					
None/week	62.8 (4.1)	61.5 (2.2)	63.1 (2.1)	71.2 (3.5)	0.432
1–3 times/week	29.7 (3.9)	29.2 (1.9)	28.8 (1.9)	22.7 (3.1)	
≥4 times/week	7.6 (2.2)	9.3 (1.3)	8.1 (1.2)	6.1 (1.7)	
Income					
Low	10.6 (2.6)	8.1 (1.3)	7.5 (1.4)	9.0 (2.5)	0.625
Mid-low	31.4 (4.2)	24.5 (2.0)	28.2 (2.3)	29.5 (3.9)	
Mid-high	25.4 (3.6)	31.9 (2.3)	29.9 (2.0)	30.8 (3.6)	
High	32.6 (4.4)	35.5 (2.5)	34.4 (2.5)	30.7 (4.0)	
Education					
Below elementary school degree	22.2 (2.9)	11.3 (1.1)	3.6 (0.9)	5.8 (1.5)	<0.001
Middle school degree	16.6 (3.5)	12.0 (1.4)	8.1 (1.2)	11.6 (2.3)	
High school degree	26.1 (3.5)	34.4 (2.0)	46.6 (2.2)	46.6 (3.5)	
Above college degree	35.1 (4.3)	42.3 (2.3)	41.7 (2.3)	36.1 (3.3)	
Marriage status					
Yes	30.6 (3.9)	49.7 (2.1)	71.1 (2.1)	80.3 (3.1)	<0.001
No	69.4 (3.9)	50.3 (2.1)	28.9 (2.1)	19.7 (3.1)	

Values are presented as mean ± standard error (SE) or % (SE)

BMI body mass index

[a] Statistical significance was determined by the general linear model (GLM), chi-square analysis

tolerance and lipid abnormalities, shown in the blood tests are associated with age.

Most of the cross-sectional studies that have examined the relationship between the age of menarche and metabolic syndrome show that metabolic syndrome and cardiovascular mortality increased in association with an early age of menarche. A large-scale study in Latin America indicated that an early age of menarche increased the risk of diabetes and cardiovascular metabolic diseases [10]. Studies conducted in Europe have demonstrated similar results [7, 9]. A cross-sectional study in China, which included both pre- and postmenopausal women, also indicated that the risk of metabolic syndrome increased in association with a younger age of menarche [17]. Furthermore, a cross-sectional study conducted in Korea, based on KNHANES 2005, analyzed the relationship between reproductive factors in postmenopausal women and the incidence of metabolic syndrome, but no association was observed between the age of menarche and the risk of metabolic syndrome [18]. There are no other studies that have analyzed the association between age of menarche and metabolic syndrome in premenopausal women in Korea. A systematic review and meta-analysis that studied the association between the age of menarche and overall or cardiovascular mortality showed that the relative risk of overall mortality increased by 23 % in a group of women with an age of menarche <12 years, and mortality from ischemic heart disease also increased by 24 %. According to this study, 1 year of delayed menarche decreased the relative risk of mortality by 3 % [19].

Onset of menarche is influenced by genetic and environmental factors. Studies have shown that phenotypic expression associated with genetic factors is involved in the relationship between the age of menarche and BMI or obesity [20, 21]. In addition, nutritional intake and standard of living are important environmental factors. In a study on refugees (immigrants) from North Korea, in whom the average age of menarche was 16.0 ± 2.1 years in a population with an average

Table 2 Age at menarche and metabolic abnormality

		Age at menarche (years)				
		<12	12–13	14–15	≥16	*P* value[a]
Abdominal obesity (waist circumference ≥ 80 cm)	Yes	24.8 (3.4)	16.9 (1.7)	20.5 (1.9)	22.4 (2.9)	0.111
	No	75.2 (3.4)	83.1 (1.7)	79.5 (1.9)	77.6 (2.9)	
Fasting glucose (≤100 mg/dL or medication use)	Yes	7.8 (2.1)	12.7 (1.4)	14.6 (1.5)	20.9 (3.0)	0.004
	No	92.2 (2.1)	87.3 (1.4)	85.4 (1.5)	79.1 (3.0)	
Triglyceride (≥150 mg/dL or medication use)	Yes	11.4 (3.0)	11.9 (1.4)	13.9 (1.5)	19.8 (3.2)	0.073
	No	88.6 (3.0)	88.1 (1.4)	86.1 (1.5)	80.2 (3.2)	
HDL cholesterol (<50 mg/dL or medication use)	Yes	30.5 (3.8)	25.1 (2.0)	28.6 (1.8)	32.5 (4.2)	0.252
	No	69.5 (3.8)	74.9 (2.0)	71.4 (1.8)	67.5 (4.2)	
Blood pressure (≥130/85 mmHg or medication use)	Yes	9.0 (2.5)	7.0 (1.0)	8.9 (1.3)	15.9 (2.4)	0.004
	No	91.0 (2.5)	93.0 (1.0)	91.1 (1.3)	84.1 (2.4)	

Values are presented as % (standard error, SE)

[a] Statistical significance was determined by chi-square analysis

Table 3 Odds ratios (95 % CI) of metabolic syndrome and components by age at menarche[a]

	Age at menarche (years)			
	<12	12–13	14–15	≥16
Abdominal obesity				
Crude OR	1.14 (0.71–1.83)	0.70 (0.46–1.09)	0.90 (0.59–1.36)	1.00
Age adjusted OR	0.30 (0.17–0.52)	0.77 (0.49–1.21)	0.88 (0.58–1.34)	1.00
Multivariate adjusted OR[b]	4.24 (2.28–7.88)	1.46 (0.88–2.43)	1.31 (0.82–2.09)	1.00
High fasting glucose				
Crude OR	0.32 (0.16–0.63)	0.55 (0.36–0.84)	0.65 (0.43–0.98)	1.00
Age adjusted OR	1.21 (0.59–2.51)	1.03 (0.70–1.53)	1.24 (0.82–1.89)	1.00
Multivariate adjusted OR	0.72 (0.28–1.84)	0.99 (0.62–1.59)	0.90 (0.57–1.42)	1.00
High triglyceride				
Crude OR	0.52 (0.26–1.05)	0.55 (0.34–0.87)	0.65 (0.41–1.04)	1.00
Age adjusted OR	0.80 (0.39–1.65)	1.10 (0.68–1.78)	1.26 (0.79–2.02)	1.00
Multivariate adjusted OR	2.00 (0.91–4.39)	1.02 (0.59–1.77)	0.89 (0.50–1.58)	1.00
Low HDL cholesterol				
Crude OR	0.91 (0.54–1.54)	0.70 (0.45–1.07)	0.83 (0.53–1.29)	1.00
Age adjusted OR	0.90 (0.53–1.52)	1.27 (0.83–1.96)	1.15 (0.74–1.78)	1.00
Multivariate adjusted OR	1.15 (0.58–2.30)	0.82 (0.50–1.32)	0.89 (0.55–1.46)	1.00
High blood pressure				
Crude OR	0.52 (0.27–0.99)	0.40 (0.25–0.63)	0.52 (0.33–0.81)	1.00
Age adjusted OR	0.42 (0.21–0.84)	1.12 (0.69–1.81)	1.43 (0.88–2.32)	1.00
Multivariate adjusted OR	2.52 (1.15–5.51)	1.01 (0.58–1.74)	0.80 (0.48–1.33)	1.00
Metabolic syndrome				
Crude OR	0.60 (0.29–1.23)	0.54 (0.30–0.97)	0.72 (0.42–1.26)	1.00
Age adjusted OR	2.36 (1.08–5.13)	1.16 (0.64–2.11)	0.99 (0.56–1.73)	1.00
Multivariate adjusted OR	3.84 (1.52–9.70)	1.33 (0.64–2.78)	1.20 (0.60–2.40)	1.00

OR odds ratio, *CI* confidence interval

[a] Statistical significance was determined by multivariate logistic regression analysis

[b] Adjusted by age, smoking, alcohol, exercise, income, education, marriage status

age of 31.3 ± 6.2, the group with the lowest average age (<24 years) showed the most delayed menarche relative to the other groups (average age of menarche 16.3 ± 2.0). These findings were probably the result of this age group having experienced insufficient nutritional intake and sudden economic transition [22]. Adolescent obesity caused by excessive nutrition or fat accumulation can affect sexual maturation and, therefore, the onset of menarche. Hence, early onset of menarche due to environmental and genetic factors is associated with childhood/adolescence obesity, as well as adult obesity, and it can further increase the risk of developing metabolic syndrome [23]. Therefore, it is important to properly manage childhood/adolescent obesity at the appropriate stage. As the nutritional state in childhood is gradually improving, and the dietary intake is transitioning to a high-fat and high-calorie diet in Korea after industrialization, management of childhood and adolescent obesity has become more important. Although the prevalence of extreme obesity is not as high as in western societies, its management is critical in order to reduce the risk of cardiovascular disease.

There are a few limitations of this study that should be acknowledged. First, since it is a cross-sectional study, a clear causal relationship between age of menarche and metabolic syndrome cannot be claimed. Second, because the study was based on the results of a self-administered questionnaire, the subjects might have responded somewhat subjectively depending on the social environment. Furthermore, as it is an assessment based on recollection of past events, we cannot exclude the possibility of bias in measurement. Third, numerous studies have reported that the prevalence of metabolic syndrome markedly increases in menopausal women compared to premenopausal women, and menopause itself can be an independent risk factor for the incidence of metabolic syndrome related to the action of female hormones [18, 24–26]. Considering that during menopause the prevalence of metabolic syndrome increases and other metabolic factors change rapidly, we conducted this study in premenopausal women. As a result, we cannot presume that the results of the present study represent the characteristics of the entire female population. When premenopausal women were divided according to the age of menarche, the results showed that there was a significant difference in average age between each group. Although the group with the highest average age showed relatively late menarche, their risk of metabolic syndrome was found to be lower when the risk was adjusted for covariates. Age is a known risk factor for metabolic syndrome; however, in the present study, the risk of metabolic syndrome was highest in the group with the lowest average age. Therefore, age of menarche can be considered as a factor associated with the prevalence of metabolic syndrome. These results might have been due to the fact that the study subjects were premenopausal women and the average age of the group with the highest age of menarche (>16 years) was 39.8 ± 0.7, which is still relatively young compared to the total life expectancy or the average age of menopause in women in Korea. Regarding such results, further large-scale prospective studies must be conducted. However, the fact that these results were observed even when adjusted for age indicates the significance of the findings.

In addition, taking into account that the average age of menarche varies depending on race, and that the prevalence of metabolic syndrome and its components also varies depending on race and nationality, the present study reflects the national characteristics of Korea as it used data from KNHANES and included a relatively large sample size, conferring significance to our study. Another strength of this study is that the most recent KNHANES data was used, and thus, the current trend is reflected in our results. Showing a significant association between the age of menarche and various factors associated with metabolic syndrome after adjusting for covariates adds further significance to our findings. Furthermore, the inclusion of premenopausal women in the study, which was mentioned previously as a limitation, can also be a strength, as the concentration of female hormones rapidly decreases in postmenopausal women and the risk of metabolic syndrome increases. Minimizing the bias that can result from this by analyzing only premenopausal women adds further significance to this study.

In conclusion, after adjusting for covariates, the risk of metabolic syndrome in premenopausal women in Korea was higher in women who reached menarche at a younger age (<12 years) relative to those who reached menarche later. As the age of menarche is decreasing in Korea, we must pay close attention to the risks of obesity and metabolic syndrome in childhood and adolescence.

Compliance with ethical standards The details of this study and the KNHANES methodology have been approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention and with the 1964 Helsinki declaration and its later amendments.

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

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ORIGINAL ARTICLE

Prevalence and risk factors of metabolic syndrome among an endangered tribal population in Malaysia using harmonized IDF criteria

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Abstract The prevalence and risk factors associated with metabolic syndrome (MetS) of endangered subtribes are scantly reported. The purpose of this study was to assess the risk factors associated with MetS among the endangered Orang Asli (OA) populations using the latest harmonized International Diabetes Federation (IDF) definition. This cross-sectional study was conducted in geographical locations of the endangered subtribes namely Che Wong, Kensiu, Lanoh, and Orang Kanaq by random selection, and Semai was selected as a subtribe with a larger population as a comparison area in Peninsular Malaysia. A total of 160 respondents aged between 18 and 72 years were recruited. The respondents were measured for their weight, height, waist circumference, and blood pressure. Overnight fasting venous blood samples were analyzed for lipid profile and plasma glucose. The overall prevalence of MetS was 17.0 % (27/159). MetS rate among the endangered population only was 20.5 % (24/117). MetS prevalence was higher among the suburban Orang Kanaq (63.6 %), Che Wong (18.5 %), and Kensiu (16.4 %) subtribes and lower among the rural Lenoh (12.5 %) and Semai (7.1 %) subtribes ($P = 0.003$). MetS was significantly higher in females (23.8 %) compared to male (5.2 %) respondents. The risk factors identified for higher prevalence of MetS in females included overweight and obesity ($P < 0.001$), increased waist circumference ($P < 0.001$), and reduced high-density lipoprotein cholesterol (HDL-C) ($P < 0.001$). The prevalence of MetS among the endangered OA females is alarmingly high, especially among Orang Kanaq subtribe, which needs immediate attention.

Keywords Orang Asli · Malaysia · Prevalence · Metabolic syndrome · Risk factors

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Introduction

Metabolic syndrome (MetS) is defined as a constellation of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) risk factors including dysglycemia, elevated triglyceride (TG) levels, low high-density lipoprotein cholesterol (HDL-C) levels, raised blood pressure (BP), and obesity (particularly central adiposity) [1]. It is a complex disorder associated with adverse health outcomes and is considered as a worldwide epidemic [2, 3]. Based on the National Health and Nutrition Examination survey data from 2009 to 2010, the prevalence of MetS in USA was 22.9 % [4]. Ten population-based cohort studies in seven countries in Europe

observed that the MetS prevalence in obese subjects ranged from 43 to 78 % and 24 to 65 % in men and women, respectively [5]. The high prevalence of MetS involves not only developed countries but also some developing countries. Women of urban Indian population were found to have greater prevalence of MetS compared to men [6]. A nationwide survey conducted in Malaysia indicated that there were approximately 42.5 % of adults diagnosed with MetS whereas 43.9, 42.1, and 51.9 % were reported in Malay, Chinese, and Indian ethnic groups, respectively [7]. According to Chu and Moy, MetS is closely linked with modifiable factors such as overweight, obesity, and physical inactivity [8]. There have been several different definitions of MetS based on the International Diabetes Federation (IDF) [9], National Cholesterol Education Program Adult Treatment Program III (NCEP ATP III) [10], World Health Organization (WHO) [11], and the recently proposed harmonized IDF criteria [1].

Orang Asli (OA) is a Malay term which means original people or the first people. They are the indigenous minority people of Peninsular Malaysia. OA can be classified into three main ethno-linguistic groups, namely the Senoi, Proto-Malays, or Aboriginal Malays, and the Negritos, each consisting of several dialectic subgroups. The Senoi is the largest OA tribe constituting around 55 % of the population and mainly distributed from the middle to northern part of the Peninsular Malaysia [12, 13]. The Senoi subgroups include the Semai, Temiar, Che Wong, Jah Huat, Semoq Beri, and Mahmeri. The physical characteristics of Senoi include a wide range of skin color and wavy hair, and they live as both hunter-gatherers and traders [14]. Proto-Malay or Aboriginal Malay is the second largest tribe of OA constituting around 42 % of the population [12]. Proto-Malays consist of Jakun, Temuan, Semelai, Orang Kanaq, Orang Seletar, and Orang Kuala. They work as farmer-traders and have a lighter skin color and straight hair [15]. The Negrito comprises about 3 % of the population [12]. The Negritos include the Bateq, Kensiu, Kintaq, Jahai, Lanoh, and Mendriq. The Negrito population has dark skin and curly hair and lives as hunter-gatherers [14]. The Orang Asli Development Department (JAKOA) reported that the total population of OA in the year 2013 was 178,197 people [16]. However, the number of people in each subtribe varies widely. Some subtribes represent a small fraction of the total population and thus could be classified as endangered. These subtribes and their distribution of population are presented in Table 1.

Several health studies focusing on nutritional status [17–19], parasitic infections [20, 21], and anemia [22] were conducted among OA population; however, no studies were done on chronic diseases such as cardiovascular disease (CVD) and diabetes in this population. An earlier study reported the prevalence of MetS among female OA only [23]. The objectives of the present study were (1) to assess the prevalence of MetS by sex and subtribes based on the harmonized IDF definition among the endangered Orang Asli tribal population in Peninsular Malaysia and (2) to identify the risk factors of MetS among this population.

Materials and methods

Study population

This cross-sectional study was conducted from November 2011 to May 2013 among OA population in Peninsular Malaysia. Based on the 2013 record, seven subtribes including Kensiu, Kintak, Lanoh and Mendriq of Negrito tribe, Che Wong of Senoi tribe, and Orang Kanaq and Orang Seletar of Proto-Malay tribe were considered endangered (Table 1). For this study, four subtribes including Orang Kanaq, Che Wong, Kensiu, and Lanoh were selected randomly as the endangered subtribes, and Semai was selected as a comparison subtribe based on the population size.

The selection of villages was conducted using the systematic sampling method according to the tribal village list provided by the authority. The selection of each participant was performed using the purposive sampling method based on the defined inclusion and exclusion criteria. Due to the shy behavior of the OA population, it is often hard to reach the people to be selected. A snowball sampling method was also applied during recruitment because the procedure is quicker to recruit subjects when compared with probability sampling. Both purposive and snowball sampling approaches are non-random sampling methods which may have limitations but normally used in OA research [24].

Kg. refers to “kampung” which means village. Of the endangered subtribes, location of Orang Kanaq was at Kg. Sungai Selangi (Johor), which was 25 km from the nearest town of Kota Tinggi; Che Wong was located at Kg. Sungai Enggang (Pahang), 15 km from the Lanchang town, and Kensiu was located at Kg. Lubuk Legong (Kedah), 22 km from the Baling town, making them suburban for their locations. On the other hand, Lanoh and Semai were considered rural because of having no facilities of electricity or paved roads in these locations. Lanoh was located at Kg. Air Bah (Perak), 20 km from the Lenggong town, and Semai was located in a jungle of Kuala Lipis (Pahang), about 70 km from the nearest town of Raub.

The inclusion criteria were individuals aged between 18 and 72 years old who provided informed consent. Anyone with mental or physical disabilities or those who were pregnant or lactating were excluded. Ethical approval was obtained from the Universiti Sains Malaysia Human Research Ethics Committee. The purpose and procedures of the study were explained to the authorities of the Department of Orang Asli Development and the head (*tok batin*) of each village. Written informed consent was obtained from all individual

Table 1 Characteristics of the study population of Orang Asli subtribes, Malaysia

Tribe	Subtribe	Population of 2013[a]	Name of the area	Location type
Negrito	*Kensiu*[b]	237	Kg. Lubuk Legong, Baling, Kedah	Suburban
	Kintak	194		
	Lanoh[b]	382	Kg. Air Bah, Lenggong, Perak	Rural
	Jahai	2387		
	Mendriq	362		
	Beteq	1447		
Senoi	Temiar	31,038		
	Semai[c]	51,437	Pos Tual, Kuala Lipis, Pahang	Rural; comparison area
	Semoq Beri	5313		
	Che Wong[b]	651	Kg. Sungai Enggang, Lanchang, Pahang	Suburban
	Jah Hut	5618		
	Mah Meri	3799		
Proto-Malay	Temuan	27,590		
	Semelai	7727		
	Jakun	34,722		
	Orang Kanaq[b]	148	Kg. Sungai Selangi, Kota Tinggi, Johor	Suburban
	Orang Kuala	3525		
	Orang Seletar	1620		
Total		178,197		

[a] Data obtained from the Orang Asli Museum, Gombak, viewed 26 March 2015

[b] Study population—endangered

[c] Comparison population

participants included in the study. Researchers stayed several days in the village to establish rapport with the local people prior to subject recruitment.

Measurements

Height was measured to the nearest 0.1 cm using a portable stadiometer (Seca, Germany). Weight was measured in the upright position to the nearest 0.1 kg using a body composition monitor (TANITA SC-330, Japan). Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Waist circumference was measured at the end of normal expiration in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest [9]. Waist measurements were recorded to the nearest 1 cm.

BP was measured using an automated BP monitor (Omron, Japan). Measurements were taken when respondents were in the resting position with their hands resting on an adjutant table so that the cuffs were at same level with the heart. BP was measured two times, and the mean value was used in the analysis.

About 9 ml of venous blood samples was collected from the forearm of respondents in the morning after overnight fasting. The samples were stored in the ice box and were centrifuged at 4500 rpm for 10 min. The specimens were then stored at −80 °C until laboratory analysis. Serum samples were analyzed for TGs and high-density lipoprotein cholesterol (HDL-C). Plasma samples were used to measure glucose level. All laboratory assays were performed using commercially available kits (Roche, Germany). All analyses were performed using COBAS INTEGRA® 400 plus analyzer (Roche, Switzerland) in the Centre for Pathology Diagnostic and Research Laboratories (CPDRL), Universiti Teknologi MARA.

The definition of MetS used in this study was in accordance with the harmonized IDF [1]. Respondents who had at least three of the five risk factors were classified as having MetS. The definition includes elevated waist circumference (male ≥90 cm, female ≥80 cm), elevated TGs [≥150 mg/dL (1.7 mmol/L)], reduced high-density lipoprotein cholesterol (HDL-C) [<40 mg/dL (1.0 mmol/L)] in males and [<50 mg/dL (1.3 mmol/L)] in females, elevated BP (systolic ≥130 and/or diastolic ≥85 mmHg), and elevated fasting glucose (≥100 mg/dL).

Statistical analysis

Statistical analysis was carried out using the SPSS 22 statistical software package (SPSS Inc., Chicago, IL). General characteristics were compared between males and females by using Student's *t* test for continuous variable and chi-square test for categorical variables. Prevalence of MetS was compared between sex, subtribes, and age groups while prevalence of individual risk factors of MetS was compared between sex and subtribes. *P* values of less than 0.05 were considered as statistically significant.

Results

A total of 160 respondents were enrolled, of them one person having no completed data on the major variables was excluded. Table 2 shows that the prevalence of MetS in the study population was 17.0 %. The age group more prevalent of MetS was 46 to 55 years (45 %), followed by 36 to 45 years (20.8 %) ($P = 0.036$).

Among the subtribes, Orang Kanaq had the highest prevalence (63.6 %), followed by Che Wong (18.5 %), Kensiu (16.4 %), and Lanoh (12.5 %). The prevalence of MetS was significantly lower (7.1 %) among the comparison population of Semai ($P = 0.003$).

Table 3 presents the risk factors of MetS by sex. Females had a significantly higher prevalence of MetS than their male counterparts (23.8 vs. 5.2 %, $P = 0.002$). Among the risk factors, females had significantly higher rates of overweight and obesity (34.7 vs. 5.1 %, $P < 0.001$), increased prevalence of waist circumference (45.5 vs. 1.8 %, $P < 0.001$), and reduced HDL-C (72.3 vs. 35.1 %, $P < 0.001$) compared to males. There was no difference in fasting glucose, whereas males had a higher rate of increased systolic BP than females.

Table 4 shows the risk factors for MetS by subtribes. MetS was higher in females irrespective of subtribe of the population. The proportion of people with decreased levels of HDL-C ($P = 0.02$), increased systolic BP ($P = 0.05$), increased diastolic BP ($P = 0.01$), and increased levels of fasting glucose ($P = 0.001$) was significantly higher among the Orang Kanaq subtribe. Some of the risk factors such as female sex, decreased HDL-C, and increased fasting blood glucose were more often observed among the suburban populations including Orang Kanaq, Che Wong, and Kensiu subtribes, compared to the rural populations of Lanoh and Semai subtribes.

Table 2 Prevalence of metabolic syndrome among Orang Asli population by their age group and subtribe

Characteristics	Metabolic syndrome present no. (%)	*P* value
Age group (years)		0.036
<25	2/36 (5.6)	
25–35	10/66 (15.2)	
36–45	5/24 (20.8)	
46–55	9/20 (45.0)	
≥56	1/11 (9.1)	
Subtribe		0.003
Orang Kanaq (suburban)	7/11 (63.6)	
Che Wong (suburban)	5/27 (18.5)	
Kensiu (suburban)	9/55 (16.4)	
Lanoh (rural)	3/24 (12.5)	
Semai (rural)	3/42 (7.1)	
Total population	27/159 (17.0)	

Discussion

In this study, the overall prevalence of MetS among the OA population was 17.0 % based on the harmonized IDF definition. The rate of MetS may vary in the same population when different criteria are used. For example, Mohamud and Suraiami found a higher prevalence of MetS (22.7 %) among female OA population using the IDF definition [23]. In an earlier study in Malaysian adults, the overall crude prevalence rates of MetS were 31.2, 34.3, 37.1, and 42.5 % based on the WHO, NCEP ATP III, IDF, and harmonized IDF criteria, respectively [7]. Because of this inconsistency, it emphasizes the need for using similar case definitions to compare population-based prevalence rates of MetS.

Obviously, the rates of MetS also vary in different populations. In a cross-sectional study in China, the prevalence of MetS was similar in either sex (27.6 % in males and 24.4 % in females) based on harmonized IDF definition [25]. Based on NCEP ATP III criteria, a higher rate of MetS was observed among males (47.2 %) compared to females (40.3 %) in Saudi Arabia [26]. Using the same criteria of that of Saudi Arabia, Oman reported a much lower rate of MetS (24 %) among adults [27]. A high prevalence (34 %) of MetS was reported in hypertensive patients in Kuwait based on the ATP III definition [28]. A subsequent study among the adult population in Kuwait confirmed a similar rate of MetS using the ATP III definition but a higher rate (40–42 %) using the IDF definition [29]. A study on aborigines from central Australia reported a prevalence of 44 % based on ATP III definition [30].

The higher rate of MetS in females observed in our study may be attributable to the sedentary lifestyle more commonly observed among the female OA community, especially after resettlement in suburban communities. The high prevalence of MetS in Kuwait [29] and in some developed countries [30] was reportedly due to excess calorie intake and decreased energy expenditure leading to obesity. A study among isolated aboriginal Canadians showed that poor levels of physical

Table 3 Prevalence of metabolic syndrome and risk factors by gender

Characteristics	Male (n = 58) no. (%)	Female (n = 101) no. (%)	P value
Metabolic syndrome	3 (5.2)	24 (23.8)	0.002
Age (years, mean ± SD)	34.4 ± 14.4	34.3 ± 11.6	0.96
BMI (kg/m^2)			<0.001
<25	55 (94.8)	66 (65.3)	
25–29.9	2 (3.4)	23 (22.8)	
≥30	1 (1.7)	12 (11.9)	
Increased waist circumference	1 (1.8)	46 (45.5)	<0.001
Increased triglycerides	13 (22.4)	15 (14.9)	0.28
Reduced HDL-C	20 (35.1)	73 (72.3)	<0.001
Increased blood pressure			
Systolic	23 (43.4)	27 (27.0)	0.047
Diastolic	12 (22.6)	15 (15.0)	0.27
Increased fasting plasma glucose	7/38 (18.4)	16/87 (18.4)	1.0

BMI body mass index, *HDL-C* high-density lipoprotein cholesterol

activity and fitness were associated with a higher prevalence of MetS [31]. Moreover, decreased physical activity was an important factor for obesity among aboriginal and non-aboriginal adults [32].

Gender differences of MetS are not consistent across geographic locations. The findings of a higher prevalence of MetS in females in our study were comparable with studies in two aboriginal populations using the ATP III definition [33, 34]. However, studies among the Japanese population found a higher prevalence of MetS in males [35, 36].

One unique observation in our study was that the prevalence of MetS was higher in settlements that were near urban areas compared to rural areas. The endangered population of Orang Kanaq, Che Wong, and Kensiu subtribes who lived in suburban areas had higher prevalence of MetS (63.6, 18.5, and 16.4 %, respectively), compared to the Lanoh (12.5 %) and Semai subtribes (7.1 %), who lived in rural area and in a jungle. The higher rate of MetS and individual risk factors of MetS among Orang Kanaq indicate a high risk of this subtribe to develop T2DM and CVD. According to Alberti et al., individuals with MetS were at twice the risk of developing CVD over the next 5 to 10 years and a fivefold increase in T2DM risk [1]. The location of the four endangered subtribes from the nearest town varied from 15 to 25 km and that of Semai subtribe was 70 km from the nearest town of Raub. People of Lanoh and Semai had no access to paved roads or electricity, making them less accessible to urbanized lifestyle and food, which may contribute to lower rates of MetS in these populations. Another study among Malays in an urban area of Kuala Lumpur reported higher rates of MetS based on modified NCEP (41 %) and IDF (38 %) definitions [37]. The dietary changes from traditional to urbanized diet due to socio-economic development and availability of high-fat foods lead to a high prevalence of MetS among Temuan and Bidayuh tribes [38]. Gittelsohn et al. observed that consumption of foods that

Table 4 Risk factors of metabolic syndrome among the study population by subtribe

Characteristics	Subtribe					P value
	Orang Kanaq (n = 11)	Che Wong (n = 27)	Kensiu (n = 55)	Lanoh (n = 24)	Semai (n = 42)	
Female	9 (82)	18 (67)	38 (69)	13 (53)	23 (55)	0.32
Increased waist circumference	5 (46)	6 (22)	19 (35)	8 (35)	9 (21)	0.37
Increased triglycerides	1 (9)	6 (22)	6 (11)	6 (25)	9 (21)	0.53
Decreased HDL-C	11 (100)	14 (52)	35 (65)	11 (46)	22 (52)	0.02
Increased systolic BP	8 (73)	7 (26)	17 (34)	7 (30)	11 (26)	0.05
Increased diastolic BP	5 (46)	2 (7)	13 (26)	2 (9)	5 (12)	0.01
Increased fasting plasma glucose	6 (75)	6 (22)	4 (11)	0	7 (17)	0.001

BP blood pressure

were high in fat and low in dietary fiber and food prepared with lard were contributing factors for increased prevalence of diabetes among native Canadian populations [39].

In the present study, the most common abnormalities observed among females with a higher rate of MetS included overweight and obesity, increased waist circumference, and reduced HDL-C levels. A study among the aboriginal community in Ontario, Canada, was comparable with this finding, where high prevalence of low HDL-C level and abdominal obesity was reported in female aborigines [34]. This finding was also consistent with the reports for adult Malaysian and Thai populations [7, 40]. Low level of HDL-C was a common risk factor affecting 80 % of the Iranian population [41]. According to Chateau-Degat et al., the female aboriginal community in Quebec, Canada, had dominant abnormality profile of hyperglycemia and low HDL-C levels, while the males had hypertension, hypertriglyceridemia, and hyperglycemia [42]. O'Dea and Rowley had reported that social and environmental factors could contribute to the abnormality of MetS risk factors [43].

To the best of our knowledge, this is the first study reporting risk factors of MetS among the endangered Orang Asli tribal population using the latest harmonized IDF definition. However, some of the limitations of the study should be acknowledged. First, the question of sampling bias and the degree of generalizability remain a potential issue associated with the non-random sampling method used in this study. Secondly, the nature of the cross-sectional study was unable to elucidate the causal inferences. Third, the study population was small. Generally, the OA is an extremely conservative tribe and they try to avoid contacts with outsiders. Hence, it was challenging to obtain a large sample in our study as well as another study with the same population [23]. To overcome this barrier, the team stayed in the village for a couple of days, talked with the village leaders and other influential people, and tried to convince them the purpose of the study. Still, a larger study among the endangered population could enhance the generalizability of the findings.

Conclusion

In conclusion, the prevalence of MetS was high among the endangered OA females especially those living near urban areas. Therefore, immediate actions by health professionals and government agencies are needed to educate the people at risk for further control and prevention of health risks.

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Compliance with ethical standards 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.

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

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REVIEW ARTICLE

Glycemic targets in diabetes

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Abstract Target setting is an important strategy in diabetes. The commonly used glycemic targets are blood glucose and HbA1c. The target values can be fixed based upon normative data or outcome data. Individualization of glycemic targets is based upon age of patient, duration of diabetes, life expectancy, type of diabetes, type of therapy, presence of complications, propensity for hypoglycemia, hypoglycemia awareness, availability of family support, patient motivation, and patient education. Currently, the rate of attainment of glycemic target is improving, and almost 50 % of diabetics achieve HbA1C targets. In pregnancy, glycemic targets recommended are strict. Furthermore, the concept of individualization needs to be extended to the pregnant state. We propose that the glycemic targets in pregnancy with diabetes should be different in gestational diabetes, pre-gestational type 2 diabetes, and type 1 diabetes.

Keywords Diabetes · Blood glucose · Glycemic targets · HbA1c

Target setting is an important strategy in the therapeutics of a chronic disease like diabetes. Evaluation of various modalities of treatment against the targets achieved by them brings out the deficiencies in the management of diabetes and leads to evolution of effective therapeutics. Using accepted targets, it is possible to compare outcomes at different treatment centers, at different time periods with varying treatment modalities.

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Selecting targets

HbA_{1c} Among various measurements of glycemia, blood glucose and HbA_{1c} are the most commonly used parameters. Although blood glucose is an older criterion, for many reasons, HbA_{1c} has surpassed it in its utility. The blood glucose estimation, although considered a simple assay, is beset with various methodological problems, the most important being pre-analytical errors. Even when the sample is collected in a fluoride tube, enzymatic degradation of glucose can proceed further, causing spuriously low values [1–2]. On the other hand, HbA_{1c}, is a very sturdy analate and lately has been fully standardized and harmonized in advanced countries [3–4]. The intraindividual variability of blood glucose is high without any alterations in diet, drug, and exercise from day to day. Glycemic excursions bear an important relationship with endothelial health. However, their quantitation in terms of mean amplitude of glycemic excursion and many such parameters are yet to be used routinely. Such calculations require continuous monitoring of blood glucose, which was not being practised extensively earlier, but is picking up presently.

For the reasons stated above, HbA_{1c} holds a preeminent position in this regard. However, HbA_{1c} does not reflect the glycemic variability, although it faithfully reflects the mean blood glucose. Additionally, in each population, depending upon the prevalence of hemoglobinopathies, the reference values need to be worked out, which has only been accomplished in a few advanced countries. The intraindividual coefficient of variation of HbA_{1c} estimation is less than 1 % while that of plasma glucose is about 4 % [5–7]. Hence, HbA_{1c} coupled with self-

monitoring of blood glucose (SMBG) is now established as the best parameter to measure glycemia.

Continuous glucose monitoring systems At present, HbA_{1c} is the most common biochemical parameter used to evaluate glycemic control and to guide therapeutic changes. However, HbA_{1c} is an inappropriate marker for detecting rapid fluctuations in blood glucose levels, i.e., glycemic variability. Glycemic variability is a complex phenomenon that includes both intraday and interday variability taking into account minor and major blood glucose fluctuations. Real-time continuous glucose monitoring systems (CGMS) provide detailed information about the direction, magnitude, duration, and frequency of fluctuations in blood glucose levels. Clinically, CGMS data interpreted in the light of diet, physical activity, and medications can help identify and prevent unwanted periods of hypoglycemia and hyperglycemia. The accuracy of CGMS-generated data still varies from simultaneous capillary blood glucose measurements by an average 10–20 % [8], but it serves as a valuable learning tool. CGMS data can be used to study the effects of glycemic variability expressed as standard deviation from the mean (mean ± SD) and mean amplitude of glycemic excursions (MAGE). Higher standard deviation (SD) reflects greater glycemic variability. Currently, a 2 SD of <54 mg% is considered acceptable variability of blood glucose [9]. MAGE is not dependent on the mean glucose value as it quantitates glucose swings. It has been demonstrated that glycemic variability, expressed as MAGE, exerts a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia [10]. Future studies on glycemic variability can help identify the relationship of oxidative stress is linked with major glucose fluctuations, and whether lowering glucose variability reduces the risk of microvascular and macrovascular complications.

Self-monitoring of blood glucose SMBG is an important component of diabetes management as an estimation of blood glucose at many time points directs theraputic adjustments towards optimal glycemic control. Over the years, numerous studies have been carried out to determine the appropriate frequency and true impact of SMBG on glycemic control. Many published studies have demonstrated that regular and frequent SMBG improves control in patients regardless of type of diabetes or therapy used [11, 12]. SMBG remains a vital clinical tool in clinical practice as motivation and empowerment of patients to self-manage diabetes is enhanced by SMBG data.

Fixing glycemic targets

For fixing glycemic targets, theoretically, there are at least two approaches: the HbA_{1c} or blood glucose can be rendered completely normal or alternatively lowered to the extent that it minimizes complications without producing distressing incidence of hypoglycemia. Reduction of HbA_{1c} to the normal level is difficult to achieve in most diabetics without significant hypoglycemia. The only exception to this would be a newly discovered type 2 diabetic who is controlled on lifestyle measures alone or on a small dose of metformin. Hence, HbA_{1c} value seen at the threshold of microvascular complications is considered as a valid target [13]. Of all the vascular complications, retinopathy is used for this purpose as it reflects the outcome of hyperglycemia and its duration most faithfully [14–15]. Macrovascular complications may start before manifest hyperglycemia [16], and are closely related to comorbidities. Additionally, interventions may reveal a difference in macrovascular disease only in the long run [17–19]. Hence, they cannot be employed in target setting. When our understanding of macrovascular disease and its relationship with hyperglycemia improves, we may be able to conceive glycemic targets and the period of time over which they need to be sustained to prevent the macrovascular complications. Till then, we have to confine our outcome studies in this regard to microvascular disease. Another area where outcome studies may be more precise is setting of glycemic targets in pregnancy, as the outcomes in pregnancy lend themselves to precise measurements.

Evolution of glycemic targets

Historically, glycemic targets have evolved over the past three to four decades. The impetus to set these targets was a series of landmark studies [9, 20], where HbA_{1c} of 7 % [NGSP method (National Glycohemoglobin Standardization Program)] appeared to represent the threshold for complications. With considerable enthusiasm, this value was promulgated as a target. In fact, most patients know of this as the magic figure.

Initially, several committees formulating guidelines proposed same glycemic targets for type 1 and type 2 diabetes [21]. This appeared quite anomalous to physicians practising diabetology. It was very easy for a treating physician to discern the fact that same degree of intensive control without hypoglycemia is difficult to achieve in type 1 diabetes as compared to type 2 diabetes. Hence, some of them proposed far ahead of the standard ADA/EASD recommendations that the glycemic targets have to be different in type 1 and type 2 diabetes. The impact of duration of diabetes was also appreciated by practising physicians far ahead of ADA/EASD recommendations [22]. The ADA/EASD proposed such criteria as late as in the year 2009 [23], and subsequently, other committees including the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE), International Diabetes Federation (IDF), Canadian Diabetes Association (CDA), and National

Institute for Clinical Excellence (NICE) revised their recommendations as well (Table 1).

The impact of intensive glycemic control on the macrovascular complications of diabetes came to be appreciated following the publication of ADVANCE, ACCORD, and VADT studies [28–30] where not only patients of long-standing diabetes but also those with pre-existing complications were enrolled for the study and where intensive control either failed to improve vascular outcomes or at times accelerated the vascular complications [31]. In the past 5 years, individualization of targets has become the watchword and "Moving Goal Posts" sums up the current approach very aptly.

Basis of individualization of glycemic targets Table 2 lists the criteria on which individualization of glycemic targets can be based.

Age, duration of diabetes, life expectancy

Elderly age, short life expectancy, and long duration of diabetes are likely to occur simultaneously in many type 2 diabetics [17–19, 22, 28–30, 32, 33]. These factors call for relaxation of glycemic targets. The vascular complications as well as use of insulin therapy is also likely to occur in the same group. Hence, in any given patient, individualization of glycemic targets will require consideration of several coexisting facts.

Type of diabetes

Most internists deal with a large number of type 2 diabetes, but usually not a substantial number of type 1 diabetics. The endocrinologists and diabetologists dealing with both the groups appreciate the different behavior of these diseases. Most part of their diabetic life, type 2 are treated with OAD's while type 1 diabetics are always on insulin. Because of a low C-peptide, type 1 diabetics have unstable hyperglycemia [34]. Insulin therapy, in spite of current advances, continues to exhibit 20–40 % intraindividual coefficient of variation [35, 36]. Hypoglycemia is also more frequent with insulin therapy [18, 37]. Although most clinicians have set different glycemic targets for their type 1 and type 2 diabetics for more than three to four decades [22], these facts have only recently been reflected in the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and International Diabetes Federation (IDF) guidelines [23].

Type of therapy

Although type of therapy does not have a direct bearing on the glycemic targets, it is an indirect reflection of the stage and type of diabetes in an individual patient. Pharmacotherapy becomes more complex in patients with type 2 diabetes with increased duration of disease [38]. Hence, the targets need to be relaxed with more complex therapy. The coefficient of variation of insulin response discussed above also imparts considerable instability to blood glucose, increasing the incidence of hypoglycemia [35–36].

Currently, type 2 diabetics, especially during the first 5–10 years of their disease, are being treated only with oral antihyperglycemic agents (OAHAs) like metformin, pioglitazone, DPP-4 inhibitors, and nutrient blockers (e.g., acarbose and voglibose) rather than oral hypoglycemic agents (OHAs) like sulfonylureas, meglitinides, and insulin. This preference is due to a lower risk of hypoglycemia with OAHAs. It is possible to exhibit an OAHA in full dosage, in the first 5–10 years of type 2 diabetes mellitus, leading to good control without much hypoglycemia. In fact, it is possible to target a HbA_{1c} as low as 5–6 % at this stage. Not only is this goal attainable, it is most desirable to undertake such an approach because first 5–10 years of good control translates into much greater benefits than latter 10 years of good control [17–19, 39].

The above-described approach is more likely to result in attainment of lower glycemic targets in a larger section of type 2 diabetics. For example, in many patients with type 2 diabetes, sensitizing agents like pioglitazone, metformin, and addition of DPP-IV inhibitors have permitted use of lower dosage of insulin, less hypoglycemia and, hence, attainment of better glycemic control. Newer therapeutic agents such as the DPP-IV inhibitors can be used at four stages of type 2 diabetes: initial therapy with or without metformin; metformin failures, triple drug therapy as add-on to metformin and sulfonylurea, and lastly along with insulin therapy. Furthermore, use of an insulin pump almost eliminates a major drawback of subcutaneous insulin therapy as intrasubject coefficient of variation of insulin with pump is as low as 2 % [40]. Thus, the targets on pump therapy can be quite strict. It is important to point out that a sensitizing agent may be required even in pump therapy in type 2 diabetes mellitus [41].

Table 1 Current recommendations for glycemic targets in type 2 diabetes in non-pregnant adults

	ADA/EASD [23]	AACE/ACE [24]	IDF [25]	CDA [26]	NICE [27]
Fasting glucose	70–130 mg/dL	<110 mg/dL	<115 mg/dL	72–126 mg/dL	Not mentioned
2-h postprandial glucose	<180 mg/dL	<140 mg/dL	<160 mg/dL	90–180 mg/dL	Not mentioned
HbA_{1c}	<7 %	≤6.5 %	<7 %	<7 %	6.5–7.0 %

Table 2 Criteria for individualization of glycemic targets

Sr no.	Criteria	Reference
1	Age	[28–30]
2	Duration of diabetes	[17–19, 22, 28–30]
3	Life expectancy	[32, 33]
4	Type of diabetes	[18, 23, 34–37]
5	Type of therapy: OAD, standard insulin therapy, intensive insulin therapy, insulin pump therapy	[45, 46, 48–51]
6	Presence of complications	[28–30, 42]
7	Propensity to hypoglycemia; hypoglycemia unawareness	[43–47]
8	Availability of family support, education, diabetes self management education, adherence	[48, 49, 50]

Presence of complications

Microvascular complications are usually seen after a decade or two of type 2 diabetes although occasionally onset of such complications has been described at the time of diagnosis. Macrovascular disease may develop even before the diagnosis of type 2 diabetes and often its progression is dependent not only on diabetes, but on other comorbid conditions like hypertension, elevated LDL-cholesterol, tobacco abuse, and obesity. Significant complications are only seen after 10–20 years of type 2 diabetes mellitus and usually are vascular in nature, but occasionally severe peripheral neuropathy may dominate the scene [14, 16].

As discussed above, ADVANCE, ACCORD, and VADT studies [28–30] have pointed out the hazards of over-zealous glycemic control, especially with pre-existing vascular complications. A subset analysis of ADVANCE study has, however, shown that speed with which metabolic control is achieved may be an important determinant of complications. Currently, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consider HbA_{1c} of 7.5 % or even up to 8.5 % acceptable in diabetics with complications [42].

In case of painful, acute, or sub-acute peripheral neuropathy of diabetes, meticulous glycemic control may be rewarding and may have to be attempted. For example, a HbA_{1c} of 6.5 % with elimination of prandial peaks may be required to obtain optimal relief of neuropathic pain [14].

Propensity to hypoglycemia and hypoglycemia awareness

Theoretically, potent oral anti-diabetic drugs (OAD) and insulin can successfully lower blood glucose in any diabetic, but for the overwhelming barrier of hypoglycemia. When there is presence of hypoglycemia unawareness, this barrier becomes formidable [43]. Recognizing the preventable causes of hypoglycemia, apart from the OAD and insulin, is an important strategy in achieving glycemic targets. Thus, issues of variable diet, sick day routine, unanticipated exercise, and drug interactions have to be addressed. Unfortunately, after addressing these issues, there remains a significant incidence of hypoglycemia in many diabetics. Recurrent hypoglycemia is closely related to patients' endogenous insulin reserve. Hence, type 1 diabetics are particularly prone to hypoglycemia as they are insulin deficient and require exogenous insulin to regulate glucose levels. The increased susceptibility toward hypoglycemia in patients with type 1 diabetes is further exacerbated by impaired glucagon release in response to hypoglycemia [44].

The inimical consequences of hypoglycemia have been adequately emphasized in a large number of studies. The consequences include cardiac arrhythmias, cognitive defects, autonomic failure, and probably some deaths [45–47]. In the presence of hypoglycemia unawareness, it is clearly recommended that glycemic targets be revised upwards for 6 weeks or more to restore hypoglycemia awareness. Because the basic causes of unawareness continue to prevail, it appears difficult for the present authors to accept that the glycemic targets can be lowered after 6 weeks, as it is likely to lead to a recurrence of hypoglycemia unawareness. Probably, the targets will need to be revised permanently.

Availability of family support, patient motivation, and education

Each of these factors limits the possibility of achieving strict targets without producing significant hypoglycemia. A thorough understanding of the interaction of food, drugs, and physical activity is essential for obtaining good glycemic control. Elderly people, living alone, may suffer from severe hypoglycemia and its consequences and, hence, need to have relaxed targets. A poor acceptance of lifestyle management may necessitate upward revision of glycemic targets, as pushing of hypoglycemic drugs indiscriminately in this situation will produce significant hypoglycemia [48–50].

Individualizing glycemic targets

Optimal glycemic control is fundamental to the management of diabetes mellitus. Due to the heterogeneous nature of diabetes and the necessity of achieving a fine balance between progressive glycemic control and increased risk of hypoglycemia, tailoring therapeutic regimens and selecting appropriate glycemic targets can be quite challenging for a physician. Based upon theoretical considerations and clinical perspectives discussed above, we have endeavored to propose a framework for setting individualized glycemic targets for patients with type 1 or type 2 diabetes taking into account several key parameters (Table 3).

In type 1 diabetes, the key factors to take into consideration when selecting glycemic goals are duration of diabetes, presence of microvascular complications and/or macrovascular complications, and treatment modality. As insulin therapy is the cornerstone of management among these patients, risk for hypoglycemia will remain moderate to high. A target range of HbA_{1c} 6.5–7.0 % can be used for those with disease duration <10 years with or without established microvascular complications. The lower end of this range ($HbA_{1c} \leq 6.5$ %), if safely achievable, can be targeted specially for those on insulin pump therapy. However, the selected HbA_{1c} target may need to be relaxed to a range of 6.5–7.5 % for those being managed with basal-bolus insulin therapy. As duration of diabetes increases beyond 10 years, microvascular and macrovascular complications set in; hence, the selected targets can then fall into the range of $HbA_{1c} \leq$ 7.0–8.0 %, with the lower end being pursued only if safely achievable.

Selection of targets for the management type 2 diabetes requires more factors to be considered: age, duration of diabetes, presence of microvascular and/or macrovascular complications, complexity of therapeutic regimen, and risk for hypoglycemia. Notably, the risk for hypoglycemia is strongly linked with the pharmacological therapies used. The risk is low with OAHAs, moderate with addition of OHAs and/or basal insulin, and high with further addition of prandial insulin. A glycemic target in the range of HbA_{1c} 6.5–7.0 % can be selected for patients <65 years of age, disease duration <10 years without established microvascular and/or macrovascular complications, and where treatment used does not include prandial insulin. With advancing age (65–75 years), longer duration of diabetes >10 years, and the addition of prandial insulin to achieve glycemic control, it is advisable to select a HbA_{1c} target in the range of 7.0–7.5 %. In patients >75 years of age with pre-existing macrovascular complications, it is logical to select a glycemic target between 7.5 and 8.5 % preferentially based on the potential risk for hypoglycemia. In all these situations, it is prudent to pursue lower targets only if safely achievable.

Status of glycemic targets attainment

In the past decade, the glycemic targets are increasingly being achieved in a larger percent of diabetics. This may reflect early diagnosis, better treatment and monitoring tools, and better education. However, we are yet far away from a near total achievement of ABC targets (HbA_{1c}, blood pressure, and cholesterol), most specifically when all three targets are considered.

Figure 1 shows the frequency at which HbA_{1c} targets are currently being achieved at Diabetes Endocrine Nutrition Management and Research Centre, Mumbai. At the time of initial reporting, $HbA_{1c} < 7.0$ % was seen only in 12 % of patients. On optimizing treatment using best practice guidelines, the number of patients achieving $HbA_{1c} < 7.0$ % rose to 28 %. Many of the patients attending our center are older with diabetes of more than 10 years duration and have pre-existing macrovascular complications. In this population, a HbA_{1c} of <8 % can be considered a realistic target, which means initially, 32 % of patients were at target and on follow-up, 53 % of patients achieved the HbA_{1c} target. Furthermore, institution of individualized treatment guided by expert clinical advice significantly reduced the number of patients with $HbA_{1c} > 8$ % from 68 % at initial presentation to 47 % on follow-up.

Trends in glycemic targets

Examination of HbA_{1c} trends among adults with type 2 diabetes using three consecutive waves of the National Health and Nutrition Examination Survey (NHANES) revealed a consistent decline in HbA_{1c} from 7.82 % in 1999–2000 to 7.47 % in 2001–2002 with further reduction to 7.18 % in 2003–2004. Notably, in this cohort, approximately 35 % achieved $HbA_{1c} \leq 6.9$ % in 2003–2004 [51]. Similar

Table 3 Suggested glycemic targets* for individuals with type 1 and type 2 diabetes mellitus

Type 2 diabetes mellitus	Initial 2–5 years of disease	<6.5 %
	5–10 years of disease	<7.0 %
	>10 years of disease with or without cardiovascular, renal, retinal, neurological complications	<7.5 %
Type 1 diabetes mellitus	With intensified insulin therapy or insulin pump therapy	<7.0 %
	With standard insulin therapy	<7.5 %
	With cardiovascular, renal, retinal, neurological complications	<8.0 %

*Aim for lower HbA_{1c} target, if safely achievable

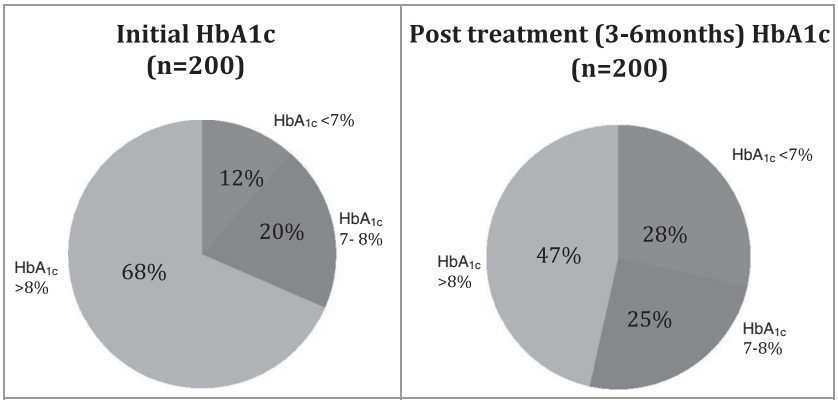

Fig. 1 Initial and follow-up HbA1c data from Diabetes Endocrine Nutrition Management and Research Centre, Mumbai

observations were seen in a longitudinal study where a mean reduction in HbA_{1c} by 0.4 ± 1.8 % was seen over a span of 10 years from 1996 to 2006 [52].

Presently, the greatest challenge in clinical practice lies in lowering HbA_{1c} in patients with type 2 diabetes whose glycated hemoglobin levels fall near 8 %. It has been well established that postprandial glycemic excursions are major contributors to mild HbA_{1c} elevation whereas fasting hyperglycemia significantly contributes toward $HbA_{1c} > 8$ % [53]. Progression of type 2 diabetes leads to stepwise deterioration in glycemic control from postprandial hyperglycemia to fasting hyperglycemia [54]. It has been observed that intensification of treatment, particularly with basal insulin, can cause alteration in the contributions from fasting and postprandial hyperglycemia towards HbA_{1c} [55]. Therefore, in this cohort, lowering HbA_{1c} to <7 % requires intelligent selection of therapies to effectively lower both basal and postprandial hyperglycemia.

Pregnancy

Physiologically, profound metabolic changes occur during pregnancy to favor optimal growth of the fetus. Maternal insulin resistance develops normally as an adaptation to ensure availability of appropriate fuels to the fetus, a process termed "facilitated anabolism." In the 1950s, Pederson's pioneering work suggested that in the offspring of mothers with diabetes, maternal hyperglycemia led to fetal hyperinsulinemia and overgrowth as a consequence of excess exposure of the fetus to maternal glucose. This hypothesis was later modified by Freinkel to include the potential contribution of other nutrients towards fetal overgrowth, termed as "fuel-mediated teratogenesis"; however, the role of fetal hyperinsulinism and control of maternal hyperglycemia remained central [56, 57]. Over the years, there has been a growing body of evidence substantiating that good maternal glycemic control is necessary to achieve favorable maternal and fetal outcomes in pregnancy complicated by diabetes. However, the definition of "good maternal glycemic control" is being continually debated.

There are two well-illustrated classic approaches to fix glycemic targets in pregnancy complicated by diabetes, i.e., based on normative data and outcome-related data.

Normative data

Recently, Hernandez et al. carried out a systematic review of data spanning 45 years describing glycemic patterns in normal pregnancy [58]. Pooled results from a total of 12 studies showed that weighted average glucose values (±1 SD) were 71 ± 8 mg/dL fasting, 109 ± 13 mg/dL at 1-h postprandial (PP), and 99 ± 10 mg/dL at 2-h postprandial. Based on these results, the 1-h PP target ranged from 96 to 122 mg/dL and the 2-h PP target ranged from 89 to 110 mg/dL. For comparison the ±2 SD values have also been noted in Table 4. Notably, the 1-h PP and 2-h PP targets, which are ±2 SD above the weighted means, are similar to currently recommended therapeutic targets.

Studies have also been carried out to establish trimester-specific HbA_{1c} reference intervals in pregnancy. O'Connor reported HbA_{1c} in the range of 4.8–5.5 % in non-pregnant Caucasian women while the trimester-specific reference intervals were 4.3–5.4 % in the first trimester, 4.4–5.4 % in the second trimester, and 4.7–5.7 % in the third trimester [59]. HbA_{1c} is lower in the first and second trimesters of pregnancy compared to non-pregnant women. At present, the ADA recommends $HbA_{1c} \leq 6$ % for women with diabetes during pregnancy. Comparatively, the Australian Diabetes Society recommends glycemic targets based on type of diabetes during pregnancy, i.e., $HbA_{1c} \leq 7$ % for pregnant women with pre-existing type 1 diabetes and $HbA_{1c} \leq 6$ % for pregnant women with pre-existing type 2 diabetes [63, 64].

Outcome-related data

Suhonen et al. studied fetal outcomes in women with type 1 diabetes (gestation age < 14 weeks) where fetal malformations

Table 4 Currently recommended glycemic targets in pregnancy compared to normative data

	Normative data			Currently recommended target
	Weighted mean ± SD (mg/dL)	+1 SD range (mg/dL)	+2 SD range (mg/dL)	
FBG	71 ± 8	63–78	55–87	<90 mg/dL [60, 61]
1-h PP	109 ± 13	96–122	83–135	<140 mg/dL [60–62]
2-h PP	99 ± 10	89–109	79–119	<120 mg/dL [60, 61]

occurred in 4.2 % compared to 1.2 % in the control group. The risk for fetal malformations was particularly high with $HbA_{1c} \geq 9.3$ % while some degree of risk (3 %) was also associated with a lower HbA_{1c} in the range of 5.6–6.5 %. The corresponding blood glucose values below which the risk of fetal malformations decreased were FBG < 104.4 mg/dL and PP < 163.8 mg/dL [65].

A review of seven cohort studies identified 117 anomalies among 1977 pregnancies. At a peri-conceptional GHb concentration 0 SD above normal, the absolute risk of a pregnancy affected by a congenital anomaly was approximately 2 %, at 2 SD above normal, the risk was 3 %, and at 8 SD, it was approximately 10 % (CI 2.3-17.8). For each 1-SD unit rise in GHb, the associated risk of a congenital malformation increased by an odds ratio of 1.2 (95 % CI 1.1–1.4). The risk in relation to HbA_{1C} followed the same pattern [66]. Similar observations in addition to an increased rate of perinatal mortality associated with $HbA_{1C} \leq 6.9$ % has also been reported in other studies [67].

Historical data has established a strong association between pregnancy loss and poor glycemic control in the first trimester [68, 69]. Mills et al. demonstrated that in normal pregnancies and among diabetic women with good metabolic control, the risk of pregnancy loss in the first trimester was similar at 16 %. Notably, the risk of spontaneous abortion significantly increased among diabetic women with poor glycemic control. Each increase of 1 SD above the normal for glycated hemoglobin was associated with a further 3.1 % rise in rate of pregnancy loss. More recent studies have also demonstrated increased risk of pregnancy loss at high and low extremes of maternal glucose concentrations [70–72]. To minimize the risk of spontaneous abortions and major congenital malformations, it is recommended to achieve HbA_{1C} as close to normal as safely possible before pregnancy.

Maternal diabetes is one of the strongest risk factors associated with large for gestation age (LGA) infants. In pregnant women with pre-existing type 1 diabetes, Mello et al. reported a significantly high rate of LGA infants (54 %) among those who achieved a mean glucose ≥95 mg/dL in the second and third trimesters of pregnancy. The HbA_{1c} and postprandial targets achieved were not reported; however, the targets selected were pre-meal 70–90 mg/dL and 2-h PP <120 mg/dL [73]. Higher rates of LGA infants have also been reported in women with gestational diabetes where it has been suggested that targeting 1-h PP ≤130 mg/dL reduces the incidence of fetal macrosomia but increases the incidence of small for gestation age (SGA) infants [74].

Assessing glycemic control in pregnancy

HbA_{1c} is used in routine clinical practice for retrospective estimation of glycemic control in the past 2–3 months. The physiological changes in erythrokinetics during pregnancy influence the interpretation of HbA_{1c} as a measure of glycemic control. The life span of erythrocytes also reduces to 90 days, which may reduce the HbA_{1c} value. New erythrocytes formed are exposed to a lower time-averaged glucose concentration compared to non-pregnant women resulting in a lesser degree of glycosylation. Hence, HbA_{1c} needs to be measured at an increased frequency of every 1–2 months. Nutrient deficiencies, particularly iron deficiency, are common, which may affect HbA_{1c} during the dynamic phase of anemia. For these reasons, HbA_{1c} is used in conjunction with capillary blood

Table 5 Suggested glycemic targets in pregnant women with diabetes

Type of diabetes	Treatment modality	Risk of hypoglycemia	Suggested glycemic target (%)
Gestational diabetes mellitus (GDM)	Metformin	Low	<5.0[a]
	Metformin ± basal–bolus insulin therapy	Moderate–high	<5.5[a]
Pre-gestational, type 2	Metformin	Low	6.0[a]
	Basal–bolus insulin therapy ± metformin	Moderate–high	6.5[a]
Pre-gestational, type 1	Insulin pump therapy	Moderate–high	<6.5[a]
	Basal–bolus insulin therapy	Moderate–high	7.0[a]

[a] Aim for lower HbA1c target, if safely achievable

glucose targets to guide treatment of pregnancy complicated by diabetes [75–78].

Individualizing glycemic targets in pregnancy

It is important to look at the feasibility of achieving glycemic targets in pregnancy. From this angle, vigorous discussion has not taken place in the literature. However, if HbA_{1c} achieved in various studies of diabetes in pregnancy is examined, a very interesting observation emerges. Weighted mean HbA_{1c} achieved in these studies in gestational, pre-gestational type 2 diabetes, and pre-gestational type 1 diabetes shows a clear gradient of 4.83, 6.15, and 6.48 %, respectively [79–92]. In this context, we would like to extend the concept of "individualizing glycemic targets" to pregnancies complicated by diabetes taking into consideration three important factors: type of diabetes (i.e., pre-existing type 1 or type 2 diabetes or gestational diabetes), risk for hypoglycemia and treatment modality. Conceptually, it is important to recognize that type 2 diabetes mellitus, pre-gestational, and gestational diabetes (GDM) represent different stages of diabetes and as proposed in the non-pregnant state, the targets recommended should logically be different in these categories. Based upon these observations, we propose HbA_{1c} targets from 5.5 to 7 % in various categories of pregnant diabetics (Table 5).

A recent systematic review and meta-analysis highlighted the lack of evidence regarding the association between different intensities of glycemic control during pregnancy and maternal and neonatal outcomes [93]. There are no RCTs comparing current vs. lower glucose targets powered on maternal and/or fetal outcomes, and no studies evaluating the effect of type of diabetes during pregnancy on feasibility of achieving current recommended glycemic targets. Based on clinical studies [79–92], the control achievable in pregnant women with pre-existing type 1 diabetes or type 2 diabetes and gestational diabetes is different. Therefore, it is advisable to select more stringent targets for pregnant women with pre-existing type 2 diabetes and gestational diabetes (FBG < 90 mg/dL, 1-h PP < 130 mg/dL, and 2-h PP < 110 mg/dL) while more relaxed glucose targets (FBG < 90 mg/dL, 1-h PP < 140 mg/dL, and 2-h PP < 120 mg/dL) may be more feasible in pregnant women with pre-existing type 1 diabetes.

Conclusion

Although an armamentarium of pharmacological agents is currently available to enable achievement of good glycemic control, the medical management of diabetes has become increasingly complex. Glycemic control remains a major focus in the management of patients with diabetes. Therefore, selection of an appropriate glycemic target to guide pharmacotherapy is of utmost importance. Over the years, practising physicians have aptly perceived that the same degree of glycemic control without an increased incidence of hypoglycemia is difficult to achieve in type 1 diabetes as compared to type 2 diabetes. At present, all guideline-formulating committees worldwide endorse the individualization of glycemic targets, which has been elaborately discussed through the concept of "Moving Goal Posts" in this paper. A number of parameters to be considered, while selecting a glycemic target in the range of HbA_{1c} 6.5–8 % for an individual patient, have been identified and addressed. It is imperative to extend the concept of individualization to the management of diabetes in pregnancy. Based on clinical studies, the degree of glycemic control achieved in pregnant women with pre-existing type 1 or type 2 diabetes is different from that attained in pregnant women diagnosed with gestational diabetes. Therefore, it is logical to propose selection of glycemic targets in the range of HbA_{1c} 5.5–7 % for the management of diabetes in pregnancy based on three key parameters: type of diabetes (pre-existing type 1 or type 2 diabetes or gestational diabetes), risk for hypoglycemia, and treatment modality. Currently, there is insufficient evidence on the effect of different intensities of glycemic control during pregnancy on neonatal outcomes, which should be addressed by future studies.

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CASE REPORT

A case of undetectable glycosylated hemoglobin

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Abstract Cation-exchange high-performance liquid chromatography separates hemoglobin species based on charge differences. Since the glycosylated hemoglobin [HbA1c] test is based on normal hemoglobin, hemoglobinopathies can affect the test by altering the normal process of glycation of HbA to A1C, producing an abnormal peak on chromatogram or making the erythrocytes more prone to hemolysis, thereby decreasing the time for glycosylation to occur and producing a falsely low A1C result. A 51-year-old male presented with complaint of generalized weakness. HbA1c test done to rule out abnormal glucose tolerance revealed undetectable levels. He had low hemoglobin, microcytic red cell indices, 86.2 % of hemoglobin E (corrected A2), and minor elevation of fetal hemoglobin. This case is significant for the incidental discovery of HbE homozygosity in an apparently healthy and active person, through incidental finding of undetectable levels of HbA1c.

Keywords HbE homozygous · HbF · Biorad D-10 · HbA_{1c} · Hemoglobinopathy · Glycohemoglobin

Introduction

Hb A_{1c} assays can be divided into methods that use molecular charge [cation exchange, high-performance liquid chromatography, and electrophoresis] and methods that use molecular structure [immunoassays, boronate affinity chromatography, and mass spectrometry] [1]. In CE-HPLC and electrophoresis assays, Hb A_{1c} can be separated from Hb A because glycation of the N-terminal valine decreases the positive charge. These methods are affected by posttranslational modifications (like carbamylation and acetylation) or by hemoglobin mutations that alter the charge.

Hemoglobin separates into major and minor hemoglobins when subjected to [CE-HPLC], the minor hemoglobins A_{1a}, A_{1b}, A_{1c}, F1, and P3 components being posttranslational modifications of globin chains. The order of elution of various components is HbA_{1a}, HbA_{1b}, HbF, LA_{1c}/CHb-1, LA_{1c}/CHb-2, HbA_{1c}, P3[Hbd component], HbA_0, and HbA_2 [2]. Hb variants (or their glycated forms) may interfere with Hb A_{1c} assays based on CE-HPLC and electrophoresis by coeluting/comigrating with Hb A_0 and/or Hb A_{1c}.or if the hemoglobin variant peaks have retention times that are very close to one of these peaks [3].

Case report

A 51-year-old male attended the outpatient department with complaints of generalized weakness. He was clinically healthy with normal growth and living an active life. He never received any blood transfusions. His family history was unremarkable.

His laboratory investigations were as follows [reference ranges in parentheses]: urea, creatinine, electrolytes, calcium, phosphorus, total protein, albumin, bilirubin, aspartate transaminase, gamma glutamyl transferase, and alkaline phosphatase were within reference range. Serum iron 38.4 μg/dl (45–182), total iron binding capacity 294 μg/dl (250–450), ferritin 245.9 ng/ml

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(30–300), transferring saturation 13.1 % (20–50), HBA_{1C} 0 % (<5.6), TSH 4.18 μIU/ml (0.25–5), free T4 11.21 pmol/l (9–20), hemoglobin 10 g/dl (13–17), total leukocyte count 5000 cells/cumm (4000–10,000), total erythrocyte count 5.05 million/cumm (4.5–5.5), hematocrit 30.4 % (45–50), platelet count 1.19 lakhs/cumm (1.5–4), mean corpuscular volume (MCV) 60.1 fl (83–101), mean corpuscular hemoglobin (MCH) 19.8 pg (27–31), mean corpuscular hemoglobin concentration (MCHC) of 33 % (31.5–34.5), and differential count was within reference range. His peripheral smear showed microcytic hypochromic RBCs with a few target cells and polychromasia. Routine stool examination revealed presence of bacteria, vegetable cells, and starch fiber. Routine and microscopic urine examination did not reveal any abnormality.

Rapid serology for HIV, HBsAg, and HCV was negative. HPLC for abnormal hemoglobins performed on D-10 [Bio-Rad] showed HBE of 86.2 %, HBA_0 6 %, HBF 1.5 % (Fig. 1). Recheck with a fresh sample on Siemens Dimension Xpand by turbidimetric inhibition immunoassay (TINIA) principle revealed HBA_{1c} to be 5 % and capillary electrophoresis showed major part to be HBE [62 %].

Discussion

The HbE gene is a mutant form of the β-globin [HBB] gene that encodes lysine instead of glutamate at position 26. This β-E chain is inefficiently produced because of a novel cryptic messenger RNA splice site, leading to thalassemic RBC indices [4]. While HBE trait is diagnosed by high HbA_2 [E+A2] approximately 30 %, homozygous HBE patients have approximately 90 % HBE+A_2 with minor elevation of HbF [5]. The anemia is due to ineffective erythropoieseis, globin chain imbalance leading to apoptosis and instability of HbE. This leads to extramedullary hematopoiesis with organomegaly.

HbE may be present in the heterozygous state [genotype AE or hemoglobin E trait], homozygous state [genotype EE or hemoglobin E disease], and a variety of compound heterozygous states such as hemoglobin E/β thalassemia [E/βthal] and sickle cell/hemoglobin E disease [SE genotype] [4]. Hemoglobin E (HbE) homozygotes have been described as clinically mild, never having been transfused and not having hepatosplenomegaly [6].

Diagnostic dilemma is often posed by the HPLC method being less specific since the HbA_{1c} peak is affected by other substances and by abnormal Hb variants [7]. Improbably low percentages of glyco-Hb, especially those below the reference

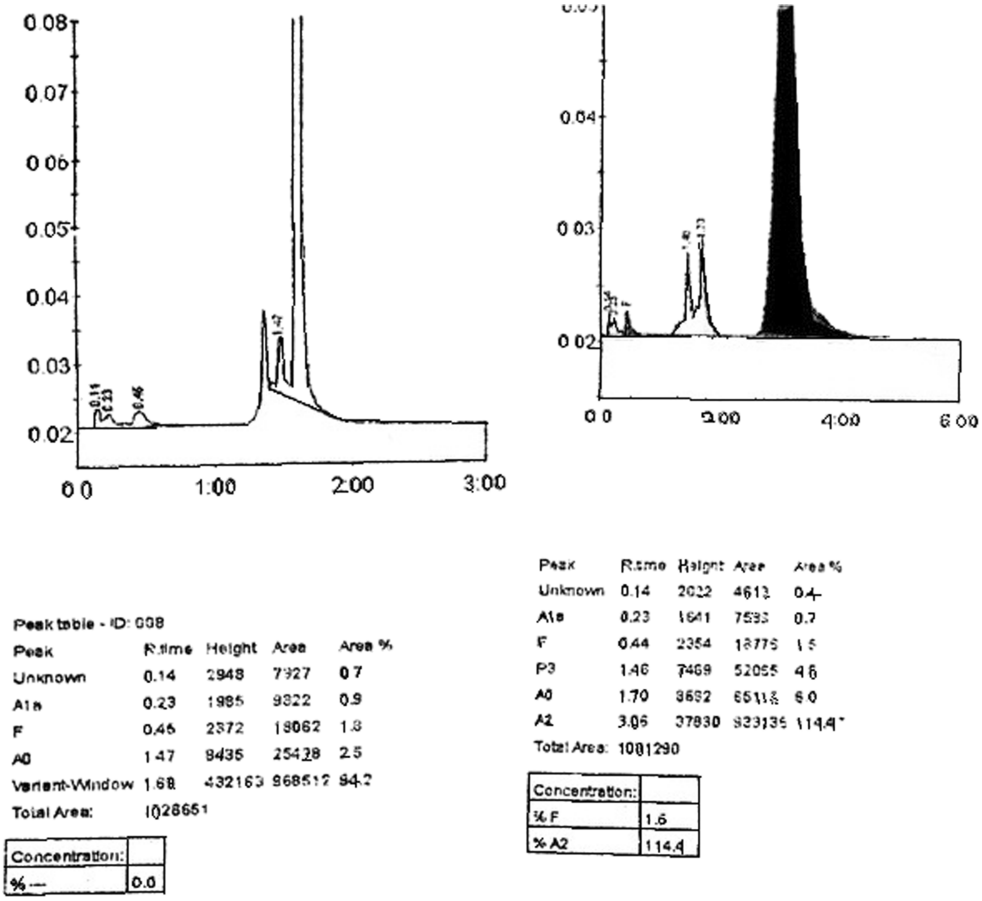

Fig. 1 HPLC report in HbA_{1c} mode [*left*] and HBA_2 mode [*right*]

range, are clear indications for the presence of hemoglobin variants. Abnormal Hb results in an abnormal peak on chromatography [making the estimation of the fraction of HbA_{1c} unreliable], or [as in cases of thalassemia and sickle cell trait], erythrocytes become susceptible to hemolysis, consequently decreasing the time available for glycosylation of Hb chains [8]. For samples that show Hb variants in the chromatograms, HPLC users can additionally use a method that is not affected by Hb variants, such as affinity chromatography or immunoassay [9].

The accept/reject criteria for HbA_{1c} in the presence of a variant Hb has been described by Behan et al. (Fig. 2) [3]. A major limitation of our case study was that we did not have DNA confirmation. However, the Bio-Rad analyzer is an appropriate reference for this study because it is FDA-approved for identifying HbA_2 and HbF and provides "presumptive" identification of hemoglobin variant [10]. Besides, we repeated the test with a fresh sample, tested the sample for a sickle screen, ran hemoglobin electrophoresis, ran it on alternate methodology of better specificity [immunoassay] in-house and discussed with physician before arriving at diagnosis. In the presence of Hb variants, fructosamine, daily multiple testing of capillary glucose or continuous glucose monitoring may be used to monitor glycemic control [1]. A similar case of undetectable HbA_{1c} by HPLC and 7.2 % by immunoassay in a case of homozygosity for HBE has been reported from India [11]. Dual reporting in both SI (IFCC) and NGSP/DCCT units should be used for reporting HbA_{1c} and calculators to convert between millimoles per mole and percentage available at (http://www.hba1c.nu/eng2.html and http://www.ngsp.org/convert1.asp) be used [12].

As the distribution of Hb variants continues to widen, the need to understand how the most common Hb variants

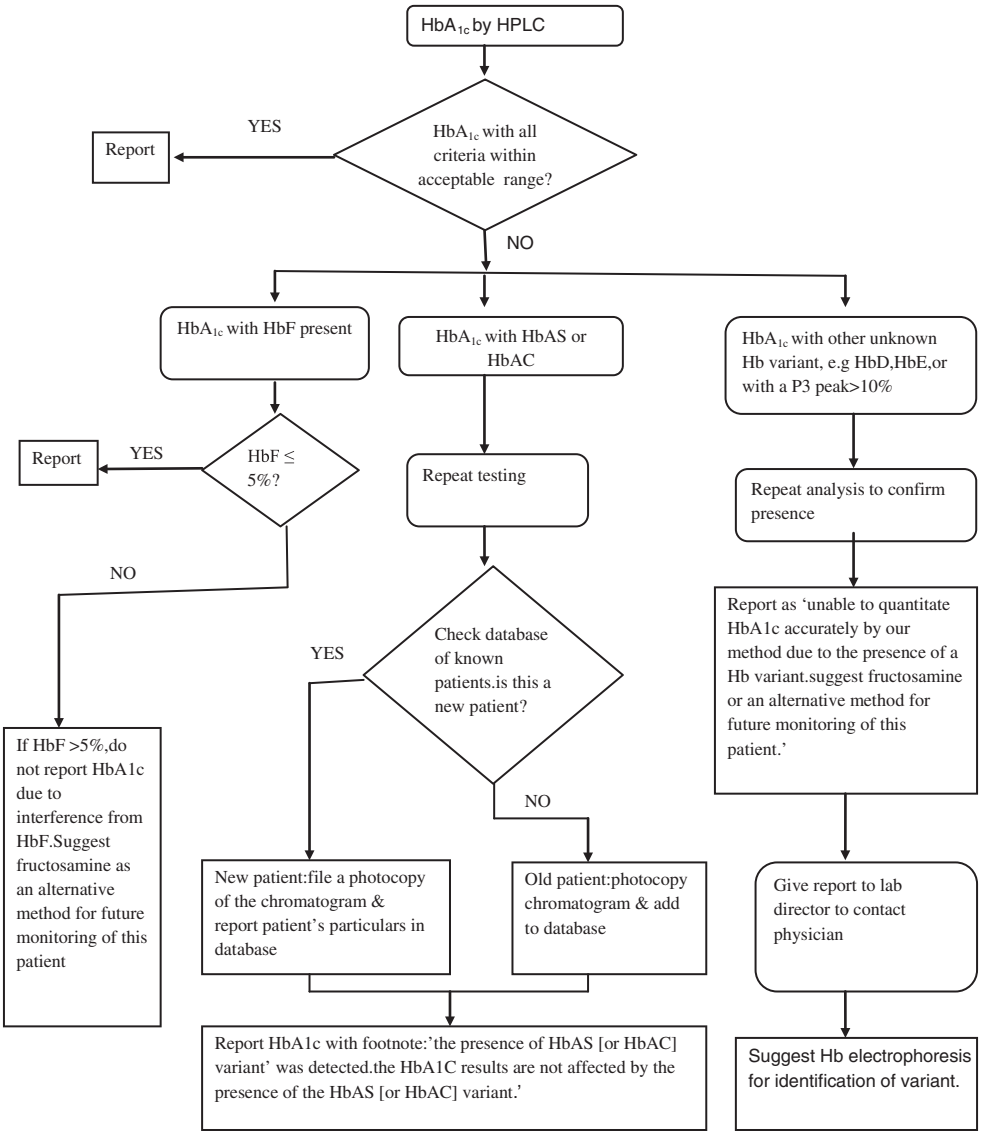

Fig. 2 Accept/reject criteria for HbA_{1C} in the presence of a variant Hb [3]

influence Hb A_{1C} interpretation is becoming increasingly important.

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CASE REPORT

Fulminant type 1 diabetes occurring in a child in association with acute hepatitis A infection: case report and review of literature

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Abstract Fulminant type 1 diabetes is a recently described form of T1DM presentation, reported mainly from Japan. This mode of presentation is very rare among Caucasians and is not reported from India before. We report a child presenting with fulminant type 1 DM in association with acute hepatitis A virus infection.

Keywords Fulminant type 1 diabetes · Hepatitis A

Introduction

Fulminant type 1DM is a recently recognized pattern of type 1 diabetes presentation reported mostly from Japan. It is characterized by an abrupt onset of diabetes with ketosis or ketoacidosis, near-normal HbA1c level at presentation, complete beta cell destruction at onset, and absence of islet-associated antibodies [1]. Fulminant type 1DM is considered as a subtype of type 1B diabetes. Owing to the heterogenous nature of T1B DM, there is appreciable variability in its mode of presentation. Ethnic variability has a significant role in the incidence of fulminant T1DM. Fulminant T1DM is rare among Caucasians and is not reported from India before. Viral infections are known to trigger T1DM. Reports of Hepatitis A precipitating T1DM are very rare.

Case report

A 3-year-old girl was brought with fever of 2 days duration and lethargy abdominal pain and vomiting for 1 day. She did not have any osmotic symptoms or loss of weight prior to the present episode. She had contact to hepatitis A viral hepatitis in the household at the same time. On evaluation, she was found to have high blood sugars (378 mg/ dl) and strong ketonuria. There was no acidosis. She was hemodynamically stable. Her heart rate was 104/min, respiratory rate 24/min, blood pressure 96/69 mm of Hg. Her weight was 12 kg (between 5th and 10th percentile) and height was 88 cm (10th percentile). Her serum sodium and potassium were 131 and 3.1 mEq/l, respectively. Her serum creatinine was 0.5 mg/dl and blood urea was 16 mg/ dl. Her liver function test showed a serum total bilirubin of 3 mg/dl, SGOT 760 IU/l, SGPT 340 IU/ l, and ALP of 560 IU/l. Serum lipase was 138 (normal 73–393 u/l) and did not suggest exocrine pancreatic damage. She improved with intravenous fluid administration, potassium replacement, and intravascular insulin infusion. Ig G HAV was done which was positive (HAV IgG 3.8 S/CO, >1.0 reactive by CMIA (chemiluminescent microparticle immunoassay)). Even though Ig M HAV is the marker of acute infection, Ig G was done because the antibody test was done 6 weeks after the episode and the patient had no history of hepatitis A in the past and was not immunized for hepatitis A. Anti GAD 65 antibody was negative (4.6 IU/mL by EIA (<10 negative)). Her HbA1c at admission was 6.2 %. Her fasting serum C peptide level was undetectable. She was discharged on a subcutaneous basal bolus insulin regimen

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with a bedtime basal insulin injection and three pre-meal bolus insulin injections. On follow-up, her blood sugars were fairly controlled and she required 0.5 units of insulin/kg of body weight daily. Her liver function test subsequently normalized.

Discussion

This report highlights a rare presentation of fulminant type 1 diabetes associated with acute hepatitis A infection. This is also the first report of fulminant type 1 diabetes from India to our knowledge. Fulminant type 1 diabetes accounts for up to 20% of all ketotic onset diabetes mellitus in Japan [2]. Balasubramanian et al. reported that none of the 55 recent onset type 1 DM patients from North India had fulminant type 1 diabetes [3]. Fulminant type 1 diabetes is very rare among Caucasians [4].

HLA polymorphisms strongly confer susceptibility or resistance to type 1 diabetes. Susceptibility polymorphisms may be different for Caucasians and for Japanese. While DR4-DQ4 is not a susceptibility factor for Caucasians, for Japanese, DR4-DQ4 confers susceptibility [5]. Imagawa et al. found that the frequency of HLA-DR4 was significantly higher in fulminant type 1DM unlike the frequency of HLA DR 9. In contrast, HLA-DR9 but not DR4 was more frequent in typical type 1A diabetes. Haplotype DR4-DQ4 was significantly more frequent, and DR8-DQ1 was less frequent in fulminant type 1DM. In type 1A diabetes, DR9-DQ3 was significantly more frequent [6]. In India while HLA DR 3 confers susceptibility to type 1DM and DR 2 protects from type 1DM, HLA DR 4 is very common in the background population, but it does not confer susceptibility to type 1DM [7]. Balasubramanian et al. could not identify any patient with fulminant type 1DM in a study of 55 recent-onset type 1DM in North India. HLA DR 4 did not impart susceptibility in this population [3]. Differential susceptibility of HLA DR 4 in part may explain the differences in incidence of fulminant type 1DM in different ethnic groups. Viral infections can precipitate fulminant type 1DM. IgA antibody titres to enterovirus are found to be significantly higher in fulminant type 1DM than in typical type 1A DM [8]. Pregnancy is another condition known to precipitate fulminant type 1 DM. Shimizu et al. reported 22 patients with fulminant type 1 DM with ketosis presenting during pregnancy or within 2 weeks postpartam [9]. Viruses may trigger type 1 DM by several mechanisms. Reports of hepatitis A viral infection triggering type 1 diabetes is very scarce in the medical literature. Adi FC reported nine patients with new-onset DM associated with an acute infectious hepatitis epidemic in Nigeria [10]. Makeen AM reported three patients who developed diabetes mellitus and presented with diabetic ketoacidosis within weeks of acute hepatitis A infection [11]. Another report of fulminant type 1 DM associated with acute hepatitis A was published from Korea [12].

Present report shows that fulminant type 1 DM occurs in India as well. Enteroviral infection, particularly hepatitis A viral infection, is more common in developing world; such infections may in part contribute to the increasing incidence of type 1 diabetes in this part of the world. There can also be regional variability in occurrence of fulminant type 1 DM between different parts of India as these are genetically diverse populations.

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Importance of adherance to yoga in management of type 2 diabetes

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Dear Sir,

In the study conducted by Nagarathna et al. [1], it was observed that yoga-based life style modification programme is similar to exercise-based life style modification in reducing blood glucose, HbA1c, triglycerides, total cholesterol and VLDL. An important feature in the interpretation of the results of the study, which the authors seemed to have missed, is the participant's adherence to the yoga programme over the 6-month period of the study. In yoga studies, adherence is usually objectively measured as the number of yoga classes the participant has attended over the given period of the intervention [2, 3]. Nagarathna et al. [1] have reported reasons for the number of drop-outs; however, depiction of the yoga adherence levels of the participants, who completed the study, could have helped better interpret the results of the study.

Researchers have opined that "decreased adherence to yoga has the potential to decrease the effect of the intervention because subjects who might sustain the greatest benefit will receive a lower dose of the intervention and subjects with higher adherence rates may be functioning closer to maximum ability before the intervention" [4]. To further research on this important concept of adherence in the field of yoga, we conducted a 4-year long-term follow-up to test the adherence to yoga and its resultant effects on blood glucose. Eighty-nine people with type 2 diabetes enrolled for yoga camps in the year 2010 in a community in Bangalore, but only 26 attended the camps in 2014 (4th year follow-up). The average (SD) age, education, and duration of diabetes of these participants was 52.21 (9.0) years, 14.15 (3.21) years, and 8.24 (6.84) years, respectively. The Integrated Approach to Yoga Therapy (IAYT) for Diabetes developed by Swami Vivekananda Yoga Anusandhana Samasthana (SVYASA) was taught for the first 8 months of the study after which they were advised home practice. Fasting blood sugar (FBS) was assessed at baseline, at the end of 3 months, 8 months and 4 years, and a qualitative interview schedule (to understand reasons for adherence and non-adherence) and Holmes & Rahe Life event scale to measure stressful life events [5] was conducted at the end of 4 years.

The results of the study showed that even though daily yoga classes were held for the first 8 months, only 39 participants out of 89 (43.8 %) attended the 8-month classes regularly, which further reduced to just 6 % in 2014. There was no statistically significant reduction in FBS levels over the 4-year period (due to high attrition rates); however, during the time the yoga intervention was provided (first 8 months), the trend showed that FBS levels were lower as compared to the baseline. This could be attributed to the fact that qualitatively, participants experienced a feeling of well-being and positive changes which possibly motivated them to complete the 8-month yoga programme. At the end of 4 years, most participants responded that they did not feel motivated to practice on their own at homes. Further there was a trend in their FBS

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Table 1 Paired sample *t* test/Wilcoxon sign rank test for fasting blood sugar over 4-year period

Time selection	Number	FBS (pre)	FBS (post)	t/z^a	*p*
Baseline 3rd month	40	134.55 (34.35)	129.52 (50.36)	0.819	0.418
Baseline 8th month	30	142.60 (32.43)	139.06 (50.48)	0.391	0.698
Baseline 4th year	19	130.16 (32.44)	139.74 (44.71)	−1.26[a]	0.21

[a] Wilcoxon sign rank test

levels being higher as compared to baseline (Table 1). The predictor analysis with FBS as a dependent variable showed a significant positive correlation between FBS and stress (r=0.42, p=0.04).

Yoga practice thus qualitatively improves diabetes health status and makes participants feel happy, enthusiastic and active. However, stress and adherence to yoga are important factors in affecting blood glucose parameters in participants with diabetes. Future studies which test the efficacy of yoga interventions for diabetes need to pay attention to these two important parameters in analysing and interpreting the results between intervention effects and blood glucose parameters.

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Compliance with ethical standards

Conflict of interest Gaurav Kumar, Aarti Jagannathan and Shridhar MK declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with animals performed by any of the authors. 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 Was obtained from all individual participants included in the study.

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LETTER TO EDITOR

Cyclic vomiting syndrome in a case of type II diabetes

Nihar Ranjan Tripathy

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Case study

A 60-year-old woman with a history of diabetes mellitus since last 8 years and hypertension since last 6 years visited our clinic in June 2011 with recurrent severe vomiting associated with pain in the epigastrium. One year back, she experienced acute onset of severe vomiting associated with mild epigastric pain for first time. She was treated with intravenous proton pump inhibitor and other antiemetic agents like ondansetron, metoclopramide, and promethazine. The symptoms lasted for about 4 to 5 days after which she was completely alright. The same episode started again next month with severe vomiting, nausea, and epigastric pain which lasted for 4 to 5 days. Management with intravenous fluid, proton pump inhibitor, and antiemetics was continued until the vomiting stopped, but it did not show any significant improvement as vomiting continued for the same duration with severity of about 15 to 20 episodes per day.

Since then, she experienced recurrent episodes of high-intensity nausea, vomiting, and epigastric pain lasting for about 4 to 6 days every month. She had no other significant past medical, gastrointestinal, endocrine, gynecological, renal, or urological disorders. No significant surgical history was present.

She was investigated at different centers for this devastating problem. Laboratory evaluation report is presented in Table 1.

CT abdomen and pelvis showed multiple indentations/scars altering the outer contours of kidneys, generalized osteopenia, and a small umbilical omental hernia. On urine culture, sensitivity towards amikacin was reported and she was treated with amikacin following which routine microscopy revealed three to four pus cells/HPF and no other abnormality.

She was on two doses of premixed (30/70) insulin with a fasting plasma glucose of 196 mg/dl and post-prandial plasma glucose of 298 mg/dl. With sliding scale, her insulin dosages were titrated and fasting plasma glucose and post-prandial plasma glucose were maintained at 98 and 178 mg/dl, respectively. Blood pressure was optimized with angiotensin receptor blocker (ARB) plus calcium channel blocker and maintained at 126/80 mmHg.

Even after maintaining plasma glucose, blood pressure in optimal levels, and treating urinary tract infection intensively,

Table 1 Laboratory investigation reports

Laboratory investigations	Parameters
Hemoglobin	12.1 g/dl
Total leukocyte count	12,400 cells/cumm
ESR	40 mm/1st h
Platelet count	3.21 lakh/cumm
Random plasma glucose	210 mg/dl
Serum creatinine	0.96 mg/dl
Serum sodium	135 mmol/l
Serum calcium	8.8 mg/dl
Serum potassium	3.5 mmol/l
Serum bicarbonate	28 mmol/l
TSH	0.84 μIU/ml
Total bilirubin	0.6 mg/dl
Direct bilirubin	0.2 mg/dl
SGPT	12 U/L
Alkaline phosphatase	138 IU/L
HIV, HbsAg, and anti-HCV antibodies	Negative
Prothrombin time	14 s
APT	28 s

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Table 2 Rome III diagnostic criteria for CVS

At least 3 months, with onset at least 6 months previously of
1. Stereotypical episodes of vomiting regarding onset (acute) and duration (<1 week)
2. Three or more discrete episodes in the prior year
3. Absence of nausea and vomiting in between the episodes
4. There are no metabolic, gastrointestinal or central nervous system, structural, or biochemical disorders
5. Supportive criteria: personal or family history of migraine headaches

Table 3 Precipitating factors for CVS

1. Stress
a. Physical: infections, sleep deprivation, exercise, trauma
b. Emotional: holidays, birthdays, family vacations, festivals, school camps, examinations, familial conflicts, anxiety, etc.
2. Menstruation
3. Pregnancy
4. Food allergies (e.g., chocolates, cheese, and monosodium glutamate)

Sources: Fleisher et al. [1] and Li and Balint [4]

she continued to suffer from the same incapacitating stereotypic episodes of nausea and vomiting every month. Every time she was managed with nil per oral feed, intravenous hydration, proton pump inhibitors, and antiemetics in the hospital followed by oral medications associated with a liquid or semi-liquid diet pattern gradually shifted to a normal dietary habit in 2 to 3 days.

The patient was severely distressed out of fear for the uncontrolled recurrent symptoms, and she was very much depressed, losing the hope of any positive outcome. As no improvement in the severity and duration of the episodes were realized, she was prescribed an antidepressant with her regular medication in October 2011 after a presumptive diagnosis of cyclic vomiting syndrome (CVS).

Next month, she had a comparatively mild episode of vomiting occurring six to eight times lasting for 2 days resulted. She was managed with rehydration fluid and antiemetic agents. This time, it was triggered by fasting which she had kept for traditional purpose. Treatment was continued, and she was further followed up, but there was no recurrence of nausea or vomiting up to next 6 months. Gradually, the antidepressant was withdrawn and the patient did not have any absurd events thereafter.

Discussion

CVS is a rare episodic disorder of recurrent high-intensity nausea and vomiting lasting hours to days, separated by intervals completely free of symptoms (Tables 2 and 3). It was first described in children but has been increasingly reported in adults with a female predominance with a ratio being 55:45 [1, 2]. Patients typically present 6 to 12 stereotypic episodes of nausea and vomiting that vary in duration and frequently go undiagnosed for years [3].

Conclusion

Cyclic vomiting syndrome is a functional vomiting disorder which should be carefully monitored to diagnose early as the devastating episodes of recurrent severe vomiting incapacitates the patient affecting the quality of life to a great extent. We present a case simply treated successfully with antidepressants, but much more is needed to really understand the gravity of the disease and more of research and analysis is awaited.

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LETTER TO EDITOR

Impairment in glycemic control and lipid profile during the Indian festival of Diwali

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Festive season in India is associated with a marked change in diet of people. It is accompanied by consumption of sweets and fat-rich fried foods. There is a concern that this dietary change can cause significant deterioration in the metabolic profile of patients with T2DM. The effect of this change in diet on blood glucose and lipid profile of patients of T2DM has not been studied [1, 2]. We studied the effect of expected changes in diet on glycemic control and lipid levels of patients with T2DM around the Hindu festival of Diwali of 2011.

The study was conducted from 12th October to 11th November 2011 at the out-patient department of MDM Hospital, Jodhpur. Seventy-two T2DM patients, treated with oral hypoglycemic drugs, were enrolled for the study. Out of them, 67 patients completed follow-up. Their mean age was 60.0±8.3 years; male-to-female ratio was 43:24. Mean BMI was 26.14±2.94 kg/m^2.

The study involved two visits, first within 2 weeks before and second within 2 weeks after Diwali. At each visit, the following biochemical parameters were estimated: fasting and 2 h post breakfast plasma glucose, lipid profile including total cholesterol, TG, LDL, VLDL, and HDL. At the first visit, height and weight were also measured. The exclusion criteria were patients on insulin therapy and those suffering from renal failure, stroke, cancer, and other conditions affecting diet and weight. The biochemical tests were performed using Bayer Semi-autoanalyzer RA-50. The paired *t* test was used for comparison of study parameters measured at both the visits and $p<0.05$ was considered significant.

The results of the study show that Diwali is followed by a significant increase in fasting (136.85±20.43 vs. 154.02±19.16, $p=1.82\times10^{-14}$) and post-prandial glucose (185.22±30.66 vs. 207.05±31.16, $p=8.63\times10^{-14}$), total cholesterol (198.47±18.84 vs. 212.98±19.06, $p=1.69\times10^{-15}$), triglycerides (136.37±25.76 vs. 153.44±23.95, $p=1.18\times10^{-15}$), LDL (130.25±16.42 vs. 142.28±17.50, $p=4.56\times10^{-13}$), and VLDL (27.27±5.15 vs. 30.68±4.79, $p=1.18\times10^{-15}$) cholesterol. Whereas, HDL was reduced significantly (40.94±3.75 vs. 40.01±2.78, $p=3.57\times10^{-4}$) after Diwali.

The results of this study show that there is deterioration of lipid and glycemic parameters after festival of Diwali. These findings have clinical implications. While managing T2DM, lifestyle and cultural factors should be considered. The anti-diabetic drugs can be adjusted in accordance with the expected dietary change during festivals. Specialized diet counseling can be of help for patients.

T2DM type 2 diabetes mellitus, *TG* triglycerides, *LDL* low-density lipoprotein, *VLDL* very-low-density lipoprotein, *HDL* high-density lipoprotein.

This study was presented as a poster at ENDO 2012 (Houston, TX) and the abstract is present online on the meeting organizer's website.

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Announcements for Research Grant

- For providing research grants, RSSDI invites proposals from Indian scientists, interested in conducting original research in the field of diabetes mellitus. Furthermore, limited grants are also available for the students of medical colleges for smaller projects
- There is no deadline for submission of the proposals, which can be sent throughout the year. These proposals may fall into one of the following two categories: Projects involving funding up to Rs 40,000 per project (preference will be given to young scientists <40 years)
- Projects involving funding up to 10 lakhs (preferably multicentric)
- The detailed proposals should include the following:
  - ◊ Title, names of principal and co-investigators, summary, introduction/background, review of literature, aims, methodology, study design, and detailed plan of work and bibliography. Brief biodata of principal investigator and other co-investigators
  - ◊ Importance of work in the context of national priorities. Detailed budget sought along with full justification/ proposed utilization, of funding sought from RSSDI
  - ◊ Whether the project is being partly funded from any other source? If yes, please mention the source and the amount received
  - ◊ Ethical committee clearance of the institution or other bonafide body.

BOOK REVIEW

REVIEW OF 3RD EDITION OF RSSDI TEXT BOOK OF DIABETES MELLITUS : Editor-in-Chief – Hemraj B Chandalia, Executive Editor – Gumpeny Ramachandra Sridhar, Editors – Ashok Kumar Das, Sri Venkata Madhu, Viswanathan Mohan, Paturi Vishnupriya Rao

The third edition of RSSDI text book contains contributions from those who have being practicing / teaching Diabetology for many years, similarly the editors too. Most of the contributors are from within the country with many years of experience behind them. A few non resident Indians have made useful contribution. This edition as pointed out by editor – in – chief has gone on considerable revision from the first two editions. This only shows the importance of making an attempt to have our own text books and keep revising, based on the experience.

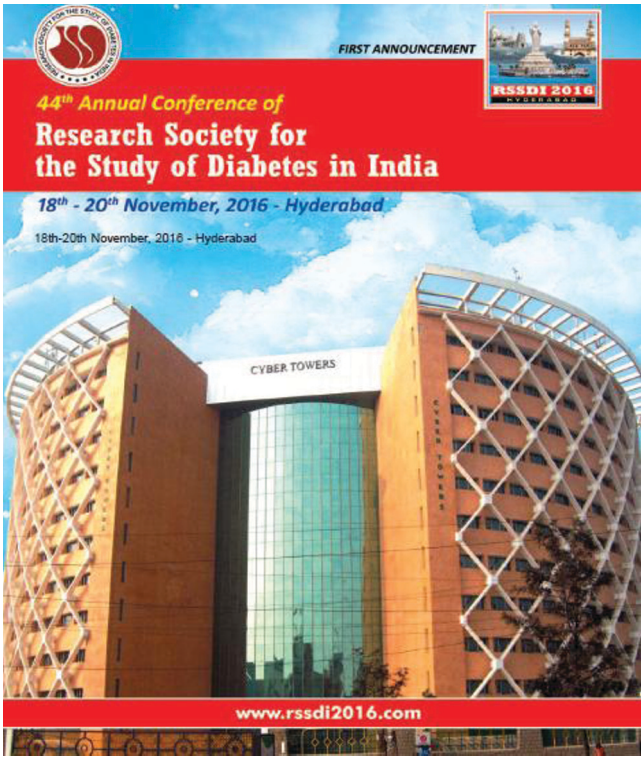
You name any thing in diabetes, this book has it. A few topics which are generally not paid much attention – like complexity of Insulin resistance, the criteria applicable in our country for metabolic syndrome, care of elderly diabetic, musculo-skeletal manifestation in diabetes are well covered. Malnutrition modulated Diabetes Mellitus and late onset of auto immune diabetes (LADA) as seen in our country is dealt with in detail.

The flow chart on management of diabetic keto-acidosis is useful and should be available in all ICU (Intensive Care Unit). The colour pictures of retinopathy and foot lesions are well presented. The usefulness of alternate therapy available in the country is extensively discussed. The Appendix is retained and gives a lot of information applicable to Indian subjects like BMI, waist circumference and laboratory values both in SI units and conventional units. The Index has reached perfection. Some controversial issues are mentioned in individual chapters but I wish an exclusive chapter was dedicated to controversies like classification of LADA and early use of insulin in these patients, need for revising the diagnostic plasma glucose values both in non-pregnant and pregnant diabetic, use of insulin in Type 2 diabetes at the time of detection to overcome the gluco and lipo-toxicity, safety of use of long acting insulin analogs during pregnancy, use of human insulin vis-à-vis insulin analogs, safety of DPP4 inhibitors, SGLT2 inhibitors and other new oral hypoglycemic molecules. Use of quantity and type of fat in the diet, role of low glycemic index diet in the management of diabetes etc.,

This book is a must for anybody who practices and teaches diabetes and students. The availability of this excellent text book has made western text books irrelevant to our country. The Novel feature of this book is mentioning the chapter number on the right edge of each page but single volume covering so many topics is bulky and heavy. I wish it was brought out in two volumes.

Prof. (DR.) C. MUNICHOODAPPA
Bengaluru

Invitation to the RSSDI, 2016 Conference



Welcome to RSSDI-2016,

Dear colleagues,
On behalf of the Organizing Committee of RSSDI 2016 we have great pleasure in welcoming you to the 44th Annual Scientific meeting of the Research Society of Study of Diabetes in India to be held in Hyderabad during 18 -20 November 2016. The RSSDI as you all know has grown to become the largest scientific body of professionals involved in managing diabetes in India and its annual meeting is the major event that all the members of RSSDI and doctors managing Diabetes in India look up to. We are privileged to host this event in Hyderabad. The Scientific program for RSSDI 2016 being crafted by Prof. SV Madhu, Chairman Scientific Committee will be designed to update our knowledge on various aspects of diabetes. The program will not only have Plenary lectures, guest lectures and symposia, but also workshops designed to provide hands-on training in several important practical areas of diabetes management. There would also be ample opportunities for young researchers to present their research work in the form of free papers. The venue for the conference will be the Hyderabad International Convention Centre which has state of art facilities for a conference of this mangnitude. Hyderabad the City of pearls is known for its rich history, food and its multi-lingual culture. It is known for its monuments like the Charminar, Golconda Fort, Falaknuma Palace and for artificially created lakes like the Hussain Sagar, Osman Sagar and the Himayat Sagar. It is also home to the top research institutions like National Institute of Nutrition and Center for Cellular & Molecular Biology and business school like Indian School of Business, IIT, IIIT, and BITS. Hyderabad is well connected by air / train with different parts of the country. We look forward to welcoming you for the RSSDI 2016. The Organizing Committee is working hard to ensure that RSSDI 2016 will be an academically and culturally enriching event for all of you.

Dr. Ch. Vasanth Kumar
Chairman, RSSDI-2016

Dr. Rakesh Sahay
Organising Secretary, RSSDI-2016