ORIGINAL ARTICLE

Prevalence of pre-diabetes and associated risk factors in an adult Omani population

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Abstract The Sultanate of Oman has experienced an epidemiological transition over the last 4 decades with rising tide of non-communicable disease such as type-2 diabetes. This study aims to estimate the prevalence of pre-diabetes and explore the associated demographic, clinical and biochemical risk factors among a semi-urban Omani population. A semi-urban satellite town, Bidbid, located about 30 km west of the capital, Muscat, was selected as the study setting. The targeted participants were Omani adults (18 to 60 years old) who had resided in Bidbid municipality for at least 6 months prior to enrollment in the study. Using multistage random sampling, 1,600 Bidbid residents were invited to participate in the study. The study protocol gathered data on the socio-demographic and clinical backgrounds of the participants. Participants' impaired glucose tolerance (IGT) impaired fasting glucose (IFG) and cholesterol and triglyceride levels were then measured. The study surveyed 1,313 individuals (490 men and 823 women) out of 1,600 who had been invited to participate. The participation rate was higher among women than men (91.5% compared to 54.3%). A total of 459 individuals (35% of participants) were diagnosed as pre-diabetic by either the IGT or IFG test; 121 (9%) were pre-diabetic by virtue of both measurements. Male gender, advanced age and obesity were each independently associated with higher prevalence of pre-diabetes. Increased prevalence of pre-diabetes also correlated with the indices of hypercholesterolemia and dyslipidaemia. Pre-diabetes is a substantial health problem in Oman that may present a significant challenge to the national healthcare system in the near future. Customized interventions targeting groups with high risk of pre-diabetes, especially men, the elderly and the obese, are urgently needed.

Keywords Diabetes · Pre-diabetes · Oman · Prevalence · Survey

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Abbreviations

BMI	Body mass index
CEA	Census enumeration area
FPG	Fasting plasma glucose
HDL	High-density lipoprotein
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LDL	Low-density lipoprotein

Introduction

Diabetes mellitus has become a global pandemic and is generating overwhelming costs and burdens upon patients as well as health care providers. Its pathological complications are associated with increased mortality and morbidity [1]. Currently, the World Health Organization (WHO) estimates that more than 180 million people worldwide have diabetes; this number is likely to exceed 360 million by the year 2030 [2]. Gaining an understanding of the causes of diabetes and its pathological processes is essential to the current campaign to quell the rising tide of diabetes [3].

The defining diagnostic feature of diabetes is an abnormal glucose metabolism, categorized as "pre-diabetes" in its early stage [4]. An individual is considered to be pre-diabetic if he/she has a blood glucose level that is above normal but below the diagnostic threshold for diabetes mellitus [5]. There are two diagnostic tests for pre-diabetes: the indices of "impaired glucose tolerance (IGT)" and "impaired fasting glucose (IFG)." [5] According to Bertram & Vos [6], these two indices, though mutually exclusive, each indicates an increased risk of type 2 diabetes. Pre-diabetes produces no symptoms but it is a major risk factor for developing type-2 diabetes mellitus and its sequel, which include heart disease, stroke, and retinopathy [7–11]. It has been estimated that a pre-diabetic person is 5 to 15 times more likely to develop type-2 diabetes mellitus compared to a person with normal blood glucose levels [12, 13].

There is growing evidence that lifestyle modifications are highly effective in delaying the onset of pre-diabetes or progression from pre-diabetes to type-2 diabetes mellitus [6]. A variety of clinical trials have shown that preventive programs resulting in at least moderate lifestyle modifications can delay the onset of diabetes mellitus by an average of 11 years and reduce the occurrence of new cases of diabetes by 20% [14, 15]. There is an urgent need to chart out the risk factors leading to diabetes in order to facilitate the development of additional mechanisms to cope with the diabetes emergency. Previous research in the region has focused solely on clinical populations showing a fully-expressed diabetic pathology [16–18], with a few exceptions [19]. Studies of pre-diabetic populations are needed to shed light on risk factors in order to design effective preventive interventions. It is well known that the cardinal symptoms of diabetes, such as polyuria, polydipsia and polyphagia, may not be subjectively noted until some of the intransigent and refractory complications of diabetes emerge [20]. Prevention of diabetes prior to onset is likely to be the most fruitful method of mitigating some of the well-known adverse consequences of diabetes.

Oman presents a particularly suitable environment for research into pre-diabetes. Recent epidemiological studies in Oman have indicated that the country is already seeing the effects of this emerging public health problem [18, 21–23]. Previous preliminary studies have suggested that abnormal glucose metabolism is common in the Omani population, with 36% of adults having all the hallmarks of pre-diabetes [24]. As a high-income country with a well-developed health care infrastructure, screening and diagnostic tools are readily available in primary health care centers nationwide [25]. This study aims to determine the prevalence of pre-diabetes among a semi-urban Omani population and to ascertain the demographic, clinical and biochemical risk factors associated with pre-diabetes.

Methods

The study took place in Bidbid, a city with approximately 25,000 inhabitants located about 30 km west of the capital, Muscat. The target population was Omani adults (18 to 60 years old) who had lived in the Bidbid municipality for at least 6 months prior to enrollment in the study. The following exclusion criteria were used: (1) diabetics who were taking medication or insulin for the disease; (2) diabetics on no medication whose fasting plasma glucose was greater than 7.0 mmol/L; (3) pregnant women or mothers within a 3 month post-partum period; and (4) subjects with conditions that were likely to interfere with research procedures, e.g. inability to communicate with staff or severe illnesses.

A total of 1,600 participants were estimated to be an adequate sample of the underlying study population. This sample size was determined based on the estimated national prevalence of glucose intolerance (16%) [24], a non-response rate of 10% of participants, an error margin of 15% on each side of the 95% confidence intervals for any prevalence estimate and a design effect of 1.5.

Selection was performed by a two-stage random cluster-sampling. In the first stage, a cluster was defined as one Census Enumeration Area (CEA), which consists of 100 households as defined by the Oman Ministry of National Economy. Out of the 100 CEAs in Bidbid, 20

were randomly selected using random number allocations in the Statistical Package for Social Sciences (SPSS) software. A sampling frame comprising 6,150 subjects was obtained by conducting a census among the 20 randomly-selected CEAs prior to the cross-sectional study. The name, family name, gender, age, household, and locality of all eligible subjects were recorded on field maps. In the second stage of sampling, 1,600 subjects were randomly selected from the sampling frame using computer generated random numbers.

One week before the screening, a research assistant visited the eligible subjects at home to deliver a personalized invitation card. Eligible subjects who were not at home were revisited twice before being excluded, and participants who failed to attend the initial interview were telephoned twice before being replaced. Enrolled participants were later instructed regarding how to prepare themselves for the study [26].

Enrolled subjects were interviewed by trained research assistants in accordance with a pre-tested structured questionnaire addressing their demographic characteristics, medical condition, family history, and dietary and exercise habits. 'Regular physical activity' was defined as at least half an hour of aerobic activity on at least 3 days each week [27]. 'Smokers' were identified if the participant has regularly and consistently consumed number of cigarettes as well as other tobacco products (e.g. shisha) during the 3 months as described elsewhere [28].

Anthropometric and laboratory measurements

The subjects' height and weight were measured using a fixed scale and a stadiometer while subjects were standing and wearing light clothing and no shoes. The increments of height and weight were 0.01 m and 0.1 kg respectively. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Overweight was defined as a BMI of 25 kg/m^2 or higher but less than 30 kg/m^2; obesity was defined as a BMI of 30 kg/m^2 or more.

Blood glucose was measured both after fasting and then 2 h after ingesting 5 g of glucose. A fasting plasma glucose (FPG) of less than 5.6 mmol (100 mg) was the baseline reference value. Isolated IFG was diagnosed upon finding a FPG between 5.6 and 7.0 mmol/L (126 mg/dl), and isolated IGT was diagnosed given a serum glucose level 2 h post load between 7.8 mmol/L (140 mg/dl) and 11.0 mmol/L (200 mg/dl). Other laboratory measurements were quantified using standard protocols [29–31].

Cholesterol Gen. 2 reagent was used to measure serum cholesterol concentration by an enzymatic, colorimetric method using a Roche Cobas Integra 800 analyser. Cholesterol levels of less than 5.2 mmol/L, 5.2–6.2 mmol/L, and more than 6.2 mmol/L were defined as desirable, borderline and high respectively.

HDL-Cholesterol plus 2nd generation (HDL-C) reagent was used to measure subjects' serum/plasma HDL-Cholesterol concentration with a homogeneous enzymatic colorimetric method using a Roche Cobas Integra 800" analyser, satisfying the 1995 NCEP goal of 13% total analytical error. Reference ranges were defined by sex: for females, desirable was defined as more than 1.68 mmol/L, borderline-high as 1.15–1.68 mmol/L, and low as less than 1.15 mmol/L; for males, desirable was defined as more than 1.45 mmol/L, borderline-high as 0.9–1.45 mmol/L, and low as more than 0.9 mmol/L.

LDL-Cholesterol plus 2nd generation (LDL-C) reagent was used to measure LDL-cholesterol concentration in serum/plasma with a homogeneous enzymatic colorimetric method using a Roche Cobas Integra 800" analyzer. The reference ranges were optimal: less than 2.59 mmol/L, near-optimal: 2.59–3.34 mmol/L, borderline-high: 3.37–4.12 mmol/L, high: 4.14–4.89 mmol/L, and very high: more than 4.92 mmol/L.

Triglyceride (TRIGL) reagent was used to measure the participants' serum/plasma triglyceride concentration with an enzymatic colorimetric method (GPO/PAP) using glycerol phosphate oxidase and 4-aminophenazone using a Roche cobas integra 800 analyser. The reference range for the fasting sample was taken as 0.4–1.8 mmol/L. Triglyceride levels measured in excess of 4.0 mmol/L were reported as 'triglycerides >4.0 mmol/L' rather than specified.

Statistical analysis

The data collected was entered into Microsoft Access software and a common dataset was created. The dataset was then exported to the SPSS package (Version 15.0) in order to conduct descriptive analysis and to calculate frequencies. Multivariate logistic regression analysis was carried out to explore independent risk factors.

Results

Out of 1,600 invited subjects, 1,332 completed the questionnaire, giving an overall response rate of 83.3%. The response rate was much higher for women (91.5%) than men (54.3%). A total of 19 subjects were excluded from the analysis due to missing important outcome data. Thus the present analysis is based on a total of 1,313 subjects.

Table 1 shows the demographic background of all participants in the study by gender. The average age for all participants was 32 years with no significant difference between men and women (31.7 versus 32.0, P=0.701). There were significantly more divorced and widowed women than

Table 1 Sociodemographic characteristics of participants by sex

	Total (N=1,313) N (%)	Men (N=490) N (%)	Women (N=823) N (%)
Age			
≤25 years	485 (36.9)	185 (37.6)	299 (36.5)
25–45 years	610 (46.5)	227 (46.3)	384 (46.6)
>45 years	218 (16.6)	79 (16.1)	139 (16.9)
Marital status			
Single	456 (34.7)	195 (39.8)	261 (31.7)
Married	758 (57.5)	290 (59.0)	468 (57.0)
Widowed/divorced	99 (7.5)	6 (1.2)	93 (11.3)
Education			
Illiterate	388 (29.6)	75 (15.4)	313 (38.0)
Basic education	380 (28.9)	194 (39.4)	186 (22.7)
High school or above	545 (41.5)	221 (45.2)	323 (39.3)
Smoking history	172 (13.1)	72 (14.6)	100 (12.2)
Regular exercise	821 (62.5)	358 (72.8)	463 (56.4)
Body mass index			
<25	644 (49.0)	239 (48.6)	405 (49.3)
25–30	366 (27.8)	157 (32.1)	208 (25.3)
>30	304 (23.1)	95 (19.3)	209 (25.4)

men (11.3% versus 1.2%, P=0.001). Furthermore, the percentage of women with no education was significantly higher compared to men (38.0% versus 15.4%, P=0.001). Approximately 15% of the participants reported having smoked or being current smokers. More than 60% of the participants reported exercising regularly, including significantly more men than women (72.8% versus 56.4%, P=0.001); women were significantly more obese than men overall.

Table 2 shows the prevalence of pre-diabetes by selected socio-demographic and clinical characteristics. Out of the 1,313 participants, 459 (35%) were found to have either IFG or IGT, including 396 (30%) with isolated IFG, 184 (14%) with isolated IGT, and 121 (9%) with combined IFG and IGT. Compared to women, men had a higher overall prevalence of either IFG or IGT. Men were more likely to have IFG, while women were more likely to have isolated IGT. However, women were more likely to have combined IFG and IGT.

The prevalence of pre-diabetes defined by all indices tended to increase with age. A higher prevalence of pre-diabetes was found among married, divorced, and widowed people compared to those who had never married. With respect to education, the highest prevalence of pre-diabetes was found among those who had only lower level of education. The unemployed tended to have a higher prevalence of pre-diabetes than those who were currently employed. Increased prevalence was also observed among smokers as compared to non-smokers. A higher prevalence of pre-diabetes was also generally found among those with hypercholesterolemia and dyslipidaemia.

Table 3 shows the results of a multivariate logistic regression analysis of the association between pre-diabetes and selected socio-demographic and biochemical variables. Taking either IGT or IFG as the indicator of pre-diabetes, a statistically significant association was found with the following risk factors: male gender, age≥45 years, being widowed or divorced, higher than average BMI, high cholesterol, high TGD, high LDL, and low HDL.

After adjusting for other confounders, male gender was found to be associated with a 78% increase in the risk of pre-diabetes relative to female gender (OR=1.78; 95% CI 1.33, 2.89). Advanced age (45 years or older) was associated with a more than threefold increase in the risk of pre-diabetes compared to age younger than 45 years (OR=3.29; 95% CI 1.40, 9.45). A BMI of 30 or above was associated with a 3.69 increase in the risk of pre-diabetes compared to normal BMI (OR=3.69; 95% CI 2.61, 6.38).

Taking isolated IFG as an indicator, pre-diabetes was found to be significantly associated with the risk factors of male gender, advanced age, and high BMI. Increased prevalence was also observed in connection with the indices of hypercholesterolemia and dyslipidaemia, although these associations were not statistically significant. Taking isolated IGT as an indicator, pre-diabetes was found to be significantly associated with advanced age and advanced BMI. As combined indicators of pre-diabetes, IFG and IGT were found to be significantly

Table 2 Prevalence of pre-diabetes indicators by selected sociodemographic and clinical characteristics

	Study population (N)	IFG or IGT (N=459) N (%)	Isolated IFG (N=396) N (%)	Isolated IGT (N=184) N (%)	Combined IFG and IGT (N=121) N (%)
Gender					
Male	490	201 (41.0)	185 (37.8)	53 (10.8)	37 (7.6)
Female	823	258 (31.3)	211 (25.6)	131 (15.9)	84 (10.2)
Age group					
<20	126	39 (31.0)	38 (30.2)	10 (7.9)	9 (7.1)
20–29	564	138 (24.5)	114 (20.2)	52 (9.2)	28 (5.0)
30–39	308	117 (38.0)	106 (34.4)	45 (14.6)	34 (11.0)
40–49	164	93 (56.7)	80 (48.8)	45 (27.4)	32 (19.5)
≥50	137	72 (52.6)	58 (42.3)	32 (23.4)	18 (13.1)
Marital status					
Single	456	114 (25.0)	98 (21.5)	44 (9.6)	28 (6.1)
Married	758	290 (38.3)	250 (33.0)	113 (14.9)	73 (9.6)
Divorced/widowed	99	39 (39.4)	34 (34.3)	15 (15.2)	11 (11.1)
Education level					
Illiterate	388	129 (33.2)	100 (25.8)	71 (18.3)	42 (10.8)
Basic education	380	231 (60.8)	209 (55.0)	74 (19.5)	52 (13.7)
Finished high school	545	55 (10.1)	47 (8.6)	19 (3.5)	11 (2.0)
Employment					
Unemployed	718	301 (41.9)	256 (35.7)	121 (16.9)	76 (10.6)
Employed	595	158 (26.6)	140 (23.5)	63 (10.6)	45 (7.6)
Body mass index categories					
<25	644	173 (26.9)	147 (22.8)	64 (9.9)	38 (5.9)
25–30	366	144 (39.3)	125 (34.2)	52 (14.2)	33 (9.0)
>30	304	142 (46.7)	124 (40.8)	68 (22.4)	50 (16.4)
Smoking status					
Non-smoker	1,198	401 (33.5)	346 (28.9)	164 (13.7)	109 (9.1)
Smoker	115	58 (50.4)	50 (43.5)	20 (17.4)	12 (10.4)
Cholesterol abnormalities					
High cholesterol	170	93 (54.7)	83 (48.8)	40 (23.5)	30 (17.6)
High TGD	48	30 (62.5)	27 (56.3)	17 (35.4)	14 (29.2)
Low HDL	138	65 (47.1)	58 (42.0)	25 (18.1)	18 (13.0)
High LDL	115	63 (54.8)	54 (47.0)	27 (23.5)	18 (15.7)
High VLDL	122	72 (59.0)	65 (53.3)	28 (23.0)	21 (17.2)

associated with advanced age, advanced BMI, and low HDL (Table 3).

Discussion

Diabetes is increasingly becoming a global challenge. In many parts of the world, the social, medical and economic ramifications of diabetes account for 80% of the total burden of chronic diseases [32, 33], and Oman is no exception [24]. There is a rising awareness that, unless concerted efforts are made, type-2 diabetes will likely become one of the world's fastest growing public health problems, with 366 million individuals anticipated to satisfy its diagnostic criteria by 2030 [34]. One clinical survey suggested that 4.8 of every 1,000 Omanis are diabetic [35]. In a community survey, the prevalence of type-2 diabetes in Oman was estimated at 12% for peopled in their 20s [21, 36]. As is often the case, prevention is preferable to symptomatic treatment, although type-2 diabetes can also be cured with certain lifestyle changes.

The present study aimed to estimate the prevalence of pre-diabetes and associated risk factors in a sample of the adult Omani population. This examination of associated risk factors was undertaken to encourage the development of preventive measures along with related health education programs.

Table 3 Adjusted odds ratios (95% CI) of association between pre-diabetes indicators and selected demographic and biochemical variables

Characteristic	IGT or IFG OR (95% CI)	Isolated IFG OR (95% CI)	Isolated IGT only OR (95% CI)	Combined IFG and IGT OR (95% CI)
Male gender	1.78 (1.33, 2.89)[a]	1.66 (1.25–2.21)[a]	0.69 (0.46–1.03)	1.30 (0.80–2.11)
Age 25–45 years	1.31 (0.09, 4.75)	1.36 (0.93–1.99)	2.15 (1.23–3.75)[a]	2.74 (1.38–5.43)[a]
Age≥45 years	3.29 (1.40, 9.45)[a]	2.23 (1.27–3.92)[a]	3.64 (1.74–7.64)[a]	3.55 (1.45–8.70)[a]
Married	0.78 (0.55, 1.39)	1.05 (0.71–1.55)	0.54 (0.31–0.94)[a]	0.49 (0.23–0.95)[a]
Widowed/divorced	1.83 (1.36, 3.35)[a]	1.71 (0.94–3.11)	0.79 (0.38–1.69)	0.89 (0.37–2.16)
Basic education	0.98 (0.70, 1.73)	0.94 (0.63–1.42)	0.59 (0.35–1.01)	0.67 (0.36–1.24)
Finished high school	0.64 (0.35, 1.41)	0.72 (0.48–1.08)	0.66 (0.392–1.12)	0.69 (0.37–1.28)
Body mass index 25–30	1.71 (1.16, 3.10)[a]	1.62 (1.19–2.20)[a]	1.40 (0.91–2.14)	1.50 (0.89–2.52)
Body mass index≥30	3.69 (2.61, 6.38)[a]	2.43 (1.75–3.37)[a]	2.57 (1.68–3.92)[a]	3.03 (1.83–5.00)[a]
High cholesterol	1.74 (1.13, 3.34)[a]	1.16 (0.82–1.64)	1.18 (0.74–1.87)	1.57 (0.89–2.77)
High triglycerides	1.64 (1.10, 3.15)[a]	1.59 (0.95–2.66)	1.26 (0.68–2.33)	1.23 (0.63–2.41)
High LDL	1.45 (1.04, 2.55)[a]	1.22 (0.87–1.71)	1.26 (0.78–2.02)	1.04 (0.58–1.87)
Low HDL	1.82 (1.25, 3.21)[a]	1.24 (0.96–1.68)	1.34 (0.90–2.01)	1.66 (1.03–2.67)[a]

[a] Statistically significant at 0.05

Pre-diabetes occurs before the full-blown onset of diabetes. Emerging evidence suggests that, once identified, people in a pre-diabetic state could be given health education so that progression of the disease itself can be arrested or reversed. Anecdotal and clinical observations have long suggested that there are large numbers of pre-diabetic Omanis. The Ministry of Health has accordingly instituted a nationwide screening program to detect pre-diabetes, targeting middle-aged people in particular [36, 37].

This study ascertained a high prevalence of pre-diabetes in Oman, consonant with the trend in neighboring countries such as Saudi Arabia, the United Arab Emirates, Kuwait, Qatar and Bahrain [38–40]. The common denominators among these countries are high income, the emergence of so-called 'diseases of affluence', and the latter's increasing impact on public health. Predictably, the prevalence of nutrition-related non-communicable diseases such as diabetes has been reported to be "very high" throughout the region [41, 42]. High rates of obesity and metabolic syndromes have likely contributed to an increased prevalence of glucose tolerance abnormalities in the region [43]. Since it has been established that a reversible pre-diabetic state which is amenable to treatment precedes the full onset of diabetes, crucial lifestyle interventions and modifications should be widely advocated to address this rising trend. Charting additional socio-demographic correlates would be further illuminating in this regard.

To assess potential risk factors, a logistic regression model was employed to elucidate the association between pre-diabetes and certain socio-demographic and physiological parameters. Variables such as male gender, age group (≥ 45), and indicators of psychosocial stresses including marital status, BMI and dyslipidaemia indices were found to be strongly associated with a pre-diabetic state. Similar risk factors have been identified for other populations in the region [44, 45]. As diabetes is often considered to be a disease of affluence [46], health education could make a substantial difference in promoting the lifestyle modifications that are the most important tool to preventing its onset during the pre-diabetic stage among the many pre-diabetics who have the means to adopt them [36]. Moreover, health education can be effective in emending the risk factors to pre-diabetes.

There are several caveats to generalizing the present findings. First, a cross-sectional study design does not necessarily support causal inferences between risk factors and the pre-diabetes state. A longitudinal study would therefore be more relevant. Second, the response rate was higher in female; there were approximately 50% more females than males in the study. A community study like this one might naturally attract more females considering that in Arab/Islamic societies as in Oman, females often remain in the domestic sphere while males tend to work outside the home. This cultural factor could operate as a selection bias. Third, it is possible that the Bidbid area is not a representative prototype of the diverse population of Oman. However, Bidbid is a typical satellite town adjacent to Muscat, the nation's capital; during the recent and rapid urbanization of Oman, towns like Bidbid have attracted many residents from other parts of Oman, making it more likely that Bidbid and similar towns increasingly reflect the ethnic and cultural mosaic that is modern Omani society. The complexity of ongoing demographic shifts means that a nationwide study is imperative to avoid uncertainty as to the representativeness of local or regional samples. Hypertension is a well-known risk factor for diabetes. Many

studies have suggested a temporal relationship between diabetes and hypertension [47]. Although participants' blood pressure could not be measured in the present study for logistical reasons, including hypertension as a variable is highly recommended for future studies. Finally, the omission of waist circumference measurements and data regarding participants' occupation in the present analysis could also affect the strength and generalizability of the results. Future studies should consider these salient factors to enhance our understanding of their role in contributing to pre-diabetes.

Despite the above-mentioned caveats, to our knowledge this is the first study in the country that explores the magnitude of the pre-diabetes problem and its correlation with risk factors of the pre-diabetes state. The present data suggest that one-third of the Omani population may have some form of pre-diabetes. Considering that men, the elderly and the obese are at the highest risk of having pre-diabetes, systematic healthcare interventions targeting these groups are recommended to reduce the burden of the disease. Additional studies employing social and behavioral paradigms are needed so that interventions with direct effects on relevant social and behavioral issues can be designed and implemented before the diabetes problem further increases in its scope and severity.

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Conflicts of interest None.

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ORIGINAL ARTICLE

Mosaic pancreas or type 3 diabetes: how do we define it?

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Abstract To document the existence and clinical characteristics of probands from families with multigenerational inheritance of early onset type 2 diabetes mellitus in Jamaica. Three probands from large families with multigenerational inheritance of early onset type 2 diabetes mellitus in at least three generations were detected at the University Hospital of the West Indies, Jamaica during a screening process for patients with MODY. Clinical, metabolic and genetic assessments were undertaken to ascertain the profile of the diabetes present in the three families. The three probands: patients 1, 2 and 3 were from families with history of ≥3 generations of early onset type 2 diabetes mellitus. All were diagnosed before age 25 years. The probands had varying metabolic profiles at the onset of diabetes ranging from decreased insulinaemia to hyperinsulinaemia (4.7 mU/L, 15.6 mU/L, 38.6 mU/L). The HbA_{1c} ranged from 12.1 to 18.4%. Two of the probands were of normal weight, the other obese (30.7 kg/m^2). All probands had insulin resistance. Sequence variants in MODY 1–6 genes were absent in the probands and family members. Islet cell antibodies (ICA) were absent in two patients and the families of all three patients. However the third patient had a positive titre for the ICA antibodies. The clinical patterns of the diabetes seen in the three Jamaican families are difficult to include in a single type of diabetes mellitus. It is proposed to name this diabetes process Mosaic Pancreas or type 3 diabetes.

Keywords Mosaic · Type 3 diabetes · Multigenerational · Insulin resistance

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Introduction

In the Americas, the number of people with diabetes mellitus was estimated at 35 million in 2000 and is expected to increase to 64 million by 2025 [1]. Type 2 diabetes mellitus is one of the major health and socio-economic problems worldwide. In Jamaica the prevalence of diabetes among persons 25–74 years old is estimated to be 12% to 16% [2–4], of which a third is unrecognized [3,

4]. Ten to fifteen percent of patients with diabetes mellitus have the classical immune mediated form of diabetes, type 1A. Classically this diabetes occurs in children and young adults. Other types of diabetes in the young include early onset type 2 diabetes and, maturity-onset diabetes of the young (MODY) [5]. With the increase in obesity in the world, childhood-onset type 2 diabetes with insulin resistance is becoming more common [5]. An increasing proportion of Non-Caucasians have been diagnosed with atypical diabetes. This diabetes is multi-faceted in which there may be insulin dependence and/or insulin resistance, ketosis resistance, onset of diabetes before age 35 years and family history [5–8].

Early-onset type 2 diabetes may simulate type 1 diabetes but runs a subsequent clinical course typical of type 2 diabetes [7, 8]. Early onset type 2 diabetes is characterized by a spectrum of β-cell dysfunction. The clinical presentation is influenced by the degree of β-cell function and insulin resistance. Oftentimes based on clinical presentation it is diagnosed as type 1 but subsequently designated as type 2, because of the lack of insulin dependence [8–10].

Rosenblom et al. described early onset type 2 diabetes as atypical diabetes mellitus (ADM) with acute onset at puberty, moderately low insulin secretion, autosomal dominant inheritance and absence of auto-antibodies [10].

Previously the World Health Organization recognized malnutrition-related diabetes (MRDM) as a type of diabetes that was distinct from type 1 or 2 diabetes mellitus. Malnutrition related diabetes (MRDM) consisted of two subtypes: a fibro-calculous pancreatic diabetes (FCPD) and a protein deficient pancreatic diabetes (PDPD). Insulin resistance was a feature of MRDM diabetes [11]. In Indonesia, Zuiderma classified a group of patients who had disseminated pancreatic calcification, severe malnutrition and muscle wasting and who were ketosis resistant with average age of onset of 31 years as being protein deficient pancreatic diabetes or Zuidema syndrome [12]. In addition, Ahren and Corrington had described a group of patients in Tanzania who had atypical diabetes mellitus. They required exogenous insulin intermittently yet they were ketosis resistant [13]. In a study done in India by Mohan et al., the authors reported severe insulin dependent diabetes that required large doses of insulin for stabilization but not resulting in ketoacidosis. These patients also had pancreatic calculi. The mean age of diagnosis was 25±1 years. Twenty five percent of patients had signs of malnutrition. Other patients had low body weight but were not malnourished. Less than 10% had first degree relatives with diabetes. Their C-peptide levels were intermediate, between that of insulin deficiency and insulin resistance [14].

In 1955 Hugh- Jones first classified atypical diabetes as J type in Jamaicans. Features of this diabetes included insulin resistance, lack of ketosis, poorly nourished, lean individuals with wasting of the muscle, age of onset of diabetes between 15–25 years. Thirty percent of these patients had a positive family history of diabetes [15]. In a later study, Morrison described a type of diabetes in Jamaicans which was characterized by severe hyperglycemia of acute onset during early adulthood. Moderate malnutrition was present. Patients had intermittent insulin resistance and intermittent dependence on insulin. He coined the name, phasic insulin dependent diabetes (PIDDM) and indicated that it was a malnutrition-related- diabetes with features of tropical pancreatic diabetes [7].

Recent research has revealed that a significant number of Jamaican adolescents and young adults are being diagnosed with type 2 diabetes, a disease once seen almost exclusively in middle-aged and elderly adults [16]. Based on the historical perspectives, the atypical presentation of diabetes[7, 15], and an increased in prevalence of diabetes in the young in Jamaicans [16] this study examined through specified probands early onset type 2 diabetes in multi-generations in three large Jamaican families.

Material and methods

The study was conducted in Jamaica at the University Hospital of the West Indies. Previously, 698 Jamaican pregnant females with a family history of diabetes occurring before age 35 years had been evaluated for the prevalence of gestational diabetes, the results of which has been previously published [17]. Three of these females belonged to large families with a family history of diabetes mellitus not requiring insulin therapy amongst its members even when diagnosed before the age of 25 years with diabetes. In addition, these families demonstrated multi-generational inheritance of the diabetes mellitus. The members of the three families were invited to participate in this study. Each participant was subjected to clinical, laboratory and genetic assessments.

The study was approved by the Faculty of Medical Sciences, University Hospital of the West Indies, Mona Ethics Committee and informed consent was obtained from the subjects after the nature of the study was explained to them.

Measurements

Height was measured to the nearest centimeter, and weight to the nearest 0.1 kg. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.

Laboratory assessments

Fasting blood samples were taken for glucose, HbA_{1C}, insulin and, C-peptide concentrations. Subjects without known diabetes mellitus were subjected to a 75 g, 2 h-oral glucose tolerance test according to the WHO (1999) criteria [18]. Diabetes mellitus was defined as a fasting plasma glucose ≥7.0 mmol/L, and a 2 h plasma glucose ≥ 11.1 mmol/L, or a previous diagnosis of diabetes with ongoing treatment with oral agents and/or insulin. Haemoglobin A_{1C} was assessed by an affinity chromatography method (Sigma Diagnostics). Islet cell antibodies (ICA) were determined by indirect immunofluorescence using
4 μm cryostat sections of rhesus monkey pancreas (Innova Diagnostics) as substrate. The manufacturer's instructions were followed when commercially prepared reagents were used. Insulin resistance and β-cell function were calculated using the Homeostasis Model Assessment (HOMA) [19]. This model was based on the assumption that a normal weight healthy subject aged<35 years has an insulin resistance of 1 and β-cell function of 100%.

Genetic analysis

The probands and two affected and two unaffected family members, were screened for sequence variants in the MODY genes by polymerase chain reaction single strand conformation polymorphism (PCR-SSCP) analysis [20].

Results

Patient 1

The mother of patient 1 had been diagnosed with gestational diabetes at age 23 years. Patient 1 had been diagnosed with diabetes mellitus at age 10 years when she was of normal weight. At the time of diagnosis, patient 1 had fasting plasma glucose of 18.2 mmol/L, postprandial plasma glucose of 25.4 mmol/L. The HbA_1c was 18.4%, the fasting serum insulin was 15.6 mU/L and the fasting serum C-peptide was 400 pmol/L. The β-cell function was 69% and insulin resistance was elevated (3.4). Patient 1, 10 years later has never had diabetic ketoacidosis although she has for periods as long as 3 months not taken any insulin. During the past 10 years she has lost and gained weight moving from lean to obese to lean again (Table 1). The maternal grandmother and maternal great-grandmother of patient 1 were also diagnosed with diabetes mellitus. The great-grandmother has been treated with insulin for 17 years. For about 7 years after diagnosis, the grandmother ignored her diabetes and occasionally took some alternative treatments involving decoction of bushes. However during the last 2 years, the grandmother has been prescribed insulin therapy. Sequence variants in MODY 1–6 genes were absent in the proband and family. Islet cell antibodies (ICA) were absent in the proband and family members.

Patient 2

Patent 2 was diagnosed with diabetes mellitus at age 24 years. She has been on insulin since diagnosis. At diagnosis her fasting plasma glucose was 16.2 mmol/L, 2 h postprandial plasma glucose 18.1 mmol/l, HbA_{1c} 13.6%, fasting serum insulin level 38.6 mU/l, fasting serum C-peptide 367 pmol/L, β cell function 150%, insulin resistance 4.5 and BMI 30.7 kg/m^2 (Table 1). Her mother was diagnosed with diabetes mellitus at age 32 years and has been on insulin since then. Laboratory assessments of the mother of patient 2, 20 years after revealed a fasting plasma glucose of 9. 5 mmol/L, 2-hour plasma glucose of 11.5 mmol/L, HbA_{1c} of 10.0%, a fasting serum insulin concentration of 12.1 mU/L, a fasting serum C-peptide of 1500 pmol/L and BMI of 30 kg/m^2. The sister of patient 2 was diagnosed with diabetes mellitus at age 28 years. Laboratory assessments of the sister, 4 years after the diagnosis had been made revealed a fasting plasma glucose of 15.6 mmol/L, a 2-hour plasma glucose of 25.5 mmol/L, a fasting serum insulin of 5.7 mU/L, a fasting C-peptide of 433 pmol/L and a BMI of 20.7 kg/m^2. Sequence variants in

Table 1 Details of the three patients with early onset diabe- tes in the study

Variables	Patient 1	Patient 2	Patient 3
Age at diagnosis (yrs)	10	24	24
Gender	F	F	F
Fasting plasma glucose concentration (mmol/L)	18.2	16.2	6.9
Plasma insulin (mU/L)	15.6	38.6	4.7
C-peptide concentration (pmol/L)	400	367	633
HBA_{1c} (%)	18.4	13.6	12.1
β-cell function (%)	69	150	45
Insulin resistance	3.4	4.5	2.9
Islet cell antibodies (ICA)	Negative	Negative	Positive

MODY 1–6 genes were absent in the proband and family. Islet cell antibodies (ICA) were absent in the family studied.

Patient 3

Patient 3 was diagnosed with gestational diabetes at age 24 years. Insulin therapy was prescribed during pregnancy. She did not comply and did not purchase the insulin. After pregnancy she was diagnosed with overt diabetes and oral hypoglycaemic agents were prescribed, she has since been intermittently compliant. Patient 3 has always been lean. She has had BMIs ranging from 18.5 to 23.6 kg/m^2. Routine blood glucose assessment 23 years after the diagnosis of GDM, at age 47 years revealed fasting plasma glucose concentration of 6.9 mmol/L, HbA_{1c} of 12.1%, fasting serum insulin of 4.7 mU/L, fasting C-peptide of
633 pmol/L, β-cell function of 45% and insulin resistance of 2.9 with a positive titer for ICA antibodies (Table 1). The mother of patient 3 was diagnosed with diabetes at age 42 years. All four of her sisters have diabetes and were diagnosed before age 25 years, one at age 17 years. Her mother's only brother was diagnosed at age 71 years. His BMI at the time of diagnosis was 20.9 kg/m^2. The fasting plasma glucose was 5.2 mmol/L, the 30 min, 60 min and 120 min postprandial plasma glucose concentrations were 13.9 mmol/L, 15.9 mmol/L and 9.5 mmol/L respectively. Fasting serum insulin level was 16 mU/L and fasting C-peptide 933 pmol/L at diagnosis. Two years earlier the values had been a fasting glucose of 3.8 mmol/L, a 1 h post challenge glucose of 5.8 mmol/L, a 2 h post challenge of 6.1 mmol/L, fasting serum insulin of 14 mU/L and fasting C-peptide of 1050 pmol/L. His BMI was 18.1 kg/m^2. He has never sought treatment for his diabetes. He feels he is well. He remains asymptomatic but he walks 4 miles daily. Patient's 3 has a son and a daughter who were diagnosed with diabetes at age 26 and 29 years respectively. Her daughter was the index pregnancy at diagnosis of GDM. Her daughter now 34 years has never taken insulin or oral hypoglycaemic agents. Patient 3 also has a brother and two sisters who were diagnosed with diabetes mellitus. Sequence variants in MODY 1–6 genes were absent in the proband and family members. Patient 3 had a positive titer for ICA however all other members of the family tested were negative.

Discussion

Diabetes mellitus with clinical characteristics that are difficult to classify in any one single type has been described previously in ethnic groups such as Native America, Hispanics and Chinese [9, 21]. These syndromes in which there is insulin resistance and the patients are ketosis resistant and have intermittent periods of normoglycemia have also been reported in African-American patients [21]. The World Health Organization and the American Diabetes Association have classified these types of diabetes mellitus as 'idiopathic type 1 diabetes, or type 1B [22, 23]. We have described in this study probands from families with multigenerational diabetes who were diagnosed with diabetes mellitus between the ages 10–24 years and who we have demonstrated have metabolic features, albeit atypical of type 2 diabetes.

Insulin resistance is a common feature of the diabetes presented in these subjects. Although insulin resistance has been implicated as one of the main determinants of type 2 diabetes [24], in early onset type 2 diabetes in Mexicans studies have reported that not all subjects with type 2 diabetes are insulin resistant [25]. The presence of markers of autoimmune destruction of the β cells [26, 27] was observed in only one of the probands and puzzlingly not in her family members. Although ICA was originally designated as a marker for type 1 diabetes [27, 28], adult with auto-antibodies to the islet cells have been previously described [29, 30]. The diabetes course is similar to that of type 2 but they are leaner and may require insulin therapy rather early. The is the so-called Latent Autoimmune Diabetes of Adult (LADA). The proband had normal C-peptide level but was ICA positive confounding the heterogeneity of the condition. The presence of this antibody, however may suggest the presence of an autoimmune polyglandular syndrome. Such patients should be screened for other organ specific autoimmune disorder [31].

The absence of the genes linked to MODY1-6 indicates that MODY1-6 is not the cause of the diabetes in this population. However, yet unidentified genes might be contributing to diabetes in the population. Multigenerational diabetes in these Jamaicans might imply the involvement of transmission of some genetic defects. The genetic pattern, the presence of insulin resistance, the impaired β-cell function, the absence of ICA except in one case, years after diagnosis of diabetes, the age of onset, the lack of insulin dependence for a few years present heterogeneity. The heterogeneity seen here does not fit the pattern of type 2 and clearly rules out type 1. Glycemic control was wholly deficient in these families yet many members survived without episodes of ketosis. Jamaica had previously described an atypical type of diabetes [7, 15].

In conclusion, Jamaican patients with multigenerational history of diabetes, features of type 2 diabetes but diagnosed between age 10–24 years is a clinically heterogenous group that does not fit in the classical picture of type 1 or 2 diabetes mellitus, Latent type 1 or 2 diabetes [29, 32]. The MODY 1–6 genes linked to Maturity Onset

Diabetes of the Young (MODY) have been ruled out as contributing to the diabetes, therefore we have classified them as type 3 diabetes mellitus, a diabetes that is clearly neither type 1 or 2.

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LETTER TO EDITOR

Disguised fasting for fasting blood glucose determination: how about its actual incidence?

Viroj Wiwanitkit

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Sir, fasting blood glucose determination is a widely used endocrine and metabolic testing in medical practice. This test is a routine investigation in follow-up evaluation of diabetes mellitus in many countries. The critical point for performing this test is a good patient preparation, fasting [1]. The problems arising out of improper fasting practices can be expected. Here, the author would like to draw attention to the problem of disguised fasting in actual clinical practice. The author verbally inquired into the fasting practice followed by 300 diabetic patients who visited to the diabetic clinic for follow-up. All cases got the fasting blood determination at a certified clinical pathology laboratory. Of interest, the author found that 12 patients (4%) reported that they did not perform correct fasting (three with no fasting and nine with incorrect fasting). Hence, a considerable rate of disguising of fasting sample can be seen. This can affect treatment strategy if the general practitioners do not make a note of this fact. The improper decision may be taken to adjust the antidiabetic regimen corresponding to the disguised high fasting blood glucose. In fact, although the laboratory has good quality system, it cannot correct the pre-pre analytical problem such as poor patient preparation [2]. Since the checking for fasting state is usually verbal, the disguising can be expected. Due to this reason, the actual rate of disguising might be higher than 4%. Some patients might also disguise to both laboratory and physician. The practice of using hemoglobin A1C for follow-up of diabetics, resolves such an issue completely [3].

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LETTER TO EDITOR

Simplified management of diabetic ketoacidosis with a novel formula

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Int J Diab Dev Ctries. 2011 ; 31 : 181

Dear Sir,

Diabetic ketoacidosis (DKA) is the endpoint of the metabolic disturbance resulting from insulin deficiency or resistance, and is the most common complication of type 1 diabetes mellitus (DM1). DKA is a potentially life-threatening condition that can cause irreversible damage and even death if managed perfunctorily [1].

Because of the severity of DKA, it is logical to prolong duration of treatment, although rapid restoration of fluid and/or lowering of blood osmolarity and acidity can predispose patients to brain edema, a dangerous condition with a high risk of morbidity and mortality [2].

There is currently a lack of consensus with regard to the duration of fluid therapy [3], but longer protocols are currently favored.

The most important facet of DKA treatment is the careful management of fluid and electrolytes. This is dependent upon a correct estimation of dehydration, proper calculation of fluid requirements and the appropriate replacement of serum electrolytes.

In children, serum sodium concentration is not reliable for determining extracellular fluid deficit because of the osmotic effect of hyperglycemia-induced dilutional hyponatremia and the low-sodium content of the elevated lipid fraction in the serum in DKA [4]. Lowering high osmolarities by more than 310 mosmol/L would be safer if fluid replacement is carried out with solutions with higher osmolarities (normal instead of half saline). Infusion of NS is stopped in all protocols as they do not permit NS to be infused for more than 10 h when blood glucose drops to less than 300 mg/dL.

It is typical for calculations of fluid deficit to be based on 10% dehydration, which is frequently an overestimate that does not appear to have clinical relevance [5]. Based on clinical reports, the degree of dehydration in a DKA patient can be estimated to be 5–10%; this estimation is safe in doubtful situation because it corrects 5% dehydration quickly and without complication (side effects of rapid correction are related to severe disturbances) and allows more severe cases to not go undetected. The current consensus on management of DKA in children and adolescents was developed by the European Society for Pediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society [3].

Pediatric patients are more vulnerable to inappropriate management of DKA; as such, the objective of this study was to create a formula to help health care practitioners to more easily calculate the fluid volume and rate of fluid administration in the treatment of DKA, and to more easily administer fluid replacement solutions.

According to the standard protocol accepted by most pediatric endocrinologists, for severe cases of DKA in which 10% dehydration is estimated, 36 h (or more) of treatment is the goal; severe cases are more frequent in developing countries [6].

Half of the fluid deficit is replaced in the first 12 h, and the remainder is replaced in the next 24 h [2].

In our new Formula Method (FM): In the resuscitation phase, 20 cc/kg NS is infused during 1st hour (same as Standard Method [SM]).

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In the 2nd phase, by using the FM, both the volume and rate of IV fluid administration can be calculated for every hour until complete improvement, as follows:

$$mL=h = 10 \quad Wt \quad \frac{Wt^2}{10}$$

Wt = Weight in kg

The FM result yields the NS volume requirement for next 10 h (compared with volumes of 1/2Maintenance +1/2 Deficits for 12 h, as described by the SM). For example, using the FM, a 20 kg patient would receive the following volume of NS:

$$10 \quad 20 \quad \frac{20^2}{10} = 160cc=h \text{ for } 10h; \text{ complete volume } 1600cc:$$

In the 3rd phase, 70% of the calculated volume from the 2nd phase is administered hourly for 24 h (compared with 1×Maintenance +1/2 Deficits for 24 h, as described in the SM). So, for a 20 kg child:

$$160 \quad 70\% \approx 110cc=h \text{ for } 24h; \text{ complete volume } 2650cc:$$

Total administered fluids would be 4650 cc (equal to that in SM).

This formula makes it easy for both physicians and nurses to control the regimen. For example:

1. Serum NS (+KCl) 160 cc/h, 1 pm to 11 pm.
2. Serum NS (+KCl) 110 cc/h, 11 pm onwards for 24 h
3. Change saline to Dextrose 5%(+NaCl & KCl) 160 cc/h, or 110 cc/h if blood glucose (BG) reaches 300 mg/dL in the 1st 12 h, or the last 24 h, respectively.

A check of BG every two hours enables nurses to follow each stage of our protocol using just two types of previously made i.v. fluids (NS or dextrose-containing NS) and the predetermined infusion rate (160 or 110 cc/h). As with all protocols, regular visits should be made by the physician to assess effectiveness of treatment and possible complications, and to reassess hydration so that treatment might be continued or discontinued, based on the physician's judgment.

In our centre, we use NS when BG is higher than 300 mg/dL, then change to a dextrose-containing solution, with dextrose concentration dependent upon BG (5% for BG ≅ 200–300 mg/dL; 7.5% for BS ≅ 100–200 mg/dL and 10% if BS drops to less than 100 mg/dL unexpectedly). A volume of 40 mEq/L KCl is added to all administered fluids, with as much as 60 mEq/L NaCl added to the dextrose solutions. We also infuse insulin at a dose as high as 0.1u/kg/h when BG is higher than 200 mg/dL; the insulin dose is reduced to 0.05u/kg/h if the BG decreases to less than 200 mg/dl.

In less severe cases of DKA, treatment can be stopped earlier, according to the physician's judgment. In the rare situations where more severe acidosis and dehydration are observed, the treatment can continue up to 48 h; however, in the case of persistent acidosis the presence of infection must be considered.

Table 1 compares total volumes and rates of infusion for specific patient weights, as calculated using either the FM or SM.

Some protocols treated patients for DKA for 24 h when dehydration was estimated at 8.5% [7]. In these studies, the time is modified according to clinical judgment and response to therapy. Protocols in which treatment is prolonged are now prevalent; as such, the author has made the formula described here compatible with these protocols.

Utilization of the SM may lead to dangerous mistakes, especially in the calculation of total requirements, installation and regulation of infusion in the determined time, and preservation of infusion rate when nurses are ordered to change solutions to dextrose-containing fluids.

Because this formula clearly determines hourly volume administration over a total of 36 h of treatment, it omits the need to recalculate at the time of infusion fluid change. A positive aspect of this method is that it provides for stoppage or continuation of the protocol according to clinical response or reassessment of the degree of patient dehydration. This method could eliminate the aforementioned problems with the SM while helping paramedics to manage the treatment of DKAs of different severity. Compared to rapid protocols, our method could theoretically decrease the risk of brain edema. This new formula method has been utilized at this institution for more than 150 cases of DKA without any problem.

While research centres and referral hospitals that have available endocrinologists, registrars, and nurses with expertise in DKA management are not expected to alter their protocols to utilize the FM, non-referral hospitals, emergency centres (before referral), and private centres managed by pediatricians and less experienced nurses may benefit from this easy and reliable method.

Table 1 Comparison of volume calculation and infusion rate in DKA patients with different weights, using FM and SM

Weight	method	1st hour	10–12 h[a]	24 h	Total Vol. (mL)
10 kg	SM	200	1000	1500	2700
	FM	200	900	1500	2600
20 kg	SM	400	1750	2500	4650
	FM	400	1600	2650	4650
30 kg	SM	600	2350	3200	6150
	FM	600	2100	3550	6250

[a] 10 h for FM and 12 h for SM

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Conflict of interest None declared.

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ORIGINAL ARTICLE

Multi imaging approach with low field MRA in diabetic foot ulcer: hospital based study

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Abstract The aim of study was to assess the usefulness of non-invasive imaging in patient of diabetic foot ulcer with low field MRA and determine the severity and extent of lower extremity arterial disease in diabetic patients with poor socio economic status. The present study is based on 38 patients who were referred to Department of Radiology with complaint of non-healing ulcer of lower limb of more than 6 weeks duration. The patients were subjected to plain radiographs, Duplex scanning with color flow imaging and MR angiography (non contrast enhanced). The modalities were used to detect vascular calcifications, osteomyelitis, bone resorption, deformities, thickening of arteries, plaques, spectral waveforms, collaterals. MRA was used to assess subjective calibre of vessels and presence of stenosis. The patients were categorised according to age and a note of ulcer duration made. Grade of ulcer was determined (wagner's criteria) and note was made of severity of stenosis (cossman). Radiographs assessed bony destruction and vascular calcification. Doppler assessed degree of stenosis and vascularity. MRI gave a road map of vascular integrity. Integration of the tests provided a satisfactory diagnostic protocol to decide future prognosis and assessment of advancement of disease process. The data was subjected to calculation of mean, standard deviation and Pearson's chi square test. p value <0.05 was considered to be stastically significant. Majority of patients were males (80%) and highest incidence was noted in fourth-fifth decade (43.33%). 47.37% presented with grade III ulcer. Duplex scanning with color flow imaging was more accurate and sensitive in picking up calcified arteries, focal plaques, stenosed arteries and abnormal arterial waveforms. These patients had co-existent lower extremity arterial disease with moderate to severe stenosis (i.e. on comparision with peak systolic velocity (PSV), $p<0.05$. Ulcer grade had stastically significant correlation with severity of stenosis, ($p<0.05$). However MRA did not corroborate the same findings. It proved to be only 60% sensitive when compared to Duplex scanning (100%). Plain radiographs and color Doppler evaluation plays an indispensable role in imaging and evaluating patients with chronic non-healing ulcer of diabetic foot. MRA gives crucial information regarding parameters like vascularity, degree of stenosis, and extent of disease. Not all patients in our set up afford CTA or CEMRA followed by DSA or cost of stenting. When the diagnostic workup in our cases suggested poor prognosis or non salvageable vascular compromise the patient was counseled against further investigation and advised surgery. By using this approach many financially constrained patients are benefitted from unnecessary and costly diagnostic workup.

Keywords Diabetic foot · Color Doppler · MR angiography · Lower limb ulcer · Chronic wound

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Introduction

Diabetic foot ulcers have been a major source of morbidity and pose a significant burden on health care, especially among the elderly population [1]. Majority of ulcers have a vascular

etiology and require a comprehensive assessment of vessels for adequate management [2]. Invasive imaging modalities like contrast angiography(CA) remains gold standard [3]. However colour flow imaging have shown promise in the group of non-invasive imaging modalities [4, 5].

Usual diagnostic protocol starts with radiographs followed by complete Doppler assessment for lower limb vasculature and ruling out proximal aorto-iliac disease and good quality CTA/MRA as a pre-intervention work up before subjecting the patient to DSA and angioplasty/ stenting or surgical procedure.

Ulceration due to vascular causes is often multifactorial . Hypertension and atherosclerosis of peripheral vessels lead to arterial disease associated with ischemic ulcers [6, 7]. The pathological changes in diabetic foot ulcers are often a combination of vasculopathy, neuropathy and infection [8].

The aim of this study was to assess the usefulness of non invasive imaging modalities in patients of diabetic foot ulcer, to determine the severity and extent of lower extremity arterial disease in diabetic foot ulcer and to assess the favourable factors which can give a prognostic information or give clue for salvageable limb [9].

For this purpose the grading of ulcer was done (Wagner's) [10] and further assessment was made regarding degree of stenosis (peak systolic velocity: PSV: cossman) [11].

A vascular map of lower limb arteries was obtained using MRA. Further information like soft tissue abnormalities was assessed.

It was analysed whether MRA could be tailored in economically constrained group who could not afford the burden of expensive modalities like MRA with different sequences and use of contrast. Large number of patients who came to us were from very poor socio-economic section.

Subjects and methods

The patients were subjected to plain radiographs, Duplex scanning with color flow imaging and MR angiography (non contrast enhanced). The modalities were used to detect vascular calcifications, osteomyelitis, bone resorption, deformities, thickening of arteries, plaques, spectral waveforms, collaterals . MRA was used to assess subjective calibre of vessels and presence of stenosis.

As soon as the patients presented they were subjected to these modalities simultaneously, the same day.

The patients were categorised according to age and a note of ulcer duration made. Grade of ulcer was determined and a note was made of severity of stenosis using peak systolic velocity.

Plain radiographs (AP, Oblique and lateral views) were obtained with GE(Elpro)300 MA-LL at setting of 40–50 Kv and 8–10 mAs. A note of vascular calcification, osteomyelitis, deformities and soft tissue abnormality was made [12].

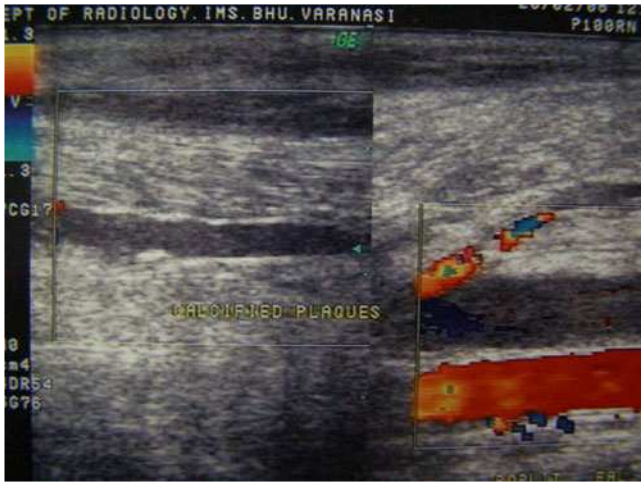

Fig. 1 Duplex scanning showing narrowing and calcified plaques

Colour Doppler was done in all patients starting right from femoral vessels to plantar arteries [13, 14]. We used GE Logiq 400, 5–10 MHz linear array transducer depending upon the patient.

A note was made of calcifications, plaques thickening of arteries, collaterals relative vascularity at ulcer area, grade of stenosis, if present and spectral waveforms along with measurement of PSV of feeding arteries.

MR angiography was performed with 0.2 T GE-SIGNA profile −I 7.7 version permanent magnet system with dedicated body coils. Lower limb vessels were visualised using FSPGR sequences. No contrast enhancement was used.

A note was made of morphology of vessels, stenotic segments and soft tissue and bony abnormalities [15, 16].

All patients were known diabetics (poorly controlled and defaulters) and had a ulcer of more than 6 weeks duration. Other causes of lower limb ulcers were not included (eg venous,sqamous cell carcinoma, or leprosy).

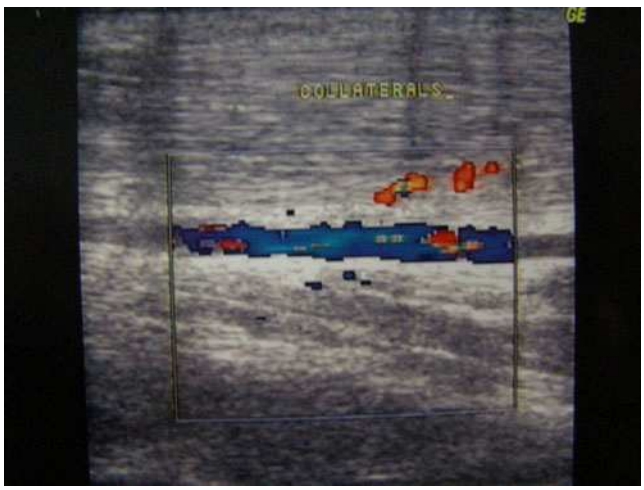

Fig. 2 Duplex scanning showing abnormal collaterals

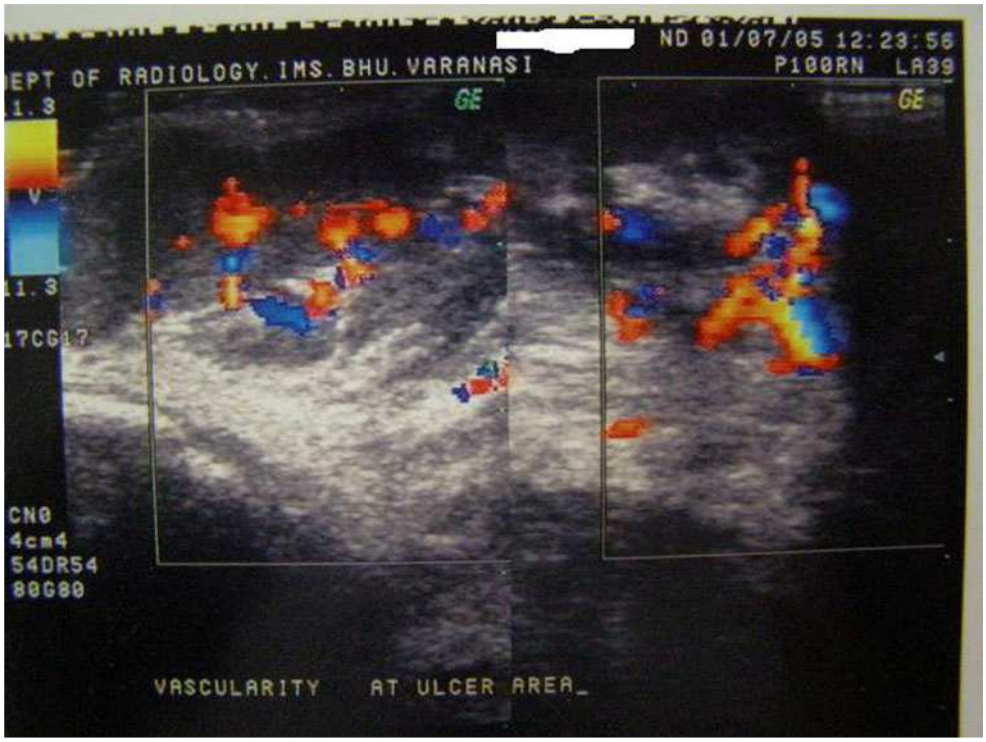

Fig. 3 Color flow imaging showing neovascularisation at ulcer area

The ulcer was graded using Wagner's criteria. Grade of ulcer and degree of stenosis was stastically compared. Co existent lower extremity arterial disease was compared with severity of stenosis. The findings of Doppler indices (PSV) and MRA was compared.

Results

Majority of patients were males (80%) and highest incidence was noted in fourth-fifth decade (43.33%). 47.37% presented with grade III ulcer. Frank vascular calcification were noted in 57.89% as picked by plain radiographs. Duplex scanning with color flow imaging was more accurate and sensitive in picking up calcified arteries, focal plaques, stenosed arteries and abnormal arterial waveforms. These patients had co-existent lower extremity arterial disease with moderate to severe stenosis (on comparison with PSV, $p<0.05$).

Ulcer grade had statistically significant correlation with severity of stenosis, ($p<0.05$). However MRA did not corroborate the same findings. It proved to be only 60% sensitive when compared to Duplex scanning (100%).

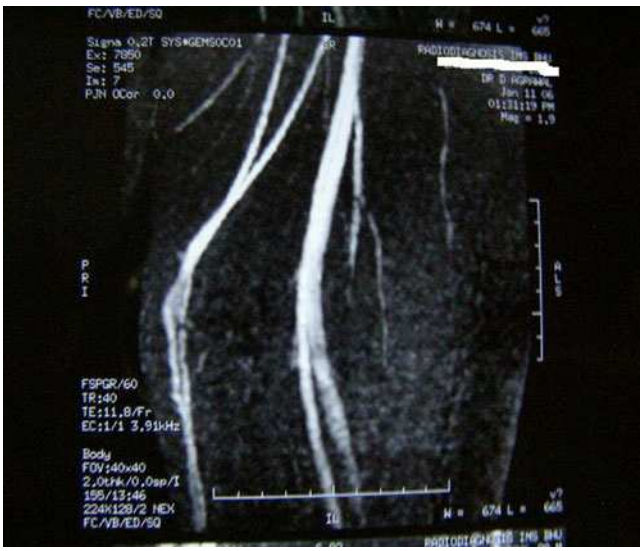

Fig. 4 Normal MR angiography of lower limb vessels

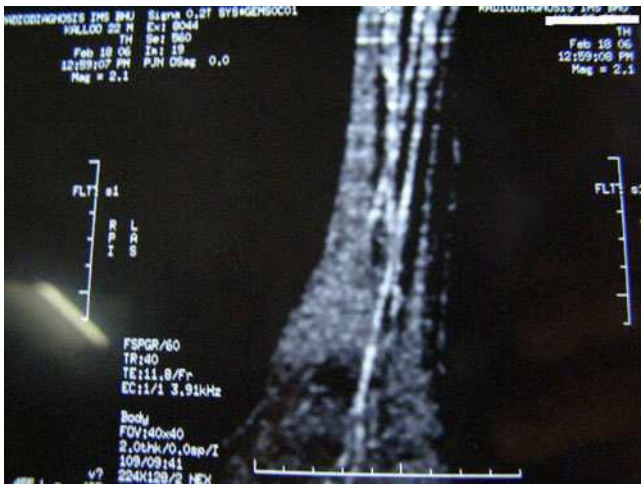

Fig. 5 MR angiography in Grade III ulcer showing severe stenosis of vessels

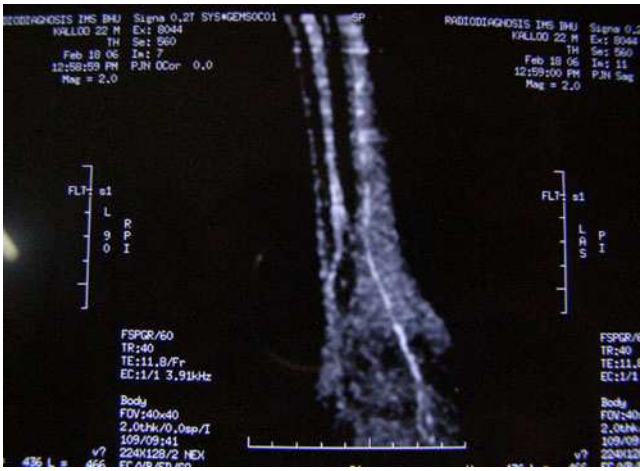

Fig. 6 MR angiography in Grade III ulcer showing severe stenosis of vessels

Discussion

In this study known diabetic patients with diabetic foot ulcer (n=38) were selected. Out of these 52.63% had positive plain radiographs (which included osteomyelitis, neuropathic foot and vascular calcification). Yuh and Baraniewski et al. [17] have reported a sensitivity and specificity of 75% each. The study also showed that 57.89% of diabetic foot ulcer had gross arterial calcification. This suggests lower extremity arterial disease in these patients. In the University Group Diabetes Program (UGDP) 16.1% reported as having arterial calcification [18]. In a study by Young, Adams et al. [19] medial arterial calcification was reported to be significantly higher in neuropathic diabetic patients with history of foot ulceration.

Duplex scanning was positive in all patients, giving vital information like degree of stenosis, abnormal waveforms, luminal narrowing and plaques (Fig. 1), collaterals (Fig. 2), neovascularisation (Fig. 3), varicosities, and abnormal venous channels.

Duplex scanning with color flow imaging was 100% sensitive in demonstrating these abnormalities. It also showed that with increasing severity of disease the frequency and number of collaterals increased with Duplex scanning.

In our study of 38 patients of diabetic foot ulcer, 47.3% presented with Grade III ulcer, 15.79% presented with Grade IV and 36.84% with Grade II ulcer. It was also found that the ulcer Grade of 19 patients with corresponded peak systolic velocity $p < 0.05$. This means that the grade of ulcer has a statistically significant relation with PSV. All patients of grade IV ulcer had peak systolic velocity >4m/s, that is stenosis of more than 75%.

In our study, MR angiography (Fig. 4) proved to be only 60% sensitive when compared to Doppler studies. A comparison done to evaluate sensitivity of MRA in patients of diabetic foot ulcer with severity of ulcer(grade) and corresponding stenosis, assessed by Doppler. Out of 38 patients 18 had grade III ulcer and only 4 of which showed abnormal MRA (Figs. 5 and 6) (66.67%) Fourteen patients presented with grade II ulcer and 2 of which showed (50%) abnormal MRA. All 6 patients of grade IV ulcer had abnormal MRA (100%). On comparing MRA of 38 patients with ulcer grade, no statistical significance was noted within the two variables ($p > 0.05$). On comparing MRA with peak systolic velocity, that is no statistical significance noted ($p > 0.05$).

Carpenter et al. [20] found that MRI was 94% accurate in evaluating lower extremity vessels when compared to conventional angiography. Owen and co-workers [21] found MRA to be more sensitive than conventional arteriography for visualising both run off vessels and arterial stenosis.

In our study, 38 patients were subjected to MR examination, with 0.2 Tesla magnetic field without any contrast enhancement.

The modality was able to pick up gross cases but unable to match color flow duplex scanning in other parameters like collaterals, early arterial stenosis, flow abnormalities and neoangiogenesis. In a multicenter trial [22] evaluating MRA and contrast angiography it was found that both are approximately equivalent in diagnostic accuracy. In another study by Ryan et al. [23] MRA had a sensitivity of 72% and specificity of 90% in differentiating high grade (>50%) versus low grade stenosis (<50%). In conclusion, MRA without contrast can serve as an effective screening procedure in diabetic foot ulcers.

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Int J Diab Dev Ctries

REVIEW ARTICLE

Periodontitis and diabetes—a complex relationship

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Abstract Periodontitis is a common problem in patients with diabetes. The interrelation between diabetes mellitus and inflammatory periodontal disease has been intensively studied for more than 50 years. The relationship between these 2 maladies appears bidirectional—insofar that the presence of one condition tends to promote the other, and that the meticulous management of either may assist treatment of the other. Inflammation plays an important role in this interrela- tion, orchestrating both the periodontal disease and diabetes mellitus pathogeny and complications. Conversely, periodon- tal infection can seriously impair metabolic control of some diabetic patients. Moreover, treatment of periodontal disease and reduction of oral signs of inflammation may have a beneficial effect on diabetes. This review examines the relationships that exist between periodontal diseases and diabetes mellitus, with a focus on potential common patho- physiologic pathways including those associated with inflam- mation, altered host responses and insulin resistance

Keywords Diabetes mellitus · Periodontal diseases · Periodontal therapy · Inflammation, insulin resistance, obesity

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Introduction

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia due to the defective secretion or activity of insulin. Diabetes is associated with an increased prevalence, extent and severity of gingivitis and periodontitis [1]. Numerous mechanisms have been elucidated to explain the impact of diabetes on the periodontium. While inflammation plays an obvious role in periodontal diseases, evidence in the medical literature also supports the role of inflammation as a major component in the pathogenesis of diabetes and diabetic complications [1].

The pathogenesis of periodontal disease is complex because it reflects a combination of the initiation and maintenance of the chronic inflammatory process by a diverse microbial flora and its numerous bacterial products [2]. The subsequent host-response to this infection mediates a complex cascade of tissue-destructive pathways [3]. Additional factors contributing to this multifaceted local disease process in the oral cavity include a number of systemic diseases, especially diabetes, that can exaggerate the host-response to the local microbial factors (for example, endotoxin), resulting in unusually destructive periodontal breakdown. In fact, aggressive periodontitis is recognized as the sixth compli-cation of diabetes according to Löe [4], who concluded that multiple epidemiologic studies have demonstrated that both type 1 and type 2 diabetes are predictors of periodontal disease when the systemic condition is poorly controlled.

Research suggests that, as an infectious process with a prominent inflammatory component, periodontal disease can adversely affect the metabolic control of diabetes. Conversely, treatment of periodontal disease and reduction of oral inflammation may have a salutory effect on the

diabetic condition, although evidence for this remains somewhat equivocal [1].

Diabetes associated factors that increase severity of periodontitis

Several altered host responses are associated with increased incidence and severity of periodontitis in diabetics. Studies have focused on the role of periodontal infection [5] and the microflora of dental plaque in people with diabetes [6] but these have not been conclusive. Thus, it is unclear if an altered microflora contributes to the greater incidence and severity of periodontal infection and destruction in subjects with diabetes. Increased calculus formation, reported in patients with diabetes, may be due to an increased concentration of serum calcium in both parotid and submandibular saliva of subjects with type 1 diabetes [7]. The gingival crevicular fluid, or GCF, of patients with diabetes may exhibit glucose levels twice those of other patients [8], and urea concentrations also may be increased [9]. These changes, as well as basement membrane thickening and glycosylation of hemoglobin should promote a unique environment, resulting in shifts of the microbial flora. However, studies have reported essentially no differences between people with or without diabetes [5, 9] suggesting that alterations in the host response to existing periodontal pathogens may be primarily responsible for the more aggressive periodontal destruction observed in patients with diabetes [10].

Factors influencing periodontal disease in diabetes

Vascular abnormalities [10, 11]

Early studies of the pathogenesis of periodontal disease in those with diabetes mellitus focused on basement membrane thickening and possible changes in the vasculature [10, 11]. These studies showed that degenerative vascular changes seen in other tissues and/or organs in patients with diabetes also occurred in the gingival tissues. It was postulated that vascular changes interfere with both the delivery of nutrients and the migration of leukocytes to the gingival tissues, resulting in decreased oxygen diffusion and elimination of metabolic waste, contributing to an increased severity of periodontitis and decreased wound healing capacity [10]. These vascular changes worsen with poor metabolic control and longer duration of the disease.

Nonenzymatic glycosylation [12–16]

A consequence of hyperglycemia in diabetes is the alteration of circulating and immobilized proteins. When proteins such as collagen, or lipids, are exposed to aldose sugars, they undergo nonenzymatic glycation and oxidation [12]. Initially, reversible alterations of the proteins exposed to sugars are seen, and eventually, complex molecular rearrangements may occur, resulting in the irreversible formation of altered proteins known as advanced glycation end products, or AGEs. Glucose-derived cross-links can contribute to reduced collagen solubility and turnover rate in humans with diabetes. Decreased solubility of gingival collagen in people with diabetes can be returned to near-normal levels by insulin treatment, presumably reflecting a reduction in glucose-derived cross-linking [13–15]. In addition, glycosylation of existing collagen at wound margins results in reduced solubility and delayed remodeling of the wound site [16]. Patients with diabetes have elevated levels of AGEs in their gingival tissues that may be associated with a state of enhanced oxidant stress, a potential mechanism for accelerated tissue injury. Elevated levels of both AGEs and cross-links between collagen molecules in palatal biopsy specimens of patients with type 1 diabetes have been correlated with HbA_{1c} levels.

AGEs act on target cells via their recognition of cell-surface polypeptide receptors. The best characterized binding site for AGEs is a member of the immunoglobulin superfamily now called the receptor for AGE, or RAGE. AGEs can interact with RAGEs on cells, such as macrophages, stimulating the production of enzymes (for example, matrix metalloproteinases, or MMPs), adhesion molecules, cytokines (for example, tumor necrosis factor-alpha, or TNF-α; interleukin-1 beta, or IL-1ß; and interleukin-6, or IL-6) as well as other mediators. This is of great interest because these mediators have been detected in the GCF of patients with poorly controlled diabetes. The overproduction of these products in response to the ligand-receptor interactions could help mediate and/or be in addition to alterations in collagen metabolism. AGE-modified proteins also are chemotactic for human monocytes. This could magnify the inflammatory response, delaying wound repair and inducing connective tissue damage and bone resorption.

Imbalances in lipid metabolism [17–19]

Diabetes complications that have been attributed primarily to hyperglycemia may also be caused by an imbalance in lipid metabolism characterized by increased serum levels of low-density lipoproteins, or LDL, triglycerides and fatty acids. Several researchers [17] correlated modifications in lipid metabolism with impaired function of monocytes and/or macrophages in successive in vitro and in vivo studies. Monocyte-derived macrophages exposed to serum lipids following endotoxin stimulation exhibit suppression in growth factor production, expressing an inflammatory

phenotype rather than a reparative or proliferative one. Several studies illustrate that hypertriglyceridemia induces an increased production of proinflammatory cytokines (TNF-α and IL-1ß) by monocytes. In addition, neutrophils exposed to triglycerides produce more IL-1ß and have altered chemotactic and phagocytic properties. Increased levels of pro-inflammatory cytokines have been observed not only in serum but also in GCF of hyperlipidemic subjects with type 2 diabetes. This disequilibrium between increased amounts of cytokines and reduced levels of growth factors with protective function may hinder repair ability and facilitate tissue breakdown [18, 19].

Altered collagen metabolism [2]

Several oral and extraoral diabetes-induced collagen abnormalities have been identified, including a large reduction in collagen synthesis and solubility in gingiva, skin and bone, and an even more profound increase in the urinary excretion of hydroxyproline, an amino acid marker of collagen and its breakdown fragments. These findings suggest that the disease increases the degradation of newly synthesized collagen in various connective tissues throughout the body.

Altered collagen metabolism may predispose people with diabetes not only to periodontal disease but also to other abnormalities of connective tissues, such as impaired wound healing. Elevations in GCF collagenase activity and decrease in gingival fibroblast collagen synthesis in patients with diabetes have been observed. The cellular source of the increased collagenase activity in the GCF of patients with type 1 diabetes was reported to be the neutrophil. However, the fibroblasts may contribute to the excess collagenase; recent studies indicate that under the appropriate circumstances, fibroblasts (and other cells such as chondroblasts) can be induced to secrete a neutrophil-type of collagenase (that is, MMP-8).

Neutrophil dysfunction [20–22]

Polymorphonuclear leukocyte, or PMN functions, such as chemotaxis and phagocytosis, have been shown to be decreased in patients with diabetes with periodontal disease. In addition, there is a strong correlation between PMN dysfunction and the severity of periodontal disease. Reports of a genetic predisposition in subjects with diabetes to the development of periodontal disease may be related to this reported PMN dysfunction. Defects other than PMN chemotaxis and reduced phagocytosis have been demonstrated in patients with diabetes mellitus, including impaired intra-cellular killing and impaired adherence. These defects in the body's immune system may predispose people with diabetes to periodontal disease.

Altered monocytic response [23]

Elevated levels of chemical mediators of inflammation known as prostanoids (prostaglandin E_2, or PGE_2) have been detected in the blood of patients with type 1 diabetes. In addition, GCF-PGE_2 levels are substantially higher in patients with diabetes. The significance of these elevated GCF-PGE_2 levels in patients with diabetes needs further evaluation by longitudinal studies to determine whether this abnormality predicts future unusually aggressive periodon- tal breakdown. It appears that increased local GCF-$PGE_{2,}$ responses observed in patients with diabetes are coincident with an upregulated monocytic phenotype. Thus, even low levels of endotoxin challenge within the periodontal pocket seem to induce high levels of PGE_2 secretion at these sites.

These clinical and basic science data have led to the proposition that therapies should include a systemic host-modulatory approach in addition to traditional techniques. This approach is in sharp contrast to approaches designed only to remove periodontal pathogens and address only the sites that are deemed to be active by rather crude diagnostic techniques, such as bleeding upon probing.

Mechanisms by which periodontal diseases may influence diabetes

Periodontal disease increases the risk of poor glycemic control and other diabetic complications [24–26], and studies have shown improved glycemic control with reduction in PD [27–29]Noteworthy improvements in glycemic control have been observed after treatment and reduction of PD [30, 31]. Periodontal diseases may induce or perpetuate an elevated systemic chronic inflammatory state [32] and may also result in increased insulin resistance and poor glycemic control [33, 34]. Treatment that reduces periodontal inflammation may restore insulin sensitivity, resulting in improved metabolic control. It is possible that PD may serve as initiators or propagators of insulin resistance in a way similar to obesity, thereby, aggravating glycemic control. A significant association between obesity and PD has been established [35].

Increased TNFα as a risk factor for periodontal disease [36]

Serum TNFα concentration is increased in obese type 2 diabetes patients. The increased TNFα, in turn may exacerbate pre-existing periodontal disease in various ways such as by stimulating fibroblsts to synthesize matrix degrading enzymes, and by stimulating osteoclasts to activate bone resorption. Thus increased circulating TNFα, in turn may be one of the mechanisms accounting for the more severe periodontal disease seen in obese patients.

TNFα-an important molecule in a 2-way relationship [36]

Increased circulating TNFα appears to exacerbate periodontal inflammation. This might be one of the reasons why obese patients are susceptible to more severe periodontal disease. Thus TNFα produced by adipose tissues, not only affects insulin sensitivity in obese patients but also influences periodontal inflammation. Exacerbated periodontal inflammation further upregulates circulating TNFα concentration by stimulating monocytes, which may have additive effects on insulin resistance by directly influencing target organs such as liver, muscle, and adipocytes and by directly enhancing the release of other insulin resistance molecules such as FFA from adipocytes. Thus, it was hypothesized that TNFα may be an important molecule accounting for the two-way relationship proposed by Grossi and Genco [34].

Influence of periodontal therapy on diabetic control

Periodontal diseases can have a significant impact on the metabolic state in diabetes. The presence of periodontitis increases the risk of worsening of glycemic control over time. Longitudinal studies have shown that that metabolic control of diabetes can be altered by controlling periodontal inflammation [37, 38]. Intervention trials during the past 15 years have resulted in varied metabolic responses in patients with diabetes. These trials often examined the effects of scaling and root planing on glycemic control, either alone or in combination with adjunctive systemic tetracycline therapy [1]. Tetracyclines usually are the antibiotic of choice because they decrease the production of matrix metalloproteinases such as collagenase, which often are elevated in patients with diabetes [39]. Some studies showed significant improvement in glycemic control after treatment [29, 30], while others showed no significant improvement in glycemic control despite improvements in patients' periodontal health [28, 40]. These conflicting study results make it difficult to determine the clinical applicability of the data. Thus, changes in glycemic control, or lack thereof, may be related to factors other than changes in periodontal inflammation. A systematic review and meta analysis suggests that periodontal treatment leads to an improvement of glycemic control in type 2 diabetic patients for at least 3 months [41]. Further research is required to determine how variations in clinical responses after periodontal therapy might be reflected in changes, or a lack of changes, in glycemic control. Diabetes and periodontal disease are closely related in many ways, though the effect of periodontal disease on diabetes control remain to be determined, with larger intervention studies. In the light of the increasing evidence of the relationship between diabetes and periodontal disease, management of oral health should form an integral part of diabetes management [42].

To conclude, diabetes is associated with an increased risk of developing inflammatory periodontal diseases and glycemic control is an important determinant in this relationship. Research reveals numerous biologically plausible mechanisms through which these interactions occur. Less clear is the impact of inflammatory periodontal diseases on the diabetic state.

While some evidence suggests that patients with diabetes who have periodontitis are at greater risk of developing poor glycemic control and that periodontal treatment aimed at reducing oral inflammation also may improve glycemic control, the evidence is not undisputed. Large, randomized, controlled intervention trials are needed to extend the evidence base. Inflammation is a common link between periodontal diseases and diabetes. Further research is needed to clarify how inflammatory periodontal diseases may affect insulin resistance, glycemic control and the risk of developing other diabetic complications.

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Int J Diab Dev Ctries

ORIGINAL ARTICLE

Population-based study of diabetic mellitus prevalence and its associated factors in adult Ghanaians in the greater Accra region

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Abstract The increasing prevalence of Diabetes Mellitus (DM) has become an issue of global concern. Diabetes affects over 100 million people the world over. It has been observed in Ghana that diet-related diseases such as DM and hypertension are on the increase. However, statistical data on the prevalence of the disease in Ghana is scanty. This study therefore investigated the prevalence and the risk-factors of DM in adults in the Greater Accra Region. The study was a cross-sectional one involving people living in purposely selected urban and peri-urban communities in the Greater Accra Region. A total of 288 men and 309 women aged between 36 and 95 years participated in the study. Subjects were screened for DM using urinary and fasting blood glucose determinations. Data on background of subject were collected and anthropometric measurements were taken. Data entry and analysis were done using Microsoft Excel, and SPSS. Statistical significance was tested at 5%. Chi-square test was used to determine the strength of association between DM prevalence and other variables. Prevalence of diabetes among subjects as determined by fasting blood glucose was 3.9%. Physical activity, family history and hypertension among subjects were significantly associated with diabetes prevalence. Positive associations were also observed between diabetes prevalence and age, BMI, and WHR. Other factors were not significantly associated with diabetes prevalence. Diabetes prevalence among subjects was high. This warrants efforts to address risk factors identified in this study.

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Keywords Diabetes mellitus · Insulin · Anthropometry · BMI · WHR

Introduction

Diabetes is among the major global public health problems. In Africa its management is complicated by poor socio-economic conditions. [1] The current increasing trend of the disease is due to unhealthy lifestyles which include intake of high fat diets and reduced physical activity. [2] Global projections predict that the prevalence of the disease is expected to increase from 171 million in 2000 to 366 million in 2030.[3] This justifies the need to probe the risk factors that may be culturally ingrained among specific populations to help in efforts to reduce the incidence of the disease.

Materials and methods

This study was a cross-sectional involving people living in purposely selected urban and peri-urban communities in the Greater Accra Region. A two-staged sampling strategy was used to select the specific community sites for the study. First, convenience sampling was used to select enumeration areas (EAs) among those mapped out by the Ghana Statistical

Table 1 Prevalence of diabetes by socio demographic and health
s tatus among participants (N = 597)

Characteristic	Diabetic N (%)	Non diabetic N (%)	p-value
Gender			
Male (n=288)	10 (3.5)	278 (96.5)	0.641
Female (n=309)	13 (4.2)	296 (95.8)	
Socio-economic class			
Lower (n=343)	9 (2.6)	334 (92.4)	0.104
Middle (n=191)	12 (6.3)	179 (93.7)	
Upper (n=63)	2 (3.2)	61 (96.8)	
Glucosuria			
Present (n=18)	16 (88.9)	2 (11.1)	0.000
Absent (n=579)	7 (1.2)	572 (98.8)	
Hypertension			
Present (n=103)	9 (8.7)	94 (91.3)	0.005
Absent (n=494)	14 (2.8)	480 (97.2)	
Family history			
Yes (n=69)	10	59	0.000
No (n=528)	13	515	
Total (n=597)	23 (3.9)	574 (96.1)	

Service (GSS). The EAs were used as the primary sampling units. Sixteen EAs were chosen. Sample size required for a 3% precision in prevalence estimates, and to detect statistically significant differences with 90% power were calculated based on absolute inter-group differences of 0.5 Z-score (assuming a standard deviation of 1.00). On the basis of these calculations, a sample size of 36 subjects in each of 16 EAs for a total of 576 subjects was the minimal required sample. From each EA, 36–40 subjects were selected by simple random sampling. A total of 597 subjects participated in the study (288 men and 309 women). Subjects recruited were those between the age range of 36 and 95 years since diabetes prevalence is more in adults; pregnant women were excluded from the study as there was the likelihood for gestational diabetes among them as well as other physiological changes that can affect other measurements taken such as blood pressure, weight and height.

Demographic and socio-economic data were collected using questionnaires. Blood pressure measurement was done using a sphygmomanometer. Anthropometric measurement, namely weight, height, waist and hip-circumferences, were measured using standard procedures. [4] The BMI and WHR of subjects were determined from these measurements.

Urinary glucose determination was also carried out for subjects. This was done enzymatically using glucose oxidase, peroxidase, a chromogen and the clinistix reagent strips. In determining the presence or absence of glucose in urine, the test end of the strip was dipped into fresh urine and removed immediately. The presence of glucose was indicated by the moistened end of the strip turning blue. Blood glucose level determination was done using a glucometer. The subject's middle fingertip was first cleaned with absorbent cotton wool containing 70% alcohol and pricked using a lancet. A drop of blood was applied to the centre of the twin-zone test area of the test strip ensuring that both twin-zone of the strip were completely covered. After 60 s, the blood was cleaned completely from the test area using cotton wool. The strip was inserted into the glucometer and the blood glucose level was read after about 120 s.

Data entry and analysis was done using Microsoft Excel, and SPSS version 16.0 respectively. Statistical significance was tested at 5%. Chi-square was used to determine statistically significant associations between DM prevalence and categorical variables. Line graphs with curves were used to show relationships between anthropometric variables and DM prevalence. Ethical clearance was obtained from the Institutional Review Board of the Noguchi Memorial Institute for Medical Research, University of Ghana.

Table 2 Prevalence of diabetes by lifestyle behaviours among participants (N=597)

Characteristic	Diabetic N (%)	Non diabetic N (%)	p-value
Smoking status			
Never smoked (n=459)	18 (3.9)	441(96.1)	0.827
Stopped smoking (n=93)	4 (4.3)	89 (95.7)	
Currently smoking (n=45)	1(2.2)	44 (97.8)	
Alcohol intake			
Never (n=280)	10 (3.6)	270 (96.4)	0.083
Occasional (n=162)	11 (6.8)	151 (93.2)	
Habitual (n=135)	2 (1.5)	133 (98.5)	
Stopped (n=20)	0 (0.0)	20 (100.0)	
Physical activity level			
Inactive (n=153)	12 (7.8)	141 (92.2)	0.010
Moderately active 9 (n=320)	9 (2.8)	311 (97.2)	
Highly active (n=124)	2 (1.6)	122 (98.4)	
Total (n=597)	23 (3.9)	574 (96.1)	

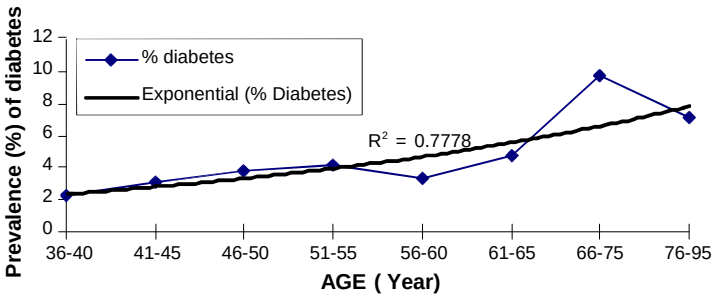

Fig. 1 Age distribution and prevalence of diabetes mellitus

Results

A total of 597 adults made up of 288 males and 309 females participated in the study. The age range of the participants was 36 to 95. Most people (343) were in the lower socio-economic class (Table 1). A greater proportion (459) of the participants never smoked while 135 were habitual drinkers. Most people (444) engaged in some form of activity and the rest, 153 were inactive (Table 2).

Fasting blood glucose determination showed that 23 (3.9%) of the subjects were diabetic (Table 1). Sixteen (16) subjects had both high fasting blood sugar and glucose in their urine. Although glucose was not found in the urine of 579 subjects, 7 of them were diagnosed as diabetics using the level of fasting venous blood glucose.

About 3.5% (10) of male and 4.2% (13) of female subjects were found to be diabetic. The association between gender and diabetes prevalence was not statistically significant ($p=0.641$), with a risk ratio of 0.83. Socio-economic class also did not show a significant association with diabetes prevalence ($p=0.104$). About 6.3% of those in the middle class were diabetic. The prevalence was lower for the other classes.

Among the hypertensive subjects 8.7% (9) were diabetic. The prevalence was very low (2.8%) among non-hypertensive subjects. The association between hypertension and diabetic status was significant ($p=0.005$) with a risk ratio of 3.1 (Table 1). About 4.3% of the subjects who stopped smoking were diabetic and 3.9% of those who never smoked were also diabetic (Table 2). Of the smokers, only 2.2% were diabetic. No statistically significant relationship was observed between smoking status and being diabetic ($p=0.827$).

Majority of the subjects were either occasional drinkers or non-drinkers. Prevalence of diabetes was higher among occasional drinkers (6.8%) and non-drinkers (3.6%) than habitual drinkers (1.5). None of those who stopped smoking was diabetic. This observation was however not significant ($p=0.083$).

Diabetes prevalence was higher among inactive subjects (7.8%) than highly active (1.6%) and moderately active subjects (2.8%). The relationship between the two variables was statistically significant ($p=0.010$).

Generally, diabetes prevalence increased with age of respondent as shown in Fig. 1 ($R^2=0.7778$). The prevalence was highest at age 66–75. The average waist -to- hip ratio among subjects was 0.89. Prevalence of diabetes among subjects increased with increasing waist-to-Hip ratio ($R^2=0.8665$). It was highest at WHR of 1.2 which was the highest WHR value observed (Fig. 2). The BMI ranged from 15 kg/m^2 to 51 kg/m^2, with an average of 27.86 kg/m^2 The correlation (Fig. 3) between BMI and prevalence of diabetes showed a J-shapes curve relationship ($R^2=0.7309$). The lowest prevalence is predicted by the curve to be within the BMI range of 16–30 kg/m^2. Above and below this range, the risk of diabetes increased.

Table 3 shows the relationship between family history of diabetes and diabetes status of study participants. Among 69 subjects who reported family history of the disease, 21 reported either mother or father being diabetic, 16 had a sibling with diabetes, 5 had diabetic cousins, 15 had a diabetic aunt or uncle, and 9 had grandparents with diabetes. Close to 24% of the subjects whose parents were diabetics were also diabetic. For the others, the prevalence was lower. Family history was strongly associated with diabetes prevalence ($p=0.000$).

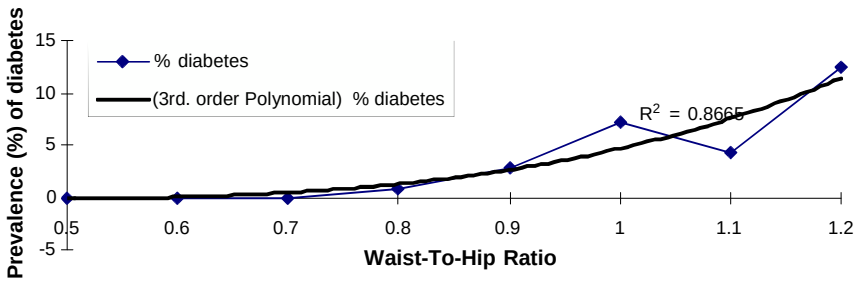

Fig. 2 Waist-to-hip ratio and prevalence of diabetes mellitus

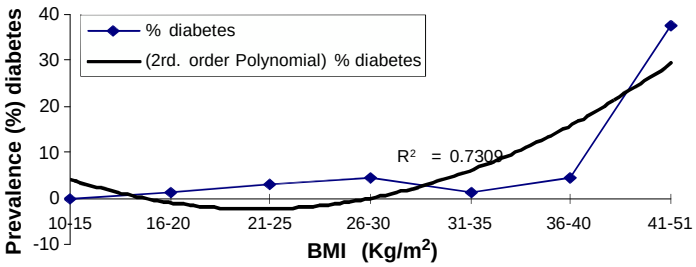

Fig. 3 BMI and diabetes prevalence

Discussion

The crude prevalence of diabetes which was 3.9% (Table 1) is about two-thirds that reported by Amoah, et al. [5] among a random cluster sample of Ghanaians in the same region (6.3%). The crude prevalence in Sudan was 3.4%[6] and that for Caucasian adults (age 50–74 years, n = 2484) was 8.3%. The overall crude prevalence of 3.9% in a sample population of 596 is indeed crude. While some of the enumeration areas had no record of the disease, some had as high as 15.8%. This implicates the influence of possible environmental factors such as nutrition and lifestyle variables on the prevalence of the disease.

Glucose was not found in the urine of 579 of the subjects. Out of the 18 whose urine had glucose 16 were found to be diabetic. The remaining 2 were non-diabetics. This may be explained by the fact that other pathological and physiological conditions such as febrile conditions can cause glucose to appear in the urine.[7] The observation thus attests to the fact that urine tests are of less value compared to fasting blood glucose in the diagnosis of diabetes. It is worthy of note that glucose appearing in the urine when the blood glucose is below 180 mg/dl, indicates low renal threshold. This is a benign condition which may run in families and commonly occurs temporarily in pregnancy. Renal glucosuria is a much more frequent cause of glucosuria in young persons.

The prevalence of diabetes was lower in the lower socioeconomic class (2.6%) than both upper (3.2) and middle (6.3%) socio-economic classes. The results therefore suggest that diabetes is a disease of the relatively affluent societies. Kosaka[8] mentioned that although DM is a genetic disorder, environmental factors after birth including "modernization or westernization" and its related life style changes play an important role for the development of diabetes. These lifestyle variables may include eating patterns and physical activity levels. It is however noteworthy that the observation between socio-economic status and diabetes prevalence was not statistically significant (p = 0.104).

Table 3 Prevalence of diabetes by family history

Relative with diabetes	Diabetes status of subject	
	Diabetic N (%)	Non-diabetic N (%)
Father/mother (N = 21)	5 (23.8)	16(76.2)
Sibling (N = 16)	1(6.3)	15(93.7)
Cousin (N = 5)	1(20)	4(80.0)
Uncle/aunt (N = 15)	3(20)	12(80.0)
Grandparent(N = 9)	0(0)	9(100.0)
Other relative (N = 3)	0(0)	3(100)
Total (N = 69)	10(14.5)	59(85.5)

It was also observed that increasing age predisposes one to diabetes as reported by Amoah et al.[5] This was evident from the study as the prevalence at 46–50 years was almost equal to the crude prevalence. There was a gallop in prevalence as age increased, with the 66–75 year group being the peak age of incidence of the disease. Some of these effects may be related to the increased adiposity that occurs with maturity, as well as to the increased central obesity that generally develops in many older persons.[9, 10]

There were more female diabetics than males. This is in line with findings of various studies.[11, 12] However the case has been different in some studies. For instance at the Diabetic Clinic in the Korle-Bu Teaching Hospital, the incidence of the disease was found to be equal in both sexes [5] whiles other researchers have found a completely opposite trend.[13, 14] These contradictions may be accounted for by differences in genetic and environmental conditions of the different study populations.

BMI of subject was found to influence the diabetic status. Generally, prevalence of diabetes increased with increasing BMI in this study, especially among women. This finding is supported by findings from other studies. [5, 9, 15] WHR also increased with diabetes prevalence. It has been reported that people with diabetes have a high central upper body fat (WHR of 1±0.07).[16] Among people with similar total body fat content, prevalence of diabetes was higher among those with family history of the disease.[17]

Hypertension and diabetes run among people of similar characteristics such as age, obesity, among others. Though they do occur independently, the presence of one may accelerate the appearance of the other. The figures obtained from this study signify that hypertensive subjects are about three times more likely to develop diabetes than normal subjects (p = 0.005). This is similar to the findings of de-

Courten[18] who reported that among the Pima Indians as much as 40% of diabetics were also hypertensive.

The results of this study suggest a significant positive association between family history of diabetes and the disease status among the study population ($p=0.00$). Genetic factors are very important in the development of diabetes.[19] Elbagir[6] has reported that family history was among the factors associated with higher prevalence rate of the disease. The sharing of common diet and lifestyle by family members may influence the prevalence within a given family.

Smoking has been reported to have an adverse effect in diabetes. [20]. However from this study, 2.2% of the smokers were found to be diabetic whereas 3.9% of the non-smokers were diabetic. These findings were similar to that found in Nigeria by Okesina.[21] Kawakami[22] published that those who were currently smoking had a 3.27 times higher risk of developing diabetes than those who never smoked; the hazard ratio was similar to 3.21 for those who were smoking currently. The results in this study suggested no significant relationship between smoking and the development of diabetes ($p=0.827$).

Various studies have reported alcohol consumption as a risk factor for diabetes. Wilkes [23] demonstrated that ethanol consumption has a long-term effect on insulin-regulated glucose transport and it was suggested to be an independent risk factor in the development of diabetes. The prevalence of the disease was rather higher among non-drinkers and occasional drinkers than habitual drinkers in this study, contrary to available reports. However this observation was not statistically significant ($p=0.083$).

Physical activity was significantly associated with diabetes prevalence ($p=0.010$). About 8% of the subjects in the relatively low active group had diabetes as against 1.6% of the highly active people. This may be explained by the fact that an active person burns his or her body fat for energy and thus prevents obesity and keeps BMI at a normal level; this is lacking in the low active group. Active people use their muscles very much, including their abdominal muscles. In effect they have a tightened and strong abdomen, resulting in lower WHR values. The lower prevalence of DM seen in highly active individuals is the inevitable corollary of lower BMI, reduced WHR and functionally active internal organs.

To conclude, prevalence of diabetes among our study population as determined by fasting blood glucose was 3.9%. Physical activity, family history of diabetes and hypertension were significantly associated with diabetes prevalence. Positive associations were also observed between diabetes prevalence and age, BMI, and WHR.

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ORIGINAL ARTICLE

Depression in patients with diabetes mellitus and its impact on diabetes self-care, medication adherence and glycemic control

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Abstract Depression is an independent risk factor for the onset of type 2 diabetes. It negatively affects the course of diabetes and is associated with increased risk of complications, hyperglycemia, and mortality. Diabetes may exert its negative effect through hormonal, neuronal, or immune system changes that directly affect the body's ability to produce or use insulin or, the effect of depression may be indirect, by resulting in poor self-care behavior, such as overeating, not exercising, skipping medication, or failing to keep medical appointments. Thus, identifying and treating depression in diabetes is strongly recommended. Cross-sectional study done in ambulatory care. A total of 320 diabetic patients who have duration of diabetes more than 1 year with out-patient diagnosis of diabetes (including fasting blood glucose >126 mg% twice in 1 year, random blood glucose >200 mg% twice in 1 year, currently taking any anti-diabetic agent, hospital discharge diagnosis of diabetes) were identified during the study period. Multivariable logistic regression was used to estimate odds ratio (Odds Ratios) and 95% confidence intervals (CIs). Overall depression was 17.5% (95% CI: 0.13–0.22%).The mean age was 55±12 years, 138 (43%) were females. Hypertension 197(61.6%) and ischemic heart disease(IHD) (N=68; 21.3%) were the most common co-morbidities. Factors independently associated with depression were; hypertension (OR 2.75; 95% CI: 0.99–7.37), complication of neuropathy (OR 4.56; 95% CI: 1.71–12.15) and nephropathy (OR 4.10; 95% CI: 1.26–13.33), family history of depression (OR 4.46; 95%CI: 1.50–13.26) and inadequate intake of fruit and vegetable (OR 0.32; 95% CI: 0.13–0.82). Depressed diabetics had more complications and sub-optimal self care. Coexistence of depression produced poor glycemic control.

Keywords Diabetes mellitus · Depression · Self care · Glycemic control · Complication of diabetes mellitus

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Background

Prevalence of diabetes and depression is growing very rapidly. Worldwide distribution of these problems complicates the issue further and impact of depression causes poor diabetes control [1]. Projections for 2020, based on

modeled estimates by WHO, show a marked escalation of diabetes related burden in South Asia. The number of people with diabetes is expected to rise by 195% in India during 1995–2025 to reach 57.2 million in 2025. Pakistan is expected to have about 14.5 million people with diabetes by that year [2, 3]. The American Diabetes Association publishes standards of medical care yearly to promote the importance of achieving optimal glycemic control [4]. Diabetic patients are more likely to have depression as compare to individuals who do not have diabetes but diabetic patients might require depression treatment at early part of their diagnosis as depression is going to affect them negatively causing disability in later life. Adults with diabetes having co-morbid depression, may have poor metabolic control, more complications, increased healthcare use and costs, reduced quality of life, greater disability and lost productivity, and higher mortality rates [5]. Previous studies have addressed the association between depression and diabetes outcomes, the effects of depression on glycemic control in adults with diabetes. Psychological issues can interfere with a patient's ability and confidence to manage their diabetes [5]. Evidence suggests that depression may relate to poorer glycemic control which further predicts a poorer course of depression in adult samples [6]. Depression may increase complications, not only because of poor self-care, but possibly through the brain chemistry and nervous system abnormalities that accompany depression [7]. Research has yielded increasing evidence that treating the depression can also help improve the outcome of treating the co–occurring illness. Depres- sion has negative effects on diabetes outcomes, diabetes complicates depression, and these problems are both worse and growing, therefore the efforts to identify and treat depression in the diabetic should be encouraged [8]. Screening for depression in diabetics has prime importance in this part of the world as Pakistan is having a burden of health care cost of non-communicable diseases [9]. This study was done to screen depression in diabetics and to study its impact on clinical characteristics, diabetes self- care and glycemic control.

Methods

Study design

A cross sectional study was done in ambulatory consecutive out-patients who met the inclusion criteria and gave informed consent. They were admitted to the study to assess the association between depression and diabetes, and possible differences between depressed and non-depressed patients with its relationship to clinical characteristics, diabetes self care, medication adherence and glycemic control. All diabetic patients who have duration of diabetes more than 1 year with out-patient diagnosis of diabetes including fasting blood glucose >126 mg% twice in 1 year, random blood glucose >200 mg% twice in 1 year, currently taking any anti-diabetic agent, hospital discharge diagnosis of diabetes.

For all patients history was taken including diabetes self management behavior for diet, exercise, adherence to oral hypoglycemic drugs, blood glucose testing, foot checks, and smoking status . Clinical measures to identify complication of diabetes chart review for retinopathy, neuropathy, nephropathy, cardiovascular, cerebrovascular disease, peripheral vascular disease, ketoacidosis was carried out. All patients were examined for weight, height, BMI, blood pressure. For physician initiated preventive care for diabetes record of HbA1c and glucose level in blood was checked.

Screening of depression was done on self-reported validated questionnaire and the cut off score was 9. Depression questionnaire's Urdu translation was done. This is a valid instrument for assessing depression with high internal consistency, good construct, concurrent validity and modest test and retest reliability. All patients with score 9 or above were referred to psychiatry clinic of one of our co authors.

Statistical analysis

A descriptive analysis was done for demographic and clinical features. Results are presented as mean ± standard deviation for quantitative variables and number (Percentage) for qualitative variables. Prevalence of depression with 95% Confidence Interval (CI) was calculated with Epi-Info version 6.04 (CDC, USA). To evaluate the association between depression and non-depressed patient with diabetes each of the clinical, nutritional and physical factors were assessed by using the Chi-square test or Fisher exact test where appropriate. In univariate analyses, comparison between depressed and non-depressed was done for each variable of interest. Multivariable analysis was conducted to identify the factors or determine association between depression and diabetes.

All analyses were conducted by using the Statistical package for social science SPSS (Release 16.0, standard version, copyright © SPSS; 1989–02). All p-values were two sided and considered as statistically significant if <0.05.

Results

A total of 336 patients presenting in ambulatory care clinic at the Aga Khan University were interviewed. Among these 320 patients were enrolled in the study. Out of the 16 who were not included in the study, 9 refused to give consent while 6 had language barrier and were not able to give the

Table 1 Demographic character- istics of study population (n=320)

Characteristics	N	%
Age, years	54.54±12.50	
Type 2 diabetes	301	94.1
Duration of diabetes, years	10.49±7.34	
Gender		
Male	182	56.9
Female	138	43.1
BMI	28.17±5	
Co-morbidities		
Hypertension	197	61.6
Depression	22	6.9
Hypothyroid	21	6.6
IHD	68	21.3
Complication of diabetes		
Retinopathy	57	17.8
Neuropathy	169	52.8
Nephropathy	20	6.3
Ischemic heart disease	54	16.9
Family history		
Diabetes	250	78.1
Hypertension	189	59.1
Ischemic heart disease	143	44.7
Depression	28	8.8
General self care activities in past week		
Five serving of fruit/vegetables	273	85.3
High fat food >6 times/week	72	22.5
Physical activity >30 min/day started before onset of diabetes	16	5.0
Physical activity >30 min/day started after the onset of diabetes	85	26.6
Drugs		
Oral hypoglycaemic	283	88.4
Insulin	134	41.9
Anti lipid drugs	222	69.4
Anti hypertensive drugs	189	59.1
Recent HbA1c level	7.78±1.76	

interview. The participants were from a diverse patient population coming from all the four provinces of Pakistan.

Approximately more than half of the patient population were male(56.9%), and the mean age of the patients were 55±12 years with 53.4% of the participants having completed their graduate studies. 94.1% of the patients were suffering from type 2 diabetes with mean duration of the diabetes amongst the patients being 10.49±7.34 years. The prevalence of depression amongst the participants was 17%. The mean BMI was 28 kg/m² and 9% were smokers (Table 1). The most common co-morbid conditions reported by the patients during the interview were hypertension (61.6%) and ischemic heart diseases (21.3%). More than half of the patient population suffered from neuropathy as a complication of long standing diabetes either in the form of sensory or autonomic neuropathy checked clinically. Majority of the patients had family history of diabetes. Around 88% of the patients received oral hypoglycemic agents while 42% received insulin either alone or in combination with the oral hypoglycemic agents. Regarding general self-care activities only 27% of the patients reported some sort of physical activity. The mean number of HbA1c tests done per year was 1.2. The mean HbA1c level amongst the patients was 7.78±1.76%.

The prevalence of depression was 17.5% (95% CI 0.137%–0.22%). Diabetic patients suffering from depression were compared with non-depressed diabetics in order to study the factors associated with depression. Univariate

Table 2 Univariate analysis of factor associated with depression (n=320)

Characteristics	No depression, N=264(82.5%)	Depression, N=56(17.5%)	Odd ratio [95% CI]	P value
Gender				
Male	158(86.8)	24(13.2)	1.0	
Female	106(76.8)	32(23.2)	1.98[1.10–3.56]	0.02
Comorbidities				
HTN				
No	112(91.1)	11(8.9)	1.0	
Yes	152(77.2)	45(22.8)	3.01[1.49–6.08]	0.002
Complications				
Neuropathy				
No	138(91.4)	13(8.6)	1.0	
Yes	126(74.6)	43(25.4)	3.62[1.86–7.04]	<0.001
Nephropathy				
No	251(83.7)	49(16.3)	1.0	
Yes	13(65)	7(35)	2.75[1.04–7.26]	0.04
Ischemic heart disease				
No	224(84.2)	42(15.8)	1.0	
Yes	40(74.1)	14(25.9)	1.86[0.93–3.73]	0.07
F/H of diabetes				
No	63(90)	7(10)	1.0	
Yes	201(80.4)	49(19.6)	2.19[0.94–5.08]	0.06
F/H of hypertension				
No	115(87.8)	16(12.2)	1.0	
Yes	149(78.8)	40(21.2)	1.93[1.02–3.61]	0.04
F/H of IHD				
No	152(85.9)	25(14.1)	1.0	
Yes	112(78.3)	31(21.7)	1.68[0.94–3.008]	0.07
F/H of stroke				
No	238(83.8)	46(16.2)	1.0	0.09
Yes	26(72.2)	10(27.8)	1.99[0.89–4.40]	
F/H of depression				
No	246(84.2)	46(15.8)	1.0	
Yes	18(64.3)	10(35.7)	2.97[1.28–6.84]	0.01
5 serving of fruit and vegetable/week				
No	34(72.3)	13(27.7)	1.0	
Yes	230(84.2)	43(15.8)	0.48[0.23–1.002]	0.05
High fat food >6 times/week				
No	209(84.3)	39(15.7)	1.0	
Yes	55(76.4)	17(23.6)	1.65[0.87–3.14]	0.12
Duration of diabetes				
<5 years	91(85.8)	15(14.2)	1.0	
5–10 years	74(88.1)	10(11.9)	0.82[0.34–1.93]	0.65
>10 years	99(76.2)	31(23.8)	1.90[0.96–3.74]	0.06
HbA1c level				
<6.5	30(90.9)	3(9.1)	1.0	
≥6.5	147(80.3)	36(19.7)	2.44[0.70–8.47]	0.15

analysis revealed a higher prevalence of depression amongst the female population (p=0.02), those with hypertension (p=0.002), or neuropathy (p<0.001), or nephropathy (p=0.04), or family history of hypertension

Table 3 Factors predicting depression by multivariable logistic regression analysis

	Odd ratio[95% CI]	P value
Comrbids		
HTN		
No	1.0	
Yes	2.75[0.99–7.37]	0.05
Complications		
Neuropathy		
No	1.0	
Yes	4.56[1.71–12.15]	0.002
Nephropathy		
No	1.0	
Yes	4.10[1.26–13.33]	0.01
F/H of depression		
No	1.0	
Yes	4.46[1.50–13.26]	0.007
5 serving of fruit and vegetable/week		
No	1.0	
Yes	0.32[0.13–0.82]	0.01

(p=0.04), family history of diabetes (p=0.06), or ischemic heart disease(IHD) (p=0.07) or stroke (p=0.09), those with infrequent intake of fruit and vegetables (p=0.05), or with duration of diabetes more than 10 years (p=0.06) There was no difference between the depressed and non-depressed patients with regards to physical activity, consumption of fatty food, self monitoring of blood glucose as well as foot checks (Table 2).

Multivariate logistic regression analysis performed after adjusting for the effect of other variables in the model identified hypertension, diabetic complication of neuropathy and nephropathy, family history of depression and fewer intakes of fruits and vegetables as independent predictors of depression in diabetic patients (Table 3).

Discussion

There is a growing body of literature on the relationship between diabetes and depression as well as the effect of diabetes and co-morbid depression on health outcomes and costs [10]. Specifically, the coexistence of diabetes and depression is associated with increased health care use, increased health care costs and adverse health outcomes of diabetes [11].

Frequency of depression in our study sample was 17.5%, predominantly involving females. Diabetes patients were having higher score for depression than the control in a study done in Iraq [12]. Depression when linked to diabetes leads to a higher degree of morbidity or mortality due to decreased or diminished self-care related to diabetes.

Presence of diabetes doubles the odds of co-morbid depression. Female preponderance was present in our study, as well as that of Anderson, where 28% women and 18% men were afflicted by depression. [13]

More than half of the patient population suffered from neuropathy as a complication of long-standing diabetes either in the form of sensory or autonomic, as diagnosed clinically. Those who were overweight and obese were more depressed [14]. Depression was significantly high in those who had hypertension, nephropathy neuropathy and ischemic heart disease. It is a known fact that diabetes can lead to various co-morbidities as well as complications. In our study we found that hypertension and ischemic heart disease were the most frequent co-morbid conditions in diabetes while patients who had superimposed depression reported an increased frequency of hypertension as well as family history of hypertension, diabetes, stroke, ischemic heart disease and depression [15].

Diabetic complications such as neuropathy and nephropathy was also more frequently reported in patients with depression. de Groot and associates in their study identified the fact that depression was consistently associated with increased severity of diabetes complications [16]. Therefore diagnosis of depression or early detection of symptoms of depression is imperative to limit the initiation of co-morbidities as well as diabetic complications such as neuropathy and nephropathy. Our study population had significant history of hypertension in depressed group. Carney et al. in their study found that there is a threefold increased risk of developing ischemic heart disease in patients having depression [17]. Patients with diabetes and depression had higher odds of functional disability compared with either diabetes or depression [18]. In our study depressed diabetics had more neuropathy and nephropathy as compare to non-depressed diabetics.

These alarming figures of depression will have negative impact on cost of managing diabetes in low resource countries, since depression increased subsequent health care costs among adults with diabetes by 50% [10, 19]. A depression collaborative program improved depression outcome compared with usual care and reduced the mean total medical cost [18].

Depression appears to influence patient-initiated activities more than physician-initiated services In particular, diabetic patients with depression need support for self-management activities such as lifestyle modifications and medication adherence [19, 20]. Nearly half of our study participants were on insulin. Mean HbA1C was 7.78 and mean tests per year was 1.2.

Mean BMI in our patients were 28 kg/m^2 while other studies show that 48.9% had BMI >30 and major depression was associated with less physical activity unhealthy diet, lower adherence to drugs and suboptimal self-care [20, 21].

In our study patients with diabetes reported a decreased trend towards general self-care activities such as daily physical activity, feet check and healthy eating of fruits and vegetables. Patients having symptoms of depression reported even lower frequency of fruit and vegetable intake when compared with the normal diabetic population but surprisingly no difference was found regarding physical activity, feet check, self monitoring of blood glucose or intake of fatty food. [22]

Only one third of our patients indulged in any physical activity and there was no difference in depressed and non-depressed diabetics. A better understanding of the specific self care activities that are compromised in depression can shed light on the relationship between depression and unfavorable diabetes outcomes such as impaired blood glucose levels and more diabetes complications [23, 24]. Depressed took less fruits and vegetable and high fat diet. Clinical data showed suboptimal levels of diabetes-care across a continuum from self-management and medication adherence to preventive care. This study highlights three notable deficiencies in diabetes management: lack of physical activity, high non-adherence rates to oral hypoglycemic medicines and inadequate clinical monitoring of glycemic control. A better understanding of specific self-care activities that are compromised in depression can shed light on the relationship between depression and unfavorable diabetes outcomes, such as higher HbA_{1c} levels and more diabetes complications [25, 26]. Lin et al. in her study found no difference in self-care activities such as glucose monitoring and foot checks in both depressed and non-depressed diabetics. On the other hand, depressed patients reported very infrequent exercise and healthy diet and more smoking [20, 25]. In our study we did not find any strong association of smoking between depression and diabetes and only a fraction of the diabetic patients were smokers.

There are a few limitations to our study. This study was done in a single tertiary care centre where patients were not the true representation of the general population due to the fact that majority of the patients are from upper and middle class background while our general population mainly consists of people from middle to low socio-economic status. Therefore patients from general population should have been included in the study as well. Further this study was a cross-sectional study due to which we cannot ascertain the observed correlation between depression and diabetes. This issue could have been resolved if the study was performed in prospective longitudinal manner. One of the most important aspects of diabetes care is compliance with the medications by the patients but we do not have any system by which we could ascertain the prescription refill by the patients and hence medication compliance.

In conclusion, depressed diabetics had more complications and sub-optimal self care with poor glycemic control. Patients having both diabetes and depression are at an increased risk of developing complications and co-morbid conditions which can lead to both functional and mental disability and higher health-care costs. Therefore it is imperative to screen diabetic patients for early depressive symptoms and start treatment as early as possible.

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Competing interest The authors declare no competing interest.

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ORIGINAL ARTICLE

A critical analysis of the concept of secondary Oral Hypoglycemic Agent (OHA) failure in type 2 diabetes at a tertiary care hospital

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Abstract Data from UKPDS study suggests that the onset of ß cell dysfunction in diabetes occurs well before the development of hyperglycemia. To study the concept of secondary OHA failure in type 2 diabetes patients of more than 10 years duration in a tertiary care hospital. A retrospective analysis of all the cases of type 2 diabetes mellitus of more than 10 years duration from 2002 to 2003 was done and the data was divided into three groups: oral hypoglycemic agents (OHA) only, Insulin only, OHA + insulin. ANOVA/Students t test was the primary statistical test used. Odds ratio and 95% CI were calculated to compare risks of other diseases and drug use. 62.35% were on only OHAs, 8.82% on only insulin and 28.82% on both insulin and OHAs. This confirms good efficacy of OHAs. Diabetic population in our study tends to have a preserved beta cell function and secondary OHA failure is a late feature.

Keywords OHA failure · Beta cell dysfunction · Type 2 diabetes

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Introduction

The pathogenesis of type 2 diabetes mellitus is complex and in most instances clearly requires defects in both ß cell function and insulin sensitivity. It is well accepted that for hyperglycemia to exist in type 2 diabetes, ß cell dysfunction has to be present [1]. Data from the UKPDS study suggests that the onset of ß cell dysfunction associated with diabetes occurs well before the development of hyperglycemia, and may commence many years before diagnosis of the disease.

Not only does beta cell dysfunction in type 2 DM preceed rise in blood glucose, it progressively worsens throughout the course of the disease. In the UKPDS after 9 years, only 25% of the subjects in the intensive treatment arm were achieving a HbA1c less than 7% with monotherapy alone. Whereas a greater number of therapeutic options are available for lowering plasma glucose, none have been shown to reliably slow the progressive loss of ß cell function [1]. On the other hand, according to Daniel et al., a significant loss of ß cells does not seem likely at the early phases of clinical hyperglycemia in type 2 diabetes. This conclusion is supported by autopsy studies suggesting that at death perhaps ≤20–50% of the ß cells have been lost after many years of disease [2].

It is commonly believed that oral hypoglycemic agents (OHA) start failing at the end of 5 years [3], suggesting the onset of significant beta cell loss. However, in clinical practice we do see a fair number of patients in whom OHAs were still working at the end of 10 years. Based on the above contradictory findings, we decided to study the concept of clinical ß cell dysfunction/secondary OHA failure in type 2 diabetes patients of more than 10 years duration in a tertiary care hospital.

Materials and methods

Study design

This was a non-intervention and observational study. A retrospective analysis of the management of all the cases of type 2 diabetes mellitus of more than 10 years of duration during the year 2005–2008 was done at KMC hospital, Manipal. After taking permission from the Institutional Ethics Committee (IEC) to carry out a drug utilization study, permission was obtained from the medical superintendent (MS) of KMC hospital to study all the files of type 2 diabetes mellitus cases of more than 10 year-duration from the medical records section.

Study parameters

The following data were obtained from the anonymous patient records through a specifically designed proforma: demographic data, current prescription, initial and latest fasting blood glucose (FBG), initial and latest post prandial blood glucose (PPBG), initial and latest HbA1c, co-morbidity, concomitant medications. All the patients and the data was then divided into three groups: oral hypoglycemic agents (OHA) only (group 1), insulin only (group 2), OHA + insulin (group 3). Both males and females were included in the study. For continuous variables (glycosylated haemoglobin (HbA1c), FBG, PPBG), the mean value ± SEM was calculated.

Data analysis

For the comparision of continuous variables between the three study groups, we used the ANOVA. Chi-square test to compare risks of other diseases and disorders.

Results

There were 170 patients with at least 10-year history of diabetes. 106 (62.35%) patients were only on OHAs at the end of 10 years (group 1), 15 (8.82%) patients were only on insulin (group 2) and 49 (28.82%) patients (group 3) were on both insulin and OHAs (Fig. 1). Their clinical and demographic characteristics are given in Table 1.

Group 1

Of the 170 patients, 62.35% i.e. 106 patients were on oral hypoglycemics even after 10 years of diabetes. This group has been further divided based on the HbA1c values into Group 1a with HbA1c <7%, Group 1b with HbA1c 7–8% and Group 1c with HbA1c >8% (Table 2). The overall mean age and duration of the disease was 58.72 years and 13.7 years respectively. The incidence of complications is less in this group compared to the other two groups. The initial FBG and HbA1c values are also lower in this group when compared to the other two groups. 40.56% of the patients in this group have achieved a HbA1c of <8%. Out of these, 18.86% of the patients have a HbA1c level between 7% and 8% and 21.69% of the patients have a HbA1c below 7%.

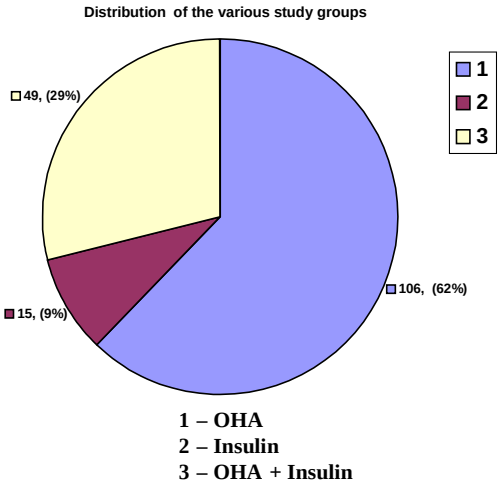

Fig. 1 Distribution of the various study groups

Group 2

Of the 170 patients, 15 (8.82%) switched from OHA to only insulin treatment and are on this therapy since 1 year. The mean age of this group was 54.93 years. The mean duration of onset of disease was 16.8 years which is almost similar to group 3. Among these 15 patients, 46.7% had a history of nephropathy, 33.3% had a history of foot ulcer, 26.7% had a history of retinopathy (Table 3). All these conditions are significantly higher in this group compared to the other groups ($p<0.005$, $p<0.0001$, $p<0.02$ respectively). The latest HbA1c level of 10.1% indicates a poor glycemic control in these patients.

Group 3

Out of 170 patients, 49 patients (28.82%) switched from only OHA to a combination therapy of OHA and insulin and are on this therapy since one year .The mean age of this group was 59.43 years and the mean duration of onset of disease was 16.97 years. Out of these, 46.9% had a history of neuropathy and is significantly higher in this group compared to the other two groups (Table 3). The latest HbA1c level of 10.1% is similar to group 2.

Table 1 Basic Clinical and Demographic characteristics of type 2 diabetic patients enrolled in the study

Variable	Group 1 (n=106)	Group 2 (n=15)	Group 3 (n=49)
Mean age (years)*	58.72±9.68	54.93±9.07	59.43±8.07
Mean duration of disease (years)*	13.70±4.55	16.80±5.79	16.97±5.65
Mean BMI*	22.26±8.24	19.77±8.51	21.58±9.14
Male (number,%)	33 (31.1%)	11 (73.3%)	29 (59.8%)
Female (number,%)	73 (68.9%)	04 (26.7%)	20 (40.8%)
Total cholesterol (mg/dl)*	185.86±50.41	142.16±34.02	177.93±52.95
LDL-C (mg/dl)*	111.55±42.72	133.70±173.75	118.03±109.85
HDL-C (mg/dl)*	42.03±14.06	38.16±11.22	38.27±12.60
Triglycerides (mg/dl)*	183.33±160.07	105.33±41.8	177.15±99.10

*Values are mean ± standard error of the mean (SEM) and p>0.05

Discussion

This study describes the current status of patients with type 2 diabetes mellitus of more than 10 years duration. These patients were of the following three types: OHA only (group 1), insulin only (group 2), OHA + insulin (group 3). Of the 170 patients, 106 i.e. 62.35% were only on OHA therapy even after 10 years of disease onset. This group of patients were comparable in age distribution, duration of diabetes and BMI with the other two groups (p>0.05) suggesting that the groups were not very different in terms of disease presentation. Lipid profile was also found to be similar in all groups (p>0.05). However complications such as nephropathy, retinopathy and foot ulcers was found to be significantly higher in the group 2 (p=0.0005) when compared to the other two groups (Table 3). These complications were probably the main reason for switching to insulin in this group. It is also to be noted that these complications make control of diabetes difficult in this group as suggested by the higher HbA1c.

Secondary failure of oral hypoglycaemic agents, defined by latest HbA1c equal to or greater than 8.0%, and maximal treatment with oral hypoglycaemic agents or an inadequate glucose-lowering effect of oral drugs after an initial good response [4–6]. In our study 40.56% of patients in group 1 had HbA1c of less than 8%. We found certain factors in our study that made these patients to continue on oral medication even after 10 years of disease, notably: lower initial FBG levels, lower incidence of complications probably suggesting that this group of patients had milder disease to begin with. Complications like retinopathy, nephropathy and foot ulcers are not at all seen in group 1 with HbA1c <8%. Only neuropathy at a rate of 4.75% has been observed which is much lower when compared to all the other groups.

In group 1, 59.44% of patients were not on insulin even though these patients have not achieved an A1c of less than 8%. The causes of secondary OHA failure include non-compliance, weight gain, declining beta cell function, infection and the use of diabetogenic drugs such as glucocorticoids, thiazides, and beta blockers [4]. However we did not find any of these factors in our patients. Regarding concomitant medications in our study only 2.8% and 12.3% of the patients in group 1 were on hydrochlorthiazide and beta blockers respectively (Table 6). The percentage of patients on these drugs is considerably higher in group 2 possibly due the higher incidence of comordities requiring these drugs, and the mild extent of the effect of these drugs in the alteration of blood sugars. In the rest, the natural course of the disease with declining beta cell function could have been the cause of OHA failure.

Regarding the patients who were not on insulin even when blood glucoses were not optimally controlled (HbA1c >8%, Table 2), it was found that insulin was advised in all of them by the treating physician. But the patient either could not afford the therapy, and requested to try oral drugs for longer period, or refused insulin because of fear of injection, or inability to take injections due to

Table 2 Distribution of patients in the Group 1 (n=106) based on the HbA1c Levels

HbA1c < 7 (group 1a)	HbA1c 7–8 (group 1b)	HbA1c > 8 (group 1c)
23 (21.69%)	20 (18.86%)	63 (59.43%)

Table 3 Complication status in the various study groups

Complication	Group 1 Number (%)	Group 2 Number (%)	Group 3 Number (% use)
Neuropathy*	21 (19.8%)	05 (33.3%)	23 (46.9%)
Nephropathy**	17 (19%)	06 (46.7%)	03 (6.1%)
Retinopathy***	10 (9.4%)	04 (26.7%)	12 (24.5%)
Foot Ulcers****	03 (2.8%)	05 (33.3%)	06 (12.2%)

*p=0.002 between the three groups by Chi-square test

**p=0.0005 between the three groups by Chi-square test

***p=0.02 between the three groups by Chi-Square test

****p=0.0001 between the three groups by Chi-Square test

Table 4 Comparision of the various study parameters in the various groups

Variable	Group 1 (n=106)	Group 2 (n=15)	Group 3 (n=49)
Initial HbA1c (%)	9.4±2.66	10.03±2.65	10.7±3.04
Latest HbA1c (%)	8.82±1.86	10.10±2.68	10.10±2.98
Initial FBG (mg/dl)	185.1±87.73	198.53±69.92	192.66±101.81
Initial PPBG (mg/dl)	250.91±104.39	242.15±171.84	292.66±122.74
Latest FBG (mg/dl)	144.12±61.38	153.69±69.23	129.02±44.43
Latest PPBG (mg/dl)	206.28±71.50	205.00±77.75	201.34±85.83
HbA1c (<8%)	43 (40.56%)	4 (26.7%)	12 (24.48%)

social circumstances. When we analysed the complica- tions in group 1c (Table 5), who needed insulin but did not take it, we found a rate of 12.69% for neuropathy, 6.34% for nephropathy and retinopathy, and 4.76% for foot ulcers which is less than what is seen in group 2 & 3. This may be due to the fact that these patients had milder disease to begin with.

After 9 years of follow-up in the United Kingdom Prospective Diabetes Study (UKPDS), 30% of the patients had switched over to insulin treatment [7]. Contrary to this in our study, only 8.82% of the patients were on only insulin at the end of 10 years and 28.82% of the patients were on insulin as an add-on therapy to oral hypoglycemics after 10 years.

The American Diabetic Association (ADA) recommends the use of insulin as an add on therapy in patients who either do not achieve glycaemic goals with metformin alone or metformin and SU together, as tier 2 or tier 3 therapy [8]. This recommendation was followed in 28.82% of patients in whom insulin was added to OHAs for control of blood glucose. Patients who switch over to insulin therapy due to secondary failure are younger at diagnosis, more frequently suffer from depression, acute myocardial infarction, lipid disorder, atrial fibrillation, and retinopathy and have higher HbA1c and total serum cholesterol values [9]. Following initial therapy with oral hypoglycemic medication in the population, switching to insulin occurred at a rate of 5.84% per year. Switching to insulin was associated with being younger, male, having low BMI and higher HbA_{1c}. Goddijn [6] studied prospectively a cohort of type 2 diabetic patients referred by GPs to an outpatient department for consideration of insulin therapy. It was found that switchers had a higher HbA1c. Similar findings are also seen in our study wherein 73.3% of patients on only insulin therapy had a HbA1c of more than 8% (Table 4).

Table 5 Rate of complications in the Group 1 (n=106) based on the HbA1c level

Complications	HbA1c < 8 (n=43)	HbA1c > 8 (n=63)
Neuropathy	4.65%	12.69%
Nephropathy	0	26.98%
Retinopathy	0	15.87%
Foot ulcers	0	4.76%

Control of glycemia in various subgroups

UKPDS has shown that more intensive management aiming for near-normal glucose levels reduces the risk of diabetes related complications, particularly microvascular disease [10]. The latest FBG and PPBG levels of 144.12±61.38 and 206.28±71.50 in our study in group 1 supports this. In this group, 59.43% of patients had A1c >8% while 18.86% of patients had a fair control with A1c between 7% and 8% (Table 2). However, 21.69% of patients had excellent control with A1c <7%, and these patients represented those who did not need any more drugs. Glycemic control in the group 3 was poor with A1c of 10.1%, as these patients had advanced disease with complications. It is inevitable, however, that an increasing number of type 2 patients with over 10 years of DM will need to be started on insulin to achieve the recommended goal of HbA1c of 7% [11]. Contrary to this, we observed that primary reason for starting insulin is comorbid conditions especially nephropathy in our study.

At present OHA failure is recognized when plasma glucose values above 10 and 14 mmol/l, (equivalent to 180 and 252 mg/dl) are constantly observed in the fasting state and 2 h after breakfast during treatment with OHA, at

Table 6 Concomitant medication use in the various study groups

Generic name		OHA only group% use	Insulin only group% use	OHA + Insulin group% use
Hydrocholthiazide		03 (2.8%)	05 (33.3%)	23 (46.9%)
Beta Blockers		13 (12.3%)	07 (46.7%)	03 (6.1%)
ACEI/ARBs		25 (23.6%)	04 (26.7%)	12 (24.5%)
Statins		17 (16%)	01 (6.7%)	09 (18.4%)
No. of OHAs	1	35.8%	–	–
	2	51.9%		
	3	10.3%		

maximal doses which have been effective for at least for 1 or 2 years [12]. Even though 59.44% of the patients in the OHA group have a HbA1c of >8%, the latest FBG and PPBG levels of 144 and 206 mg//dl is well below the above mentioned range (Table 4).

As type 2 diabetes mellitus advances, the yearly failure rate of this therapy following an optimal initial response is approximately 5–10% and increases with the duration of diabetes. The United Kingdom Prospective Diabetes Study found that 50% of normal and over-weight patients failed to maintain HbA1c of <7% after 3 years. But as demonstrated in the ADVANCE trial [13] in which the mean duration of diabetes is 8 years, a combination of OHAs can control blood glucose for a reasonable period of time (Tables 5 and 6).

Contrary to usual belief, secondary OHA failure may be a late feature in our study since 40.56% of the patients are on OHA with reasonable glycemic control even after 10 years of diabetes. High initial PPBS, HbA1c, predicts OHA failure [9]. These factors which have not been evaluated in our study could have supported our findings. Most of the patients (>50%) in group 1 required 2 groups of drugs for the glycemic control. It will be interesting to see as to how long these patients will continue on OHA.

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INVITED EDITORIAL

Type 2 diabetes can also be multigenerational like MODY

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Type 2 diabetes (T2DM) is now known to comprise of a heterogeneous group of metabolic disorders. The common garden variety of T2DM with onset in adult life is a multifactorial or polygenic disorder with multiple genes each playing a relatively minor role towards the overall risk of T2DM [1]. In addition, there is a large environmental component. Familial aggregation of T2DM is well known, and up to 40–60% of T2DM patients may have a family history of diabetes in a first degree relative [2]. This figure would obviously be higher if all the relatives were screened for diabetes rather than based on 'known' family history of diabetes. Multigenerational diabetes, with an autosomal dominant type of inheritance, is common in the monogenic forms of diabetes like Maturity Onset Diabetes of the Young (MODY) [3, 4]. Patients with MODY, typically have a diabetic parent and a grandparent, and often a great grandparent on the affected parent's side with diabetes, suggestive of autosomal dominant inheritance [5]. MODY type diabetes, is now classified into at least 6 distinct types (MODY-1 to MODY-6) based on the specific genetic mutation involved, although newer MODY types continue to be described [6, 7]. MODY 3 (due to HNF1-$\propto$ mutations) is the commonest form of MODY followed by MODY-1 (due to HNF-4 $\propto$ mutations) and together they are believed to comprise up to 75% of adult onset MODY among Europeans [3, 4, 6]. In contrast, among Asian Indians while the prevalence of MODY based on clinical criteria is high [8], MODY 3 mutations were seen only in 9% of clinically diagnosed MODY patients [9] while another 3.4% had MODY 1 [10]. In these reports, some novel MODY 3 and MODY 1 mutations were also described. Thus it is clear, that the majority of clinically suspected MODY patients in India, either have other forms of MODY or, they may in fact, have an early onset form of T2DM.

The phenotype of MODY 3 and MODY 1 is characterized by overt, and often severe, diabetes [3, 4, 6, 7]. In contrast, MODY 2 due to glucokinase mutations, is a milder form of diabetes, often exhibiting just glucose intolerance (impaired glucose tolerance or impaired fasting glucose); it is usually asymptomatic and is picked up during routine screening of children or pregnant women [11]. Tattersall's cases, obviously carrying MODY 2 mutations, rarely progressed to diabetic complications [12] while MODY 1 and MODY 3, being more severe forms of diabetes were prone to develop microvascular complications like retinopathy or nephropathy [6, 13, 14]. Most forms of MODY are characterized by insulin secretory defects and insulin resistance is less common [15].

In contrast to MODY, early onset T2DM is a form of polygenic T2DM but with onset of diabetes at younger ages. As with classical T2DM, the predominant etiopathogenic mechanism in early onset T2DM is insulin resistance [16]. Patients with early onset T2DM often have diabetes in one or both parents, but unlike MODY, multigenerational transmission through the affected parent's side, is less common. Clinically, they tend to have features of insulin resistance such as obesity and acanthosis nigricans; in addition, features of polycystic ovarian disease are quite common in girls with early onset T2DM [16].

Till recently, it had been assumed that an autosomal dominant transmission of diabetes, with the classical multigenerational occurrence of diabetes, is restricted to the

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monogenic forms of diabetes like MODY [4]. Recently, our group reported a series of multigenerational autosomal dominant form of diabetes in south Indian T2DM subjects [17]. The age at diagnosis of diabetes in the probands with autosomal dominant multigenerational transmission of T2DM in that series was above 25 years of age in 77.4% of T2DM and above 45 years of age in 28% of T2DM. This is in contrast to MODY where the age at diagnosis is below 25 years according to the classical definition of MODY by Tattersal and Fajans [5]. Thus we showed that mere presence of multigenerational diabetes is not against the diagnosis of T2DM. In the same report, we also showed that there was no difference in the clinical and biochemical profile, or the prevalence of diabetes related complications, in T2DM patients with multigenerational diabetes compared to T2DM patients without multigenerational diabetes [17]. Another study from UK comparing family histories in South Asian and European T2DM subjects, also showed that autosomal dominant multigenerational diabetes was common among south Asians in the UK [18].

The minimal criterion for autosomal dominant inheritance is the occurrence of diabetes in two generations, although most families have at least three or more generations affected. In those with autosomal dominant inheritance, by definition, only one of the parents of an affected proband need be affected. Therefore, considerable caution should be exercised before defining a family in which both parents have diabetes as a MODY family, because children who inherit a "double gene dose" of T2DM from both parents tend to have an earlier onset of diabetes [16].

In this issue of the IJDDC, Irwing et al. [19] report on what they term "Mosaic Pancreas" or "type 3 diabetes". Essentially this is a case report of three probands from large families of multigenerational inheritance of early onset T2DM in at least 3 generations, detected at the University Hospital of the West Indies, Jamaica during a screening process for patients with MODY. The authors report that all the 6 MODY gene variants were absent in the three probands. Islet cell antibodies were absent in 2 of the 3 probands studied, but positive in one. The authors propose that these 3 cases could form a new type of diabetes which they propose to call "Mosaic pancreas" or "type 3 diabetes". While the cases described by the authors are certainly of interest, it would be difficult to justify labeling them as a separate class of diabetes in the absence of specific genetic or other diagnostic markers. One could argue, that but for the presence of multigenerational diabetes, there is nothing unusual about the probands 1 and 2 described in their report. Proband 3 with the ICA positivity may well have Latent Autosomal Diabetes of Adults (or LADA). It is known that some patients with diabetes present with what initially looks like T2DM but they have ICA or GAD positivity. These patients eventually require insulin and behave like type 1 diabetes (T1DM) and are called as LADA [20]. The authors propose the new term for their patients based on "heterogeneity" in the clinical presentation of T2DM. However T2DM is well known for its marked heterogeneity; for example, young or older age at onset; presence or absence of family history of diabetes; obese or non obese types; mild to marked insulin resistance; mild to marked insulin secretory defect and presence or absence of microvascular complications. Introducing a new terminology of diabetes based on the clinical findings presented, is therefore clearly unjustified. However, the report undoubtedly shows the heterogeneity in the clinical presentation of T2DM and underscores the need for more detailed studies on T2DM in different ethnic groups to fully characterize this complex disorder. It is likely that as our knowledge of the etiopathogenic mechanisms develop further, many cases presently classified as T2DM, may well fall into newer types or categories of diabetes and thus be removed from the "mixed bag" of what is currently lumped together under type 2 diabetes.

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ORIGINAL ARTICLE

Psychological impact of type-1 diabetes mellitus on parents: an exploratory study from North India

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Abstract Due to its early age of onset, type-1 diabetes mellitus (T1DM) poses major burden of care on to the family members, especially parents. To study the psychological morbidity, social support, coping strategies, level of dysfunction and quality of life in parents of subjects with type-1 diabetes mellitus. This study was carried out in a tertiary care hospital with cross sectional design. Fifty parents of 50 subjects with T1DM were assessed by General Health Questionnaire (GHQ-12), Social support Questionnaire, Coping strategy check list, Dysfunction Analysis Questionnaire and WHO Quality of Life-Bref Scale. Those with GHQ score ≥2 were interviewed in detail by a psychiatrist to determine the presence/absence of the psychiatric illness. Mean (±SD) age of the children was 14.09±5.43 years at the time of assessment and the age (mean±SD) at diagnosis was 10.3±5.16 years. Age (mean±SD) of parents was 43.2±8.73 years. Mothers (N=27) outnumbered fathers (N=23). Nearly two-third of parents (64%) had psychological morbidity. Of the 32 parents found to be GHQ positive, more than half (N=17) had diagnosable psychiatric disorder. Parents who more frequently used internalization and externalization as a coping mechanism to overcome the stress of chronic illness in their children suffered from psychological morbidity. Parents with psychological morbidity had more dysfunction in social, personal and cognitive domains and also had significantly poorer quality of life in the physical health, psychological health and general well being domains. Hence, it can be concluded that T1DM in children and adolescents leads to poor parental mental health.

Keywords T1DM · Psychological morbidity · Coping · Quality of life · Social support

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Introduction

Type-1 Diabetes mellitus is a chronic disease of children and adolescents arising due to autoimmune destruction of beta cells and results in severe insulin deficiency and hyperglycemia. Appropriate management of type-1 diabetes mellitus includes diet, exercise, insulin administration and regular blood glucose monitoring [1].

Due to its early age of onset, sometimes as early as infancy, the major burden of care of subjects falls on to the family members, especially parents, who are not only involved in bringing the children and adolescents to the hospital for consultation, but are also involved in administration of insulin and overall management. All this has impact on daily family functioning and management [2–7]. In fact type −1 diabetes mellitus is considered as a family enterprise rather than individual's responsibility [7].

Being a chronic illness, type-1 diabetes mellitus is also associated with lot of stigma [8]. In addition, parents also experience substantial anxiety, shame, grief, guilt [9] and financial hardships. Hence, the parents of these subjects have to not only cope with the fact that their children are diagnosed with a chronic life long medical illness, but also have to fight out the stigma and overcome their guilt, shame and grief. All these fact make the

parents of subjects with diabetes mellitus vulnerable to psychological stress and morbidity. Studies have shown that maternal psychological adjustment problems (i.e., distress) are associated with maladjustment in children with chronic health conditions [10].

Against this background we aimed to study the psychological morbidity, social support, coping strategies, level of dysfunction and quality of life of parents of children and adolescents with type-1 diabetes mellitus attending a tertiary care hospital in North India.

Research design and methods

Setting

This cross-sectional study was carried out at the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, (India) which is a multi-speciality teaching tertiary-care hospital providing service to a major area of North India.

Instruments

The following instruments were used:

1. Social Support Questionnaire (SSQ) [11]: SSQ is a Hindi language adaptation of Social Support Questionnaire [12] and assesses the perceived social support. It is a self-rated instrument. It has a test-retest reliability of 0.59 and correlation with clinician's assessment at 0.80 and correlation with items of social support from Family Interactions Pattern Scale [13] at 0.65. The 18 items of the scale are rated from 1 to 4, with a possible range of 1–72. A higher score indicates better social support.
2. Coping Strategies Check List—Hindi (CSCL) [14]: It is a self-administered yes/no checklist with high reliability. It lists coping strategies used by people to deal with the situations which trouble them. The checklist covers all stressors and is not disease-specific. The 36 strategies have been factored into five factors: denial, internalize, externalize, emotional outlet, and anger. A higher score indicates greater use of coping strategies. It was translated into Hindi with Cronbach's alpha of 0.64 in our centre. The scale has good face validity, inter-rater reliability, internal consistency and agreement between English and Hindi versions [15].
3. Dysfunction Analysis Questionnaire (DAQ) [16]: It was developed at our centre and it assesses the dysfunction as compared to the pre-illness level of functioning across five domains—social, vocational, personal, family and cognitive. The scale consists of 50 items rated on a five point scale and gives a possible disability score range of 46–100 for individual domains and 206–500 for the total, a higher score indicating a higher dysfunction. It has been found to have good validity and reliability (test-retest reliability of 0.77–0.92 for various domains). This self-administered questionnaire in Hindi language provides norms for the local population and has been widely used in India on different clinical populations.
4. WHO Quality of Life Scale-Bref (WHOQOL-B): WHOQOL-B is a self-administered psychometrically sound cross-cultural instrument developed in 15 centres across developing and developed countries [17]. It is a shorter version of the WHOQOL 100 item scale. The generic scale is available in Hindi language [18], it provides the subjective (rather than the objective) evaluation of the QOL in the past 2 weeks for four domains: physical health, psychological health, social relationship, and environment and three items forming the general well being domain. The 26 items are scored 1–5 to give domain scores and a total score range of 26–130, a higher score indicating a better quality of life.
5. General Health Questionnaire-12 (GHQ-12): GHQ-12 is a derivative of General Health Questionnaire −60, which was developed as a valid and reliable self-administered screening measure for psychological problems in primary care and community settings [19]. GHQ-12 used in the present study is based on the Hindi translation of the 60-item General Health Questionnaire that has been standardized in India and in Indian population [20, 21] and has been used in our center earlier in research with patients suffering with acromegaly and Cushing disease [22, 23]. In the present study, to define a case with possible psychiatric morbidity a score ≥2 was used. This is because GHQ scores of 1 or 2 are considered as the best cutoff or threshold for psychiatric diagnosis [24].
6. International Classification of Diseases-10th revision (ICD-10) [25]: ICD-10 was used to arrive at the clinical diagnoses based on a detailed psychiatric assessment.

Procedure

All the subjects diagnosed with type-1 diabetes mellitus attending the clinic with their parents who were involved in the care of children and adolescents were eligible for the study. They were explained about the study and only those children and adolescents who themselves and their parents provided written informed consent were recruited. Initially the sociodemographic profile and the clinical profile sheets were filled. Thereafter, the parents were assessed on GHQ-

12, SSQ, CSCL, DAQ and WHOQOL-Bref on the same day, over a maximum of two sessions of 1–2 h each. Thirty two parents with GHQ score ≥2 were interviewed in detail by a Consultant Psychiatrist who used ICD-10 criteria to determine the presence/absence of the psychiatric illness. Fifty parents were recruited for the study. Those found to have a psychiatric disorder were offered treatment.

The study was approved by the institute ethics committee.

The data was analysed using SPSS-14. Descriptive analysis was computed in terms of mean and standard deviation with range for continuous variables and frequency with percentage for ordinal and nominal variables. Data was compared using Chi-square test, t-test and Mann Whitney test wherever appropriate. Pearson's product moment was used to study the relationship between psychiatric morbidity and coping, social support, level of dysfunction and quality of life.

Results

GHQ scores of parents

Of the 50 parents assessed, 32 scored 2 or more on General health questionnaire and 18 scored 0 or 1. Those with GHQ score of 2 or more were classified as GHQ positive and those with a score of 0 or 1 were classified as GHQ negative.

Sociodemographic and clinical profile of subjects with type-1 diabetes mellitus

The mean (±SD) age of the sample was 14.09±5.43 years (range 9 months to 18 years) at the time of assessment and the mean (±SD) age at diagnosis was 10.3±5.16 years (range 4–20 years). Nearly two-third of the subjects were male (N=32; 64%). There was no statistically significant difference in the mean age (±SD) of patients (GHQ positive-10.99±5.66; GHQ negative- 9.7±4.91; t value 0.565, p value – 0.575), age at diagnosis of diabetes mellitus (GHQ positive-13.65± 5.62; GHQ negative- 14.88 ±5.13; t value −0.777, p value – 0.441) and gender distribution (male patients −22 in the GHQ positive parents and 11 in the GHQ negative parents group; Chi square- 0.87).

Sociodemographic profile of parents (Table 1)

The mean (±SD) age of parents was 43.2±8.73 years. Mothers (N=27) outnumbered fathers (N=23). Slightly less than half (48%) were educated beyond 10th standard and

Table 1 Sociodemographic profile of parents: whole group and GHQ positive & GHQ negative subgroups

	Whole group (N=50)	GHQ subgroups		
		GHQ positive (N=32)	GHQ negative (N=18)	t value/Chi- Square value
Age in years (Mean ± SD)	43.24±8.73	42.06±8.94	45.33±8.16	−1.27
Gender				
Male	23 (46%)	13 (40.62%)	10 (55.5%)	1.03
Female	27 (54%)	19 (59.38%)	08 (44.5%)	
Education				
Less than 10th standard	26 (52%)	15 (46.87%)	11(61.11%)	0.935
10th Standard or more	24 (48%)	17 (53.13%)	07(38.89%)	
Occupation				
Employed	29 (58%)	17 (53.13%)	12 (66.66%)	0.867
Housewife	21 (42%)	15 (46.87%)	06 (33.33%)	
Family type				
Nuclear	31 (62%)	20 (62.5%)	11(61.11%)	0.009
Non-nuclear	19 (38%)	12 (37.5%)	07(38.89%)	
Religion				
Hindus	26 (52%)	16 (50.00%)	10 (55.5%)	0.142
Non-Hindus	24 (48%)	16 (50.00%)	08 (44.5%)	
Marital status[a]				
Currently living with spouse	46 (92%)	30 (93.75%)	16 (88.88%)	0.612
Widowed	04 (8%)	02 (6.25%)	02 (11.12%)	
Locality				
Urban	37 (74%)	24 (75.00%)	13 (72.22%)	0.046
Rural	13 (26%)	08 (25.00%)	05 (27.78%)	

[a] Fisher exact value

more than half of the parents were Hindus (52%), employed (58%) and came from nuclear family (62%). Nearly three-fourth (74%) of the sample belonged to urban background and most of the parents were living with their spouse. As shown in Table 1, there was no significant difference in the various sociodemographic variables of the GHQ positive and GHQ negative parents.

Psychological profile of parents (Table 2)

Parents who scored higher on GHQ (i.e., GHQ positive group) had higher total scores on almost all the domains of the coping checklist and total score of coping checklist, but the significant difference emerged only on the domains of internalization and externalization. When we compared the coping skills between mothers and fathers, it was seen that mothers more frequently used externalization as a coping compared to fathers (t value 0.266; p=0.004). Further when coping skills of mothers and fathers were compared in parents with psychiatric morbidity (diagnosable psychiatric disorder), it was seen that mothers more frequently used internalization (t value 3.13; p=0.007) and externalization (t value 2.93; p=0.01) as a coping mechanism as compared to fathers.

Similarly GHQ positive parents also scored significantly higher on the social, personal, cognitive and total dysfunction score compared to GHQ negative parents suggesting that GHQ positive parents experienced higher dysfunction in these domains and had overall higher level of dysfunction. On WHO-QOL Bref GHQ positive parents had significantly poorer quality of life in the physical health, psychological health and general well being domains. In other domains also QOL was poor but was not significant statistically. There was no difference in the social support questionnaire scores between the two groups.

Table 2 Psychological profile: whole group and GHQ positive & GHQ negative subgroups

	Whole group (N=50) (Mean ± sd)	GHQ subgroups		
		GHQ positive (N=32) (Mean ± sd)	GHQ negative (N=18) (Mean ± sd)	t value/Mann Whitney U
Social Support (SSQ)	53.66±9.64	52.06±10.53	56.50±7.25	−1.58
Coping (CSCL)				
Denial	7.60±2.10	7.91±2.20	7.06±1.83	1.38
Internalize	5.14±3.03	6.38±2.76	2.94±2.12	4.54***
Anger	3.18±1.38	3.28±1.44	3.00±1.28	0.688
Externalize	1.72±1.17	2.09±1.20	1.06±0.80	3.27**
Emotional[a]	0.88±0.89	0.88±0.90	0.89±0.90	285.00
Total	18.46.2±4.28	20.53±3.38	14.78±3.09	5.93***
Dysfunction (DAQ)				
Social	49.00±17.47	55.25±18.90	37.89±4.96	3.80***
Vocational	44.59±11.26	46.88±12.56	40.52±7.09	1.97
Personal	48.71±11.37	51.60±12.05	43.56±8.01	2.52*
Family	43.07±10.50	44.07±8.71	41.29±13.20	0.89
Cognitive	43.52±7.81	45.38±8.80	40.22±4.05	2.33*
Total dysfunction score	228.88±49.43	243.17±52.84	203.47±29.73	2.92**
Quality of life				
Physical health	25.86±4.69	24.44±4.77	28.39±3.36	3.09**
Psychological health	20.70±4.00	19.47±3.81	22.89±3.41	−3.15**
Social relationship	11.16±2.33	10.69±2.33	12.00±2.14	−1.96
Environmental health	27.88±4.64	27.28±4.84	28.94±4.19	−1.22
General well-being	6.70±1.11	6.44±1.13	7.17±0.92	−2.32*
Total	92.30±12.50	88.31±12.39	99.38±10.27	−3.21**

*p<0.05, **p<0.01, ***p<0.001. SSQ Social Support Questionnaire, CSCL Coping Strategies Check List—Hindi, DAQ Dysfunction Analysis Questionnaire, WHOQOL-B WHO Quality of Life Scale-Bref

[a] Mann Whitney U value

Table 3 Correlates of GHQ scores for subjects with GHQ score of 2 or more

Variables	Pearson correlation coefficient
Coping (CSCL)	
Internalize	0.490**
Dysfunction (DAQ)	
Social	0.493**
Vocational	0.409*
Personal	0.489**
Familial	0.380*
Cognitive	0.403*
Total dysfunction score	0.524**
Quality of life	
Physical health	−0.632**
Psychological health	−0.538**
Total	−0.580**

CSCL Coping Strategies Check List—Hindi, DAQ Dysfunction Analysis Questionnaire, WHOQOL-B WHO Quality of Life Scale-Bref, **p<0.01

Psychiatric diagnosis of GHQ positive parents (Table 3)

All the GHQ positive parents were evaluated by a qualified psychiatrist using a clinical interview for a possible psychiatric diagnosis. Of the 32 GHQ positive parents 17 fulfilled the ICD-10 criteria of a psychiatric diagnosis. Of the various psychiatric diagnoses made, 15 parents had adjustment disorder and two had dysthymia. There was no difference in the psychiatric morbidity between mothers and fathers; nor was there any difference in the morbidity as per gender of the patient.

In the GHQ positive group use of internalization as a coping strategy, dysfunction in all the domains on DAQ and poor quality of life in psychological and physical health domain and total QOL scores correlated with GHQ scores (Table 3).

Discussion

Of the 50 parents who participated in this study, nearly two-third (64%) had psychological morbidity. Of the 32 parents found to be GHQ positive, about half (nearly one third of the total) had diagnosable psychiatric disorder. This suggests that parents of subjects with type-1 diabetes mellitus suffer from a significant psychological morbidity which needs to be addressed.

It is known that parental mental health, especially maternal mental health is an important determinant of outcome of chronic medical conditions in children and adolescents. This was an exploratory study which aimed to study the psychological impact of type-1 diabetes mellitus on parents of subjects with diabetes mellitus. Being an exploratory study we did not aim to study the relationship between the psychological morbidity of parents and treatment outcome of type-1 diabetes mellitus.

Coping involves the use of cognitive and behavioral strategies to deal with the demands imposed by the stressful experience. We found that parents who more frequently used internalization and externalization as coping mechanisms to overcome the stress of chronic illness in their children suffered psychological morbidity. Internalization as a coping mechanism is understood as a maladaptive coping in which a person blames self for all the wrong things, which can lead to psychopathology. Similarly excess use of externalization as a coping mechanism can also be maladaptive and can have impact on the patients. As there are no studies that have used coping strategies check list in parents of subjects with diabetes mellitus we are not able to compare our findings with the existing literature.

Further it was seen that parents with psychological morbidity had more dysfunction in social, personal and cognitive domains and also had significantly poorer quality of life in the physical health, psychological health and general well being domains.

In the correlation analysis it was seen that higher GHQ scores were associated with internalization as a coping strategy, dysfunction in all the domains on DAQ and poor quality of life in psychological and physical health domain and total QOL scores. These findings suggest that higher psychological morbidity leads to poor QOL and higher level of dysfunction in parents of subjects with type-1 diabetes mellitus. These findings suggest that psychological morbidity leads to increased dysfunction needing clinical attention.

Being an exploratory study, our study was limited by small sample size, purposive sampling and lack of assessment of severity of diabetes in the patients, lack of a control group and lack of assessment of relationship between parental psychological morbidity and outcome of children's physical illness. We also did not assess psychological problems if any, in children, family functioning and family conflicts.

To conclude, our study suggests that type 1 diabetes mellitus in children and adolescents leads to poor parental mental health especially maternal mental health. Hence it is important to develop liaison services for assessment and management of psychological morbidity in parents and subjects with type-1 diabetes mellitus.

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Conflict of interest None.

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ORIGINAL ARTICLE

Plasma fibrinogen in patients with type 2 diabetes mellitus with and without macrovascular disease and its relationship with endothelial function, carotid intima media thickness and dyslipidemia

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Abstract Plasma fibrinogen is higher in diabetic subjects, but it is not clear whether its levels differ in patients with or without existing macrovascular disease (MVD) and whether it has any relationship with endothelial function as determined by flow mediated dilatation (FMD), carotid intima media thickness (CIMT) and lipids. To study plasma fibrinogen levels and their relationship with endothelial functions, CIMT and dyslipidemia in type 2 diabetic patients with and without macrovascular disease, twenty six diabetic subjects and thirteen matched healthy controls were recruited for the study. Subjects were divided into group I—with MVD, group II—without MVD and group III—healthy controls. Fasting blood was analyzed and radiological studies were performed. Statistical analysis was done to find any correlation between study parameters. Plasma fibrinogen was significantly higher in diabetic subjects as compared to controls. Plasma fibrinogen was significantly higher in group I as compared to group II. Plasma fibrinogen levels correlated significantly with CIMT and FMD in diabetic subjects. No significant correlation was found between plasma fibrinogen and glycemic parameters, insulin or lipids. Plasma fibrinogen levels increased progressively from controls to diabetic subjects without MVD and to those with MVD and is an independent risk factor for atherosclerosis in diabetic subjects.

Keywords Diabetes mellitus · Fibrinogen · Macrovascular disease · Intima media thickness · Flow mediated dilation

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Introduction

Diabetes mellitus (DM) is a pro-thrombotic condition and diabetic subjects are at high risk of premature atherosclerosis [1–4]. Fibrinogen has been found to be an independent risk factor for macrovascular disease among the diabetic and non-diabetic subjects [1, 5, 6]. The risk of coronary artery disease (CAD) increases 1.84 fold with increase in every 100 mg/dl of fibrinogen level [7]. A positive correlation has been found between plasma fibrinogen level and insulin level [8], body mass index [9] and reduced HDL [10]. However, its association with triglyceride levels has been inconsistent [10–13]. It is not clear from the previous studies whether plasma fibrinogen levels differ in diabetic subjects with existing macrovascular disease from those without and whether it has any relationship in this group with surrogate markers of atherosclerosis namely, endothelial dysfunction and carotid intima media thickness (CIMT) as well as dyslipidemia. Hence, this study was planned to investigate plasma fibrinogen levels and their relationship with endothelial function, CIMT and dyslipidemia in patients with type 2 diabetes mellitus with and without macrovascular disease.

Material and methods

Twenty-six type 2 diabetic subjects with age more than 30 years and duration of diabetes more than one year who were non-smoker and did not have history of inherited disorder of lipid metabolism, liver disease, endocrine diseases affecting lipids (hypothyroidism, Cushings syndrome), hypertension and congestive heart failure and were not taking drugs affecting lipid metabolism were recruited for the study. Thirteen non diabetic individuals who were age, sex and body mass index (BMI) matched, who were non-smokers, non-alcoholic and did not have overt clinical evidence of coronary artery disease (CAD), cerebrovascular disease (CVD) or peripheral vascular disease (PVD) were recruited as controls.

The subjects were divided into three study groups: Group I (n=13)—subjects with type 2 diabetes mellitus with macrovascular disease (CAD, CVD and PVD), group II (n=13)—subjects with type 2 diabetes mellitus without macrovascular disease, group III (n=13)—non-diabetic healthy individuals. CAD was defined on the basis of electrocardiography (ECG) evidence of CAD; viz. ST-T and Q-wave changes, treadmill test (TMT) evidence for reversible ischemia or angiographic evidence of CAD. CVD was defined on the basis of history of diagnosed stroke and PVD was defined on the basis of history and clinical examination and ankle/brachial index ≤ 0.9.

Study design

After taking informed written consent, subjects were recruited into the study and detailed history and physical examination was carried out for every subject as per pre-designed proforma. The subjects who were recruited in this study were called after 14 h of fasting during which water intake was allowed. After thorough physical and systemic exanimation, blood was collected for various biochemical parameters. Plasma was separated in all the samples by centrifuging it immediately after collection and stored at −20°C for various biochemical estimations including plasma fibrinogen. After withdrawal of blood sample, flow mediated dilation study for detection of endothelial function and measurement of CIMT was performed. Patients were allowed to take their usual breakfast and blood sample was drawn after 2 h for the estimation of postprandial plasma glucose.

Biochemical estimation

Following fasting biochemical parameters were estimated in all subjects—fasting and postprandial plasma glucose, glycated hemoglobin and complete lipid profile. Fasting serum insulin was determined by radioimmunoassay using commercial kit from Diasorin INSI-CTK kit.

Fibrinogen estimation

For the fibrinogen level estimation 14 h fasting blood was collected and 9 parts of blood was mixed with 1 part of the Sodium Citrate (3.2%) solution. Blood was centrifuged at 1000 rpm for 15 min. Plasma was removed from the tube and was stored in plastic tubes at −20°C. Fibrinogen level was estimated within 10 days of storage by clotting assay fibrinogen kit (Clauss) as per the guidelines prescribed.

FMD study for endothelial function

Flow mediated dilatation (FMD) was performed in all study subjects by a high-resolution B-mode ultrasonography system (P-700, PHILIPS) having an electronic linear array, high frequency transducer for superficial scanning with a mid-frequency of 7.5 MHz. The scanning was conducted at the gain setting at Time Gain Compensation (TGC) appropriate for superficial structures.

The endothelium function was evaluated, radiologically, by measuring flow mediated vasodilations (FMD) of the right brachial artery. The validity of this method has been confirmed previously [14]. Brachial artery ultrasound studies to determine FMD, was performed in a dark, quiet, temperature-controlled room. Subject was allowed to rest in the supine position for 10 min before the study. High resolution ultrasound machine equipped with a 7.5 MHz linear artery transducer was used. Longitudinal scans of the right brachial artery were taken 3.5 cm. proximal to the antecubital fossa with the probe positioned so that the best images were obtained.

Baseline brachial artery diameter (D-0) was measured. Endothelium-dependent vasodilation was determined by the maximal change in the diameter of the brachial artery during reactive hyperemia, which was created by placing a cuff on the forearm and inflating it to 250 mmHg for 5 min, thereby occluding blood flow to the forearm. The brachial artery was scanned continuously for 30 s. before and 90 s. after the cuff deflation. The brachial artery diameter of reactive hyperemia (D1) was recorded. Flow mediated vasodilation (FMD): (D1-D0)/D0x100 was used as a measure of endothelial dependent vasodilation. Values of flow-mediated dilation (FMD) expressed as the percent diameter change of the brachial artery in response to reactive hyperemia. An average of 3 consecutive measurements were taken for each subject.

Carotid intima media thickness measurement

The intima media thickness of the carotid artery was determined by a high resolution B mode USG System (HDI 1500) having an electronic linear, high frequency

broadband transducer for superficial scanning with a mid frequency of 7.5 MHz. The scanning was conducted at optimal gain settings at appropriate time Gain Compensation (TGC) appropriate for superficial structures using lowest possible PRF (Pulse Repetition and Frequency) power settings [15]. It was measured at several areas along the vessel wall including (1) the posterior aspect of the common carotid artery, (2) common carotid artery bifurcation, (3) anterior wall of internal carotid artery. IMT measurements were quantified as the average of arterial wall thickness (excluding segments involved with plaque).

Statistical analysis

The data were expressed as mean±SD for all the study groups. The significance of difference was determined using ANOVA followed by Tukey's test and correlation between different parameter was determined by Pearson correlation coefficient.

Results

As seen in Table 1, all the three study groups are age, sex and BMI matched. Central obesity as indicated by waist was significantly higher in the both diabetic groups with ($p<0.001$) and without macrovascular disease ($p<0.001$) when compared with controls. However, waist measurement was not significantly different between these two diabetic groups ($p>0.05$). The prevalence of hypertension 7/13 (11.53%) and family history of diabetes 4/13 (30.76%) was equal in both diabetic groups. Family history of CAD was present in 3/13 (23.0%) in subjects with macrovascular disease and 2/13 (15.38%) in diabetic subjects without macrovascular disease.

Table 1 Demographic profile of the patients in the three study groups

	Group I mean±SD	Group II mean±SD	Group III mean±SD	p-value
Age (years)	54.5±9.5	54.6±7.4	51.1±9.7	a > 0.05 b > 0.05 c > 0.05
Male:Female	1:3.3 (3/13)	1:3.3 (3/13)	1:3.3 (3/13)	a > 0.05 b > 0.05 c > 0.05
Duration of diabetes (yrs)	7.3 ±5.4	4.6±3.6	NA	a > 0.05
BMI (kg/m^2)	23.5±2.3	22.9±3.3	23.4±2.1	a > 0.05 b > 0.05 c > 0.05
Waist (cms)	89.6 ±5.4[b]	92.0 ±14.6[c]	78.2 ±5.2	a > 0.05 b < 0.001 c < 0.001

Group I vs II = a, Group I vs III = b, Group II vs III = c
$p>0.05$ (not significant), $p<0.05$ (significant)

Table 2 shows that fasting, postprandial plasma glucose and glycated hemoglobin were significantly higher in both the diabetic groups (group I and II) as compared to controls (group III). Fasting insulin levels were also higher in both the diabetic groups as compared to controls. However, this reached statistical significance only for group II vs group III. Fasting level of HDL was significantly lower in both the diabetic groups (group I and II) as compared to controls (group III). Fasting TC and LDL levels were significantly higher in diabetic subjects with macrovascular disease as compared to controls.

Figure 1 shows plasma fibrinogen concentration which was significantly higher in diabetic groups (Group I and II) as compared to control (group III). Furthermore, plasma

Table 2 Biochemical parameters in the three study groups

	Group I Mean±SD	Group II mean±SD	Group III mean±SD	p-value
Fasting plasma glucose (mg/dl)	157.2±45.3	145.9±46.2	84.8±9.8	a > 0.05 b < 0.001 c < 0.001
Post-prandial plasma glucose (mg/dl)	250.2±41.2	227.1±74.9	113.8±9.0	a > 0.05 b < 0.001 c < 0.001
Glycated hemoglobin (%)	8.6±1.9	8.5±1.6	6.1±0.98	a > 0.05 b < 0.001 c < 0.001
Fasting serum insulin (μIU/ml)	8.3±4.9	10.8±6.5	4.5±2.6	a > 0.05 b < 0.001 c = 0.013
Total cholesterol (mg/dl)	186.3±42.2	153.1±20.4	163.6±11.6	a > 0.05 b = 0.008 c > 0.05
Triglyceride (mg/dl)	145.0±85.3	93.3±25.8	95.8 ± 22.4	a > 0.05 b > 0.05 c > 0.05
HDL-C (mg/dl)	34.0±3.5	39.0±7.1	46.9±5.5	a > 0.05 b < 0.001 c = 0.003
VLDL-C (mg/dl)	29.0±17.0	19.6±5.1	19.2±4.4	a > 0.05 b > 0.05 c > 0.05
LDL-C (mg/dl)	123.2±40.8	96.2±23.4	85.4±10.8	a > 0.05 b = 0.004 c > 0.05

Group I vs II = a, Group I vs III = b, Group II vs III = c
$p>0.05$ (not significant), $p<0.05$ (significant)

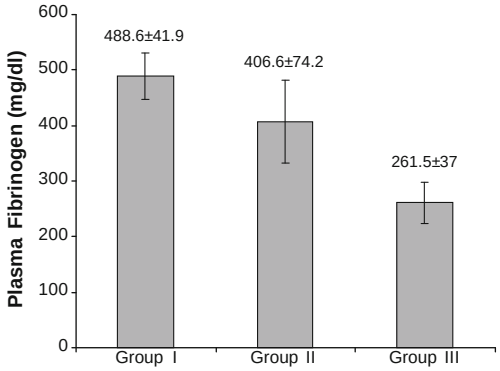

Fig. 1 Plasma Fibrinogen levels in three study group

fibrinogen concentration was significantly higher in diabetic subjects with macrovascular disease (Group I) as compared to those without macrovacular disease (Group II).

Table 3 shows that plasma fibrinogen levels have a significant correlation with CIMT and FMD in diabetic subjects as a whole as (group I and group II combined) well as in those with macrovascular disease (group I).

FMD in diabetic subjects with macrovasular disease (5.7±6.1%) was significantly lower than diabetic subjects without macrovascular (22.7±10.0%) disease and healthy controls (24.7±5.3%), but no significant difference was found between diabetic subjects without macrovascular disease and healthy controls. CIMT was significantly higher in diabetic subjects with macrovascular disease (0.8471± 0.4911 mm) as compared to those without macrovascular disease (0.2538±0.4542 mm) as well as healthy controls (0.1664±0.2138 mm)

Discussion

Fibrinogen has been found to be an independent risk factor for macrovascular disease in diabetic and non-diabetic subjects [1, 5, 6, 16–18]. The current study found that plasma concentration of fibrinogen was significantly higher in diabetic subjects as a whole and it was even more significant in diabetic subjects with existing macrovascular disease. Guardado-Mendozo et al. found that fibrinogen significantly predicted silent myocardial infarction in diabetic subjects and it may identify individuals with high cardiovascular risk [19]. Hotuajolo et al. [20] found that among diabetic subjects, hyperfibrinogenemia was more prevalent in the group with peripheral arterial disease than those without, similar to observations in the present study.

Our study also found ascending levels of plasma fibrinogen from healthy controls to the diabetic subjects without macrovascular disease and to those with macrovascular disease. This suggests that the subgroup of type 2 diabetes patients with higher fibrinogen levels are associated with greater atherosclerosis and macrovascular disease. Plasma fibrinogen measurements may help identify this subset of diabetic subjects with excess cardiovascular risk. Type 2 diabetes is believed to be a prothrombotic state and studies have shown increased PAI-1 activities [20–22] and consequent suppression of fibrinolysis in them. Hyperfibrinogenemia seen in type 2 diabetes could be related to this suppression of fibrinolytic activity. Fibrinogen is believed to be a marker of inflammation [23, 24] and hyperfibrinogenemia of diabetes may be secondary to the associated underlying chronic inflammation.

The present study found significantly greater FMD-endothelial dysfunction and CIMT in diabetic subjects with macrovascular disease as compared to those without macrovascular disease as well as healthy controls. Both the surrogate markers of atherosclerosis, had strong correlation with plasma fibrinogen levels in diabetic subjects as a whole as well as in those with macrovascular disease. ARIC study [5] and CARDIA study [6] also found that plasma fibrinogen had a positive correlation with CIMT among non-diabetic subjects. Martinez-Vila et al. [25] also reported that in adults without overt atherosclerosis, plasma fibrinogen had strong correlation with CIMT. Similarly, Allen et al. [26] found negative correlation between plasma fibrinogen levels and flow mediated vasodilation in non-diabetic subjects. It was suggested that an elevated plasma fibrinogen may decrease the artery's responsiveness to certain vasodilatory signals such as shear stress. The strong correlation of fibrinogen with both CIMT and FMD endothelial dysfunction in diabetic patients in the present study confirms the results of earlier studies in non-diabetic subjects and reinforces the role of fibrinogen as a cardiovascular risk marker in patients with diabetes. The mechanism by which plasma fibrinogen enhances cardiovascular risk are that it is an important component to decide plasma viscosity [27], it mediates platelet aggregation [28]

Table 3 Correlation of plasma fibrinogen with FMD and IMT

	Diabetic subjects (group I & II)		Diabetic subjects with MVD (group I)		Healthy controls (group III)	
	r-value	p-value	r-value	p-value	r-value	p-value
FMD (%)	−0.879	0.000	−0.807	0.001	−0.042	0.908
CIMT (mm)	0.658	0.000	0.690	0.009	−0.434	0.211

and it is an important determinant of fibrin formed during thrombosis [29], all of which promote atherothrombosis. It would appear that plasma fibrinogen should be estimated in diabetic patients for a more accurate cardiovascular risk evaluation.

Fibrinogen levels did not show significant correlation with any of the glycemic and fasting lipemic parameters overall, suggesting that the effects of fibrinogen on atherosclerosis are independent of hyperglycemia or dyslipidemia. Fibrinogen levels also showed significant correlation with body mass index and waist, which would indicate that obesity, particularly central adiposity and associated insulin resistance may be associated with hyperfibrinogenemia found in diabetic subjects. No significant association was observed between plasma fibrinogen levels and fasting insulin levels in our study. However, fasting insulin levels are affected by several other factors among type 2 diabetic subjects and may not truly reflect only insulin resistance in them. An earlier study in non-diabetic subjects found a significant relationship between fibrinogen and insulin levels [8, 17]. Hyperfibrinogenemia may thus mediate the atherogenic risk of obesity, insulin resistance as well as diabetes.

In conclusion, hypercoagulable and atherothrombotic state as indicated by plasma fibrinogen levels showed a progressive significant ascending trend from healthy controls to the diabetic subjects without macrovascular disease and to diabetic subjects with macrovascular disease. Plasma fibrinogen levels have shown significant correlation with surrogate markers of atherosclerosis, namely FMD endothelial dysfunction and CIMT but did not show any relationship with lipemic or glycemic parameters and athropometric markers of central obesity.

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