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Research Article

Metabolic Disorders in First-Degree Relatives of Patients With Type 2 Diabetes in a Southern Coastal Region in Iran

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Abstract

Background: Diabetes mellitus is a global health challenge. Metabolic disorders in first-degree relatives (FDRs) of patients with type 2 diabetes mellitus (T2DM) have been linked to a family history of diabetes.

Objectives: This study aimed to investigate the frequency of metabolic syndrome (MetS), diabetes, and prediabetes in FDRs of patients with T2DM.

Methods: This descriptive study included FDRs of patients with T2DM referred to the diabetes clinic of Shahid Mohammadi Hospital, Bandar Abbas, Iran in 2017. Waist circumference (WC) and blood pressure were measured for each participant. Fasting plasma glucose was measured in venous blood samples after 8-hour fasting. Two-hour plasma glucose was measured after a 75-g oral glucose tolerance test. Triglyceride and high-density lipoprotein were measured in venous blood samples after 12-hour fasting. The Adult Treatment Panel III (ATP III) and the International Diabetes Federation (IDF) criteria were used to diagnose MetS. Iranian-specific WC cutoffs from different studies were also used as alternatives for WC cutoffs in IDF criteria to form Iranian-specific MetS criteria.

Results: This study included 300 FDRs (male: 33.7% vs. female: 66.3%) of patients with T2DM, with a mean age of 33.56±10.64 years. Among the participants, 19.7% had prediabetes and 8% had diabetes. MetS was diagnosed in 8.3% and 15% of the FDRs based on the ATP III and IDF criteria, respectively. The frequency of MetS ranged from 6.7% to 11.7% based on six different Iranian-specific WC cutoffs.

Conclusion: The frequency of MetS, diabetes, and prediabetes was quite high in the FDRs of patients with T2DM. Screening for these metabolic disorders can help prevent future cardiovascular events in this specific group.

Keywords: Metabolic syndrome, Diabetes, Prediabetes, First-degree

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Background

The global prevalence of diabetes in adults aged 20-79 years has been estimated at 425 million cases (8.8%) in 2017, which has nearly tripled compared to the 151 million cases in 2000, and it is projected to reach 629 million (9.9%) in 2045 (1). There is no global data on metabolic syndrome (MetS); however, since the prevalence of MetS is almost 3-folds the prevalence of diabetes, the worldwide prevalence of MetS can be estimated at approximately one quarter of the world population. Differently put, over a billion people in the world are now affected by MetS (2). The diabetic population comprises nearly 70%-80% of patients with MetS (3). A national survey in Iran in 2007 demonstrated that the prevalence of MetS was about 37.4% based on the International Diabetes Federation (IDF) definition, 34.7% based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria, and 41.6% based on the ATP III/American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI) criteria (4).

Given the multifactorial nature of type 2 diabetes mellitus (T2DM), it largely depends on genetic and environmental factors and the complex interconnection between them. In other words, members of a family not only have common genes but also live in a shared environment, what is known as 'family history', which is an independent risk factor for T2DM (5). People with a family history of diabetes are twice to four times at higher risk of developing diabetes compared to those with no such history; however, the risk depends on the distance to the affected family member and the number of the affected members (6).

MetS is a cluster of risk factors for cardiovascular diseases and has been defined differently by various organizations (7), including the World Health Organization (WHO), NCEP ATPIII, and IDF. The variations in the diagnostic

criteria have led to the report of conflicting results by different studies assessing the prevalence of MetS. Nevertheless, it is well accepted that the prevalence of MetS is increasing in epidemic proportions, regardless of the criteria, in both developing and developed countries (8).

β-cell dysfunction and insulin resistance have been documented in non-diabetic first-degree relatives (FDRs) of T2DM patients (9). Glucose metabolism disturbance is related to impaired β-cell function, glucose intolerance, and defective insulin action. Moreover, early signs of metabolic disorders, including endothelial dysfunction, energy imbalance, and adiposopathy reflected as dyslipidemia and overweight/obesity have been observed in FDRs, which are associated with an increased risk of MetS (6). On the other hand, adiposopathy, characterized by abnormal distribution and function of adipose tissue with overt triglyceride, contributes to the development of MetS and is strongly associated with T2DM (10). Multiple clinical studies have demonstrated a significant difference between FDRs and individuals without a family history of diabetes (non-FDRs) regarding MetS-associated metabolic indices, particularly the indices reflecting glucose and lipid metabolism (11, 12). Nevertheless, no consensus has been reached with respect to MetS.

Objectives

The current study aimed to investigate the frequency of MetS in FDRs of patients with T2DM based on different diagnostic criteria, as well as the frequency of diabetes and prediabetes in this population.

Materials and Methods

Participants

In this descriptive study, 300 FDRs (children, siblings, and parents) of patients with T2DM aged 18-65 years were evaluated. The sample size was determined with $\alpha = 0.05$, $d = 0.06$, and frequency of T2DM and prediabetes among FDRs of patients with T2DM in the study by Keykha et al (47.1%) (13). Through systematic random sampling method, we included the medical charts of 150 T2DM patients referred to the endocrinology clinic of Shahid Mohammadi Hospital in Bandar Abbas, Iran in 2017. The patients were contacted and inquired about their FDRs. The names of the FDRs were recorded and two of them were randomly invited to take part in the study. Exclusion criteria were drug history of corticosteroids, lipid-lowering agents, cyclosporine, and tacrolimus, pregnancy, and confirmed T2DM.

Study Design

Age, gender, and relationship to the diabetic patient were recorded. We measured waist circumference (WC) twice for each participant and the average was recorded. The same stretch-resistant tape was used for all measurements and the results were recorded to the nearest 0.5 cm. Blood pressure (BP) was also measured after a 5-min rest using a standard sphygmomanometer with an appropriate cuff size. Then, BP was measured twice with measurements at least 5 min apart, whose average was recorded for each subject.

Fasting plasma glucose (FPG) was measured in venous blood samples collected following overnight 8-hour fasting using the glucose oxidase method. Then, an oral glucose tolerance test (OGTT) with 75 g glucose (dextrose monohydrate powder from Iran Dextrose Co. dissolved in 250-300 ml of water) was performed. A second blood sample was collected 2 hours after the ingestion of 75-g glucose to measure 2-hour plasma glucose (2-h PG). Venous blood samples were collected on another day following overnight 12-hour fasting and triglyceride (TG) and high-density lipoprotein (HDL) were measured for each participant using the enzymatic method.

According to the American Diabetes Association (ADA) criteria, diabetes was defined as FPG ≥126 mg/dL and/or 2-h PG during a 75-g OGTT ≥200 mg/dL. Since different types of hemoglobinopathies are common in the south of Iran, glycated hemoglobin (HbA1c) was not considered a diagnostic test in our population. Diabetes was confirmed in a repeat test if only one of these was met. Impaired fasting glucose (IFG) was defined as 100 ≤FPG < 126; impaired glucose tolerance (IGT) was defined as 140 ≤2-h PG < 200; isolated IFG was defined as 100 ≤FPG < 126 and 2-h PG < 140; and isolated IGT was defined as 140 ≤2-h PG < 200 and FPG < 100. Prediabetes was defined as individuals with isolated IFG, isolated IGT, or combined IFG and IGT.

NCEP ATPIII has defined MetS as presence of any three or more of the following:

1. WC ≥102 cm in men, ≥88 cm in women
2. FPG ≥100 mg/dL or drug treatment for elevated blood glucose
3. HDL < 40 mg/dL in men, < 50 mg/dL in women or drug treatment for low HDL
4. TG ≥150 mg/dL or drug treatment for elevated TG
5. BP≥130/85 mm Hg or drug treatment for hypertension

IDF has defined MetS as WC ≥94 cm in men or ≥80 cm in women along with the presence of two or more of the other statements in the previous criteria (numbers 2-5). Iranian-specific WC cutoffs from different studies (14-19) were used as alternatives for WC cutoffs in IDF criteria to form Iranian-specific criteria for the diagnosis of MetS.

Data Analysis

We used the Statistical Package for the Social Sciences (SPSS) software (version 25.0, Armonk, NY: IBM Corp.) for data analysis. Quantitative variables were described using mean and standard deviation. Qualitative variables were described using frequencies and percentages. The Chi-squared and Fisher's exact tests were used to compare

frequencies between the groups. *P* values ≤0.05 were considered statistically significant.

Results

In this study, out of a total of 300 FDRs of patients with T2DM, 101 (33.7%) were men. The mean age of the participants was 33.56 ± 10.64 years. Also, 281 (93.7%) FDRs were offspring, 18 (6%) were siblings, and only 1 (0.3%) was a parent of T2DM patients. In addition, 59 (19.7%) patients had prediabetes and 24 (8%) had diabetes. Isolated IFG, isolated IGT, and IFG + IGT were found in 27 (9%), 24 (8%), and 8 (2.7%) FDRs, respectively. IFG + IGT, IFG and/or IGT, and isolated IGT were more frequent in women, while diabetes and isolated IFG were more frequent in men; however, only the difference in isolated IGT was statistically significant (*P* = 0.022) (Table 1).

Participants were divided into three age groups: 18-24 (23%), 25-44 (62.3%), and 45-65 (14.7%) years. Table 2 demonstrates the frequency of diabetes, prediabetes, isolated IFG, isolated IGT, and IFG+IGT in different age groups. Diabetes, prediabetes, and isolated IGT were significantly more frequent in FDRs aged 45-65 years (*P* = 0.046, *P* = 0.007, and *P* = 0.021, respectively).

MetS was diagnosed in 8.3% of the FDRs based on the ATP III criteria and in 15% based on the IDF criteria. The frequency of MetS ranged from 6.7% to 11.7% based on six different Iranian-specific WC cutoffs as a part of the IDF diagnostic criteria for MetS (Table 3).

Table 4 demonstrates the frequency of separate components of MetS in the study population. TG ≥150 mg/dL was significantly more frequent in FDRs with prediabetes and diabetes (*P* < 0.001), and BP≥130/85 mmHg was significantly more common in FDRs with diabetes (*P* < 0.001). To assess the number of MetS components, we used Esteghamati and colleagues' WC cutoffs since the frequency of MetS (based on population-specific WC cutoffs) in the study population was the highest using these cutoffs (Table 3). While 32.7% and

Table 1. Frequency of Diabetes, Prediabetes, Isolated IFG, Isolated IGT, and IFG + IGT in FDRs

Variable	Female No. (%)	Male No. (%)	Total No. (%)	*P* Value*
Diabetes	14 (7)	10 (9.9)	24 (8)	0.387
IFG and/or IGT (Prediabetes)	42 (21.1)	17 (16.8)	59 (19.7)	0.379
Isolated IFG	15 (7.5)	12 (11.9)	27 (9)	0.214
Isolated IGT	21 (10.6)	3 (3)	24 (8)	0.022
IFG + IGT	6 (3)	2 (2)	8 (2.7)	0.722**

Abbreviations: N, number; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.
*Analyzed by the Chi-squared test. **Analyzed by the Fisher's exact test.

Table 2. Frequency of Diabetes, Prediabetes, Isolated IFG, Isolated IGT, and IFG + IGT in Different Age Groups

Variable	18-24 yrs. (N = 69) No. (%)	25-44 yrs. (N = 187) No. (%)	45-65 yrs. (N = 44) No. (%)	*P* Value*
Diabetes	2 (2.9)	15 (8)	7 (15.9)	0.046
IFG and/or IGT (Prediabetes)	9 (13)	34 (18.2)	16 (36.4)	0.007
Isolated IFG	5 (7.2)	14 (7.5)	8 (18.2)	0.070
Isolated IGT	3 (4.3)	13 (7)	8 (18.2)	0.021
IFG + IGT	1 (1.4)	7 (3.7)	0 (0)	0.445**

Abbreviations: N, number; yrs., years; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.
*Analyzed by the chi-squared test. **Analyzed by Fisher exact test.

Table 3. Frequency of MetS in FDRs of Patients With T2DM

MetS Criteria	WC cut-off	Female (N = 199) No. (%)	Male (N = 101) No. (%)	Total No. (%)	*P* Value*
NCEP ATPIII	≥ 102 (male) ≥ 88 (female)	16 (8)	9 (8.9)	25 (8.3)	0.797
IDF	≥ 94 (male) ≥ 80 (female)	30 (15.1)	15 (14.9)	45 (15)	0.959
Azizi et al (14)	≥ 90 cm	15 (7.5)	15 (14.9)	30 (10)	0.046
Delavari et al (15)	≥ 89 (male) ≥ 91 (female)	14 (7)	15 (14.9)	29 (9.7)	0.030
Esteghamati et al (16)	≥ 91.5 (male) ≥ 85.5 (female)	20 (10.1)	15 (14.9)	35 (11.7)	0.221
Hadaegh et al (17)	≥ 94.5 cm	9 (4.5)	15 (14.9)	24 (8)	0.002
Mirmiran et al (18)	≥ 92 cm	13 (6.5)	15 (14.9)	28 (9.3)	0.019
Talaei et al (19)	≥ 92.6 (male) ≥ 97.8 (female)	5 (2.5)	15 (14.9)	20 (6.7)	<0.001

Abbreviations: FDR, first-degree relative; T2DM, type 2 diabetes mellitus; N, number; MetS, metabolic syndrome; WC, waist circumference; NCEP ATPIII, National Cholesterol Education Program Adult Treatment Panel III; IDF, International Diabetes Federation.
*Analyzed by the Chi-squared test.

Table 4. Frequency of Individual Components of MetS in FDRs

	Gender			Glycemic Status				
	Female (n=199) No. (%)	Male (n=101)	*P* Value*	Normal (n=217)	Prediabetes (n=59)	Diabetes (n=24)	Total (N=300)	*P* Value*
TG ≥ 150 mg/dL	37 (81.4)	39 (38.6)	<0.001	40 (18.4)	25 (42.4)	11 (45.8)	76 (25.3)	<0.001
BP ≥ 130/85 mm Hg	19 (9.5)	16 (15.8)	0.109	20 (9.2)	6 (10.2)	9 (37.5)	35 (11.7)	<0.001
FPG ≥ 100 mg/dL	33 (16.6)	24 (23.8)	0.134					
HDL<40 mg/dL (male) HDL<50 mg/dL (female)	91 (45.7)	19 (18.8)	<0.001	80 (36.9)	22 (37.3)	8 (33.3)	110 (36.7)	0.938
NCEP ATPIII WC	61 (30.7)	22 (21.8)	0.105	46 (21.2)	23 (39)	14 (58.3)	83 (27.7)	<0.001
IDF WC	119 (59.8)	43 (42.6)	0.005	97 (44.7)	44 (74.6)	21 (87.5)	162 (54)	<0.001
Esteghamati et al's WC (16)	76 (38.2)	49 (48.5)	0.087	72 (33.2)	35 (59.3)	18 (75)	125 (41.7)	<0.001
MetS Components***								
None	47 (23.6)	26 (25.7)	0.685	71 (32.7)	2 (3.4)	0 (0)	73 (24.3)	<0.001
One	74 (37.2)	30 (29.7)	0.198	88 (40.6)	14 (23.7)	2 (8.3)	104 (34.7)	0.001
Two	55 (27.6)	28 (27.7)	1.000	52 (24)	25 (42.4)	6 (25)	83 (27.7)	0.019
Three	20 (10.1)	7 (6.9)	0.372	4 (1.8)	13 (22)	10 (41.7)	27 (9)	<0.001
Four	3 (1.5)	10 (9.9)	0.001**	2 (0.9)	5 (8.5)	6 (25)	13 (4.3)	<0.001**

Abbreviations: FDR, first-degree relative; N, number; MetS, metabolic syndrome; TG, triglyceride; BP, blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; WC, waist circumference; NCEP ATPIII, National Cholesterol Education Program Adult Treatment Panel III; IDF, International Diabetes Federation.
*Analyzed by the Chi-squared test. **Analyzed by the Fisher's exact test. ***With regard to Esteghamati and colleagues' cutoff for WC.

40.6% of FDRs without prediabetes or diabetes had no MetS components and one MetS component, respectively ($P<0.001$ and $P=0.001$). Having two components was more common among FDRs with prediabetes (42.4%), and having three and four components was more common among FDRs with diabetes (41.7% and 25%, respectively).

Discussion

Almost 20% of the FDRs of patients with T2DM in this study had prediabetes (those with IFG and/or IGT) and 8% had diabetes. Moreover, isolated IFG, isolated IGT, and IFG + IGT were found in 27 (9%), 24 (8%), and 8 (2.7%) of FDRs, respectively. In another Iranian study with similar diagnostic criteria, the frequency of isolated IFG and isolated IGT in FDRs of patients with T2DM was reported as 18% and 8.3%, respectively (20). Compared to the 7.3% global prevalence of IGT in the adult population in 2017 (21), both studies demonstrated higher rates of IGT in FDRs. A positive family history of T2DM nearly doubles the risk of diabetes in the offspring and is an important risk factor for prediabetes, especially combined IFG and IGT (22); therefore, it is not unreasonable to assume that the frequency of diabetes and prediabetes should be higher in FDRs of patients with T2DM compared to the general population. However, the diagnostic criteria and terminology associated with prediabetes vary considerably between organizations, and care must be taken when interpreting and describing prevalence and incidence data (1).

In the current study, the male to female ratio was 0.8 for prediabetes and 1.4 for diabetes; prediabetes was more frequent in female FDRs while diabetes was more frequent in male FDRs. Also, isolated IGT and IFG + IGT were more frequent in women, while isolated IFG was more frequent in men. Similarly, in the study by Iraj et al, among FDRs of patients with T2DM, IFG was more frequently found in men and IGT in women (20).

Hepatic insulin resistance is associated with IFG, while insulin resistance in skeletal muscles and impaired insulin secretion are more often linked to IGT. The former is considered the more important predictor of diabetes risk than the latter (23). Moreover, IFG and IGT are now considered independent risk factors for cardiovascular diseases, especially the combination of IFG and IGT; this was reported in a meta-analysis showing that, compared with normoglycemic individuals, there was an increased risk of cardiovascular disease, coronary heart disease, stroke, and all-cause mortality in those with prediabetes (24).

It has also been reported that the presence of MetS is associated with a 2-fold increase in the risk of cardiovascular disease, cardiovascular mortality, and stroke, and a 1.5-fold increase in the risk of all-cause mortality rates (25). In this study, MetS was diagnosed in 8.3% of the FDRs based on the ATP III criteria and in 15% based on the IDF criteria. The IDF criteria appears to be more acceptable because it uses population-specific WC cutoffs. In the current study, the frequency of MetS ranged from 6.7% to 11.7% based on different Iranian-specific WC cutoffs. MetS was more frequent in men compared to women according to almost all the aforementioned criteria. Moon et al demonstrated a significant difference in the prevalence of MetS between healthy young adults with and without family history of T2DM (21.3% vs.

12.1%, $P<0.001$). Each component of MetS, except for HDL levels, also showed higher prevalence in subjects with a family history of T2DM (11). In the study by Hu et al, the prevalence of MetS in FDRs (36.44%) was significantly higher than non-FDRs (25.28%) (26).

Components of MetS have also been separately compared between FDRs of T2DM patients and non-FDRs. A study of a South Asian population showed that FDRs were vulnerable to dyslipidemia, especially higher TG levels (12). Prediabetic FDRs showed higher postprandial TG response and endothelial dysfunction, reported by Madhu et al (27). Additionally, diastolic blood pressure and incident hypertension was higher in FDRs (11). All these studies compared FDRs with non-FDRs; however, none of them compared MetS components in FDRs with prediabetes, diabetes, and normal glycemic status. FDRs with normal glycemic status seem to be healthier than those with prediabetes or diabetes regarding individual components of MetS, namely TG, BP, and WC. Moreover, in the current study, both no and one MetS components were significantly more frequent in FDRs with normal glycemic status, whereas two components were more common in FDRs with prediabetes and three and four components in FDRs with diabetes.

One limitation of the current study was that although the benefits of early detection of MetS, diabetes, and prediabetes were comprehensively explained to the FDRs, they were uncooperative and were not willing to take part in the study. This may be reflective of lack of an appropriate information system on these metabolic disorders and their impact on people's survival and quality of life. Another limitation of this study was that two effective factors including physical activity and diet were not taken into account. Analyses of further studies should be adjusted for these potentially influential factors.

Conclusion

The frequency of MetS, diabetes, and prediabetes is quite high in FDRs of patients with T2DM. Screening for these metabolic disorders in this specific group can help prevent future cardiovascular events. Further studies in this regard should include a control group for comparison and confirmation of our findings.

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Authors' Contribution

MK designed the study and was a major contributor in writing the manuscript. SK called the subjects, explained the aims of the study, invited them to participate, and collected the results. AA was consulted on the appropriate laboratory tests and coordinated the laboratory personnel. AD collected blood samples and performed the laboratory tests. MM determined the sample size and analyzed the acquired data. RS interpreted the analyzed data and GZ wrote the manuscript. All authors read and approved the final manuscript.

Conflict of Interests

The authors declared that they have no competing interests.

Ethical Approval

The study received ethics approval (code: HUMS.REC.1396.51) from the Ethical Committee of Hormozgan University of Medical Sciences and it complies with the statements of the Declaration of Helsinki. Written informed consent was obtained from all the participants.

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