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Incidence of metabolic syndrome and its risk factors among type 2 diabetes clinic attenders in Isfahan, Iran

Zapadalność na zespół metaboliczny i czynniki ryzyka tego zespołu u chorych na cukrzycę typu 2 pacjentów poradni diabetologicznej w Isfahanie w Iranie

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Abstract

Introduction: At present, little data exists about the incidence of, and the risk factors associated with, metabolic syndrome (MetS) in patients with type 2 diabetes mellitus (T2DM). The aims of this present study were to assess the incidence and risk factors of MetS in people with T2DM using routinely collected data from a clinical information system at Isfahan Endocrine and Metabolism Research Centre, Iran.
Material and methods: During the mean (SD) follow-up period of 11.7 (4.8) years, 3,047 patients with T2DM who were free of MetS at baseline were examined to determine the incidence and predictors of progression to MetS. The mean (SD) age of participants was 50.4 (11.0) years, with a mean (SD) duration of diabetes of 6.3 (6.2) years at initial registration. A modified National Cholesterol Education Programme- Adult Treatment Panel III definition (with body mass index [BMI] instead of waist circumference) was used for the MetS.
Results: The prevalence of MetS was 63.2% (95% CI: 62.3, 64.1). The incidence of MetS was 28.5 (95% CI: 26.8, 30.2) (25.9 men and 30.9 women) per 1,000 patient-years based on 35,677 patient-years of follow-up. Multivariate analysis revealed that higher body mass index (BMI) and education, lower HbA_{1c} and treatment with oral agent or insulin were associated with MetS.
Conclusions: These are the first estimates of the incidence and risk factors of MetS in patients with T2DM in Iran. These findings show that the natural course of MetS is dynamic. The clinical management of patients with T2DM will contribute significantly to MetS prevention. **(Pol J Endocrinol 2012; 63 (5): 372–380)**

Key words: *diabetes, incidence, metabolic syndrome, risk factors*

Streszczenie

Wstęp: Obecnie dostępnych jest niewiele danych dotyczących zapadalności na zespół metaboliczny (MetS) i związanych z nim czynników ryzyka u chorych na cukrzycę typu 2 (T2DM). Niniejsze badanie przeprowadzono w celu oceny zapadalności na MetS i występowania czynników ryzyka tego zespołu u chorych na cukrzycę typu 2 na podstawie rutynowych danych gromadzonych w systemie informacji klinicznej w *Isfahan Endocrine and Metabolism Research Centre* w Iranie.
Materiał i metody: W ciągu okresu obserwacji, trwającego średnio (SD) 11,7 (4,8) roku, przebadano 3047 chorych na T2DM, u których wyjściowo nie stwierdzono cech MetS, w celu określenia zapadalności i czynników predykcyjnych progresji do MetS. Średnia wieku (SD) uczestników wynosiła 50,4 (11,0) roku, a średni czas trwania (SD) cukrzycy w momencie pierwszej rejestracji danych — 6,3 (6,2) roku. Rozpoznanie MetS ustalano na podstawie zmodyfikowanej definicji *National Cholesterol Education Programme — Adult Treatment Panel III* (w której uwzględniono wskaźnik masy ciała [BMI] zamiast obwodu talii).
Wyniki: Częstość występowania MetS w badanej populacji wynosiła 63,2% (95% CI: 62,3–64,1). Wskaźnik zapadalności na MetS wynosił 28,5 (95% CI: 26,8–30,2) (25,9 dla mężczyzn i 30,9 dla kobiet) na 1000 pacjentolat, co wyliczono na podstawie obserwacji obejmującej 35 677 pacjentolat. W analizie wieloczynnikowej wykazano, że wyższe wartości BMI, wyższy poziom wykształcenia, niższe HbA_{1c} i leczenie doustnymi lekami hipoglikemizującymi oraz insuliną wiązały się z MetS.
Wnioski: W niniejszej pracy po raz pierwszy oszacowano zapadalność na MetS i określono czynniki ryzyka rozwoju tego zespołu u pacjentów z T2DM w Iranie. Uzyskanie rezultaty wskazują, że naturalny przebieg MetS jest procesem dynamicznym. Odpowiednie leczenie chorych na T2DM może mieć istotne znaczenie w zapobieganiu MetS. **(Endokrynol Pol 2012; 63 (5): 372–380)**

Słowa kluczowe: *cukrzyca, zapadalność, zespół metabolicznych, czynniki ryzyka*

Introduction

Metabolic syndrome (MetS) is an important public health problem worldwide, and its prevalence is increasing [1, 2]. Patients with MetS are at higher risk for many long-term complications, including micro- and macro-vascular complications [2]. This is particularly relevant in patients with type 2 diabetes mellitus (T2DM), who are at even greater cardiovascular risk [3]. In fact, cardiovascular complications are the commonest cause of morbidity and mortality in patients with T2DM [4].

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The relationship between MetS and diabetes and cardiovascular disease is well established and consistent and has been examined in many different populations [3, 5, 6]. T2DM and cardiovascular disease have many risk factors in common, and many of these risk factors are highly correlated with one another [5, 7]. MetS is very common among patients with T2DM; using the Third Report of the National Cholesterol Education Programme Adult Treatment Panel (NCEP/ATP III) definition, over 65% of patients with T2DM have MetS [8]. This is a much higher prevalence than in comparable general populations [9, 10]. The higher prevalence of MetS in patients with T2DM may be explained by medication-, disease- and lifestyle-related factors. Limited information is available about the incidence of MetS and its risk factors in patients with T2DM, and no information whatever in Iran.

Accurate information regarding the incidence of MetS and associated risk factors in people with T2DM is important in order to get a better understanding of the natural course of metabolic and cardiovascular risk in a non-pre-selected cohort of diabetic patients in routine practice.

This study therefore used routinely collected data from a clinical information system for diabetes at Isfahan Endocrine and Metabolism Research Centre, Iran, to estimate the incidence of MetS and to identify its risk factors in a large sample of diabetic patients receiving routine care.

Material and methods

Participants and data collection

The recruitment methods and examination procedures of the Isfahan Endocrine and Metabolism Research Centre outpatient clinics have been previously described [11, 12]. In summary, clinical data was collected for all consecutive patients at the first attendance and at review consultations (usually annual) using standard encounter forms. These included an examination of ocular fundus and lens, the limbs, and blood pressure (BP), and measurement of height, weight, fasting plasma glucose (FPG), glycosylated haemoglobin (HbA_{1c}), urine protein, and triglyceride, cholesterol, and serum creatinine levels. The clinician compiled a list of problems, and smoking was reported via a questionnaire completed by each patient on demography, family history, and smoking.

Generally, newly diagnosed patients were referred to qualified nutritionists for evaluation; if necessary, a lifestyle and weight management programme was recommended. All newly diagnosed patients attended weight-related health education classes, free of charge.

Participants

Using routinely collected data from a clinical information system at Isfahan Endocrine and Metabolism Research Centre, Iran, we performed a retrospective longitudinal, observational study. The study population consisted of all prevalent cases of T2DM and all patients diagnosed during the study period. Between 1992 and 2009, a total of 11,281 patients with T2DM were registered in the system. However, this study uses data only for 3,047 of these patients, i.e. 1,461 (47.9%) men and 1,586 (52.1%) women who had at least one subsequent review since registration and who were free of MetS at baseline. The physician defined the type of diabetes according to the American Diabetes Association criteria [13].

Our study conformed to the Declaration of Helsinki. Institutional ethical committee approval was granted, and an informed consent was signed by each patient.

Ascertainment of MetS

A minimally modified NCEP/ATP III [14] definition, with body mass index (BMI) instead of waist circumference, was used for MetS, with the presence of three or more of the following abnormalities: blood pressure ≥ 130/85 mm Hg or a history of hypertension and current use of antihypertensive treatment; BMI ≥ 25 kg/m^2; serum triglyceride ≥ 150 mg/dL (≥ 1.7 mmol/L); high-density lipoprotein cholesterol (HDL; < 40 mg/dL (< 0.9 mmol/L) for men and < 50 mg/dL (< 1.0 mmol/L) for women); and known diabetes mellitus. BMI ≥ 25 kg/m^2 was used because waist circumference was not available. In some other studies, BMI has been adopted instead of waist circumference for the analysis of MetS [5, 8, 15, 16].

Procedures

Predictors of progression to MetS were assessed using the following data from the patient's registration consultation: gender, age at diagnosis (i.e. at the time this was first recorded by a physician on the participant's chart), current age (at the time of examination), educational level, duration of diabetes (the time between diagnosis and the baseline examination), BMI (weight/height^2 [kg/m^2]), smoking status (never or current), HbA_{1c} (measured by ion-exchange chromatography), FPG (measured by the glucose oxidase method, Clinical Chemistry Analyzer Liasys, Italy), proteinuria (measured by precipitation with 3% sulfosalicylic acid and determination of turbidity by measuring absorbance at a wavelength of 550 nm with a spectrophotometer), and levels of serum creatinine, triglyceride, cholesterol, HDL (measured using standardised procedures), and low-density lipoprotein cholesterol (LDL; calculated by the Friedewald Equation [17]).

Height and weight were measured using standard apparatus, with the subjects in light clothes and without shoes. Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height was measured to the nearest 0.5 cm, and assessed at baseline only. A physician measured the systolic and diastolic BPs of the participants (after they had been seated for ten minutes) using a mercury sphygmomanometer and standard techniques. All clinical and laboratory measurements at baseline and follow-ups were made using the same standardised protocol.

Determination of MetS incidence

Incidence of MetS was expressed as the number of cases of MetS per 1,000 patient-years of follow-up. As the relevant period, we considered the date of completion of the baseline examination between 1992 and 2009 until one of the following four events: a) occurrence of MetS; b) the date of the last completed follow-up; c) death; or iv) the end of the follow-up on December 31, 2009, whichever came first.

Statistical analysis

The statistical methods used included the Student's T-test; chi squared test, analysis of variance (ANOVA) or Kruskal-Wallis tests for normally or non-normally distributed continuous variables respectively and Cox's proportional hazards model. Univariate and multivariate Cox's proportional hazards models were fitted to identify predictors of new-onset MetS using SPSS version 18 for Windows (SPSS Inc., Chicago, IL, USA). All the significant variables in the bivariate analysis were included as independent variables in a multivariate Cox's proportional hazards models. Adjustment for age was examined in separate models. Age-adjusted means were calculated and compared using general linear models. All tests for statistical significance were two-tailed, confidence intervals (CI) were set at 95% and $p < 0.05$ was considered significant.

Results

Subject characteristics

Differences in distribution of several risk factors among 1,461 men and 1,586 women are shown in Table I. Women had slightly lower creatinine, were less likely to be smokers, and were younger at registration and had lower dyslipidaemia than men. Men had lower BMI, total cholesterol, HDL and LDL cholesterol than women. The mean (SD) BMI was 24.0 (3.3) for men and 25.7 (4.3) for women. The prevalence of overweight (BMI ≥ 25) was 25.1% (95% CI: 22.7, 27.4%) in men, and 45.1% (95% CI: 42.5, 47.8%) in women. Only 8.1% (95% CI: 6.7, 9.8%) of men and 5.10% (95% CI: 4.0, 6.4%) of women were underweight (BMI ≤ 20). The majority of patients were on oral agent (61.0%), and 22.6% of the sample was on diet and exercise; 16.4% of the patients were on insulin treatment.

Table I. *Age and age-adjusted means (SE) and proportions of selected characteristics among 1,461 men and 1,586 women*

Tabela I. *Średnie i skorygowane względem wieku wartości (SE) wybranych parametrów i ich rozkład w grupie 1461 mężczyzn i 1586 kobiet*

Variables	Men	Women
	Mean (SE)	Mean (SE)
Age at registration (yr.)	52.3 (0.28)	48.7 (0.27)**
Duration of diabetes (yr.)	6.5 (0.16)	6.2 (0.15)
Age at diagnosis (yr.)	43.9 (0.16)	44.2 (0.15)
BMI [kg/m^2]	24.0 (0.11)	25.7 (0.10)**
Systolic BP [mm Hg]	116.1 (0.37)	115.1 (0.35)*
Diastolic BP [mm Hg]	72.0 (0.27)	71.8 (0.25)
Fasting blood glucose [mg/dL]	203.4 (2.11)	199.0 (2.02)
HbA_{1c} (%)	8.8 (0.10)	8.5 (0.10)*
Creatinine [mg/dL]	1.04 (0.03)	0.88 (0.02)**
Triglycerides [mg/dL]	164.2 (3.21)	156.0 (3.10)
Cholesterol [mg/dL]	201.0 (1.25)	213.1 (1.20)**
HDL cholesterol [mg/dL]	46.9 (0.66)	55.8 (0.66)**
LDL cholesterol [mg/dL]	118.4 (2.32)	126.6 (2.34)*
	%	%
Obesity (BMI ≥ 30)		
Current smoker	32.5	2.6**
Dyslipidaemia†	37.1	32.6*
Therapeutic regimen		
Diet	21.7	23.4*
Oral agent	61.5	60.6
Insulin	16.9	16.1
Education		
Primary or below	46.7	72.2**
Secondary	32.3	22.2
Matriculation or above	21.0	5.6

*$p < 0.05$, **$p < 0.001$, †dyslipidaemia: triglyceride ≥ 150 mg/dL (≥ 1.7 mmol/L) or HDL cholesterol < 40 mg/dL (< 0.9 mmol/L) in men or < 50 mg/dL (< 1.0 mmol/L) in women; BP — blood pressure; HDL — high-density lipoprotein cholesterol; LDL — low-density lipoprotein cholesterol

Prevalence

As defined by the modified NCEP/ATP III criteria, of the 11,281 patients with T2DM, 7,132 (2,584 men and 4,548 women) had MetS. The overall prevalence of MetS was 63.2% (95% CI: 62.3, 64.1). Prevalence rates were higher in women (68.8% [95% CI: 67.7, 69.9])

than men (55.3% [95% CI: 53.9, 56.8]). The prevalence of MetS increased with age. Of the 1,412 patients who had been insulin-treated, 772 had MetS, giving a prevalence of 54.7% (95% CI: 52.1, 57.3). This was lower than the prevalence rate for non-insulin-treated, which was 66.3% (95% CI: 65.3, 67.2).

Most diabetic patients had three components of the syndrome (36.4%); 23.4% had four, and 3.4% had five components. Only 9.2% of the diabetic patients were free from any components of the syndrome, and 27.6% had one component.

Incidence

Of the 3,047 participants without MetS, 1,017 (33.4%) (446 men and 571 women) developed MetS in 35,677 (17,205 men and 18,472 women) patient-years of follow-up. The overall incidence of subsequent MetS was 28.5 (95% CI: 26.8, 30.2) per 1,000 patient-years. Incidence rates were higher in women (30.9 [95% CI: 28.4, 33.4]) per 1,000 patient-years) than men (25.9 [95% CI: 23.5, 28.3]). This difference was statistically significant ($p < 0.01$). Of the 501 patients who had been insulin-treated, 174 subsequently developed MetS, giving an incidence of 30.1 per 1,000 patient-years (95% CI: 25.7, 34.5). This was similar to the incidence rate seen for oral agent-treated, which was 29.4 per 1,000 patient-years (95% CI: 27.2, 31.7), but slightly higher than the incidence rate seen for exercise and diet treated, which was 24.9 (95% CI: 21.0, 28.2).

Risk factors

Table II shows the group means (SE) and proportions for those who did, and did not, develop MetS. Those who developed MetS were more often women and had higher weight, BMI, cholesterol, number of follow-up visits and proportion of obesity at baseline. Those who did not develop MetS were more likely to be smokers and had slightly higher follow-up period, height, and educational level than those who developed MetS.

Univariate analysis (Table III) showed age, gender, lower HbA_{1c}, BP, triglyceride, oral antihyperglycaemic therapy, overweight and obesity, and never smoking, to be significantly associated with the risk of developing MetS. Age-adjusted Cox regression coefficient among those free of MetS at registration showed that significant risk factors for developing MetS were: shorter duration of diabetes, lower FPG, cholesterol, triglyceride, creatinine, never smoking, higher education, oral agent or insulin treatment, and overweight and obesity.

The incidence of MetS was also analysed with multivariate model. Cox's proportional hazards model showed that higher BMI (RR 1.04; 95% CI: 1.03, 1.05), higher education (RR 1.48; 95% CI: 1.29, 1.69), and lower HbA_{1c} (RR 0.90; 95% CI: 0.88, 0.93), and treatment with insulin (RR 1.22; 95% CI: 1.10, 1.35) or oral agent (RR 1.25; 95% CI: 1.09, 1.43) at baseline significantly predicted the onset of MetS after a mean 11.7 years. No other variables were significant.

Discussion

In this follow-up study of 3,047 participants, the natural course of MetS in patients with T2DM was described. The incidence of MetS was 28.5 per 1,000 patient-years over an average follow-up of 11.7 years. The incidence rates were 25.9 per 1,000 patient-years in men and 30.9 in women. It seems that the higher the BMI and educational level, and the lower the HbA_{1c} and treatment with insulin or oral agent at baseline, the higher the risk of progression to MetS. To the best of our knowledge, little research has been done to estimate the incidence of MetS in patients with T2DM. Therefore, we cannot compare our findings with those of other studies. The incidence and prevalence rates of MetS in general populations in various studies from around the world show considerable variation [18, 19]. Estimates of the incidence and prevalence of MetS will depend upon the methodological factors, the definition of MetS used, and the composition of the community examined by age, gender, ethnicity, and social class, making comparisons between studies of limited value. Several cross-sectional evaluations, conducted at different times and in different populations, have shown considerable variation. The prevalence of MetS in people with T2DM of 63.2%, as reported in this study, is much higher than the value reported in general populations [9, 20–22] and similar to the studies on T2DM from other diabetic populations [23–25].

The incidence rate of MetS that we report in the present study is lower than that reported in low-risk population studies carried out in Japan [26], Europe [27] and North America [28–30], perhaps due to routine diabetes care. Patients with higher BP and dyslipidaemia were treated during routine care. The Baltimore Longitudinal Study of Aging reported an incidence of 25.5% in men and 14.8% in women after an average follow-up of six years [28]. The Insulin Resistance Atherosclerosis Study reported an incidence of 17.1% in men and 20.9% in women after a follow-up period of five years [29]. A longitudinal study of Japanese men aged 35 to 59 reported that the incidence of MetS was 3.6 per 100 person-years [26]. A longitudinal study of Korean male workers aged 30 to 39 reported that the incidence of MetS was 77 per 1,000 person-years [31]. Another study from an urban area of Portugal reported an incidence of 47/1,000 person-years, similar in men and women [27]. But this is higher than that reported in the San Antonio Heart Study, which showed a 15%

Table II. *Age and age-adjusted means (SE) and proportions of selected baseline characteristics between 1,017 patients with type 2 diabetes who did, and 2,030 who did not, develop metabolic syndrome (MetS)*

Tabela II. *Średnie i skorygowane względem wieku wartości (SE) wybranych parametrów wyjściowych i ich rozkład w grupie 1017 chorych na cukrzycę typu 2, u których rozwinął się zespół metaboliczny (MetS) i 2030 chorych bez MetS*

Variables	Developed MetS	Did not develop MetS	Difference (95% CI)
	Mean (SE)	Mean (SE)	
Age at registration (yr.)	50.8 (0.34)	50.2 (0.24)	0.6 (–0.23, 1.43)
Duration of diabetes (yr.)	6.2 (0.18)	6.4 (0.13)	–0.2 (–0.62, 0.32)
Age at diagnosis (yr.)	44.3 (0.18)	44.0 (0.13)	0.3 (0.00, 1.59)
Follow-up (yr.)	11.6 (0.15)	12.0 (0.11)	–0.4 (–1.13, –0.39)**
Number of follow-up visits	15.6 (0.41)	9.6 (0.29)	6.0 (5.01, 6.99)**
Height [cm]	159.8 (0.29)	161.5 (0.21)	–1.7 (–2.41, –0.99)**
Weight [kg]	66.8 (0.36)	64.0 (0.25)	2.8 (1.68, 3.73)**
BMI [kg/m^2]	26.0 (0.12)	24.3 (0.09)	1.7 (1.40, 2.00)**
Systolic BP [mm Hg]	116.1 (0.43)	115.3 (0.31)	0.8 (–0.30, 1.90)
Diastolic BP [mm Hg]	72.4 (0.31)	71.6 (0.23)	0.8 (0.00, 1.56)
Fasting glucose [mg/dL]	203.5 (2.49)	200.0 (1.78)	3.5 (–2.50, 9.50)
HbA_{1c} (%)	8.7 (0.11)	8.6 (0.09)	0.1 (–0.18, 0.38)
Creatinine [mg/dL]	0.94 (0.03)	0.97 (0.02)	–0.03 (–0.10, 0.04)
Triglycerides [mg/dL]	162.8 (3.77)	158.3 (2.76)	4.5 (–4.65, 13.70)
Cholesterol [mg/dL]	210.7 (1.48)	205.5 (1.07)	5.2 (–1.61, –8.79)*
HDL cholesterol [mg/dL]	51.0 (0.74)	51.6 (0.68)	–0.6 (–2.58, 1.38)
LDL cholesterol [mg/dL]	124.0 (2.44)	121.2 (2.24)	2.8 (–3.51, 9.51)
	%	%	
Men	43.9	50.0	–6.1 (–9.9, –2.4)*
Obesity (BMI ≥ 30)	15.7	8.4	7.3 (4.7, 10.00)**
Dyslipidaemia†	33.6	35.4	–1.8 (–5.4, 1.9)
Current smoker	12.9	19.5	–6.6 (–9.71, –3.61)**
Therapeutic regimen			
Diet	20.7	23.5	–2.8 (–5.81, 0.38)
Oral agent	62.1	60.5	1.6 (–1.97, 5.35)
Insulin	17.1	16.1	1.0 (–1.79, 3.84)
Education			
Primary or below	64.2	57.6	6.6 (2.82, 10.30)*
Secondary	25.4	28.0	–2.6 (–5.92, 0.89)
Matriculation or above	10.3	14.4	–4.1 (–6.54, –1.57)*

The difference in the mean or percentage of the variables between MetS and no MetS; *p < 0.01, **p < 0.001, †dyslipidaemia: triglyceride ≥ 150 mg/dL (≥ 1.7 mmol/L) or HDL cholesterol < 40 mg/dL (< 0.9 mmol/L) in men or < 50 mg/dl (< 1.0 mmol/L) in women; CI — confidence interval; BP — blood pressure; HDL — high-density lipoprotein cholesterol; LDL — low-density lipoprotein cholesterol

incidence of MetS in men and 17% in women after eight years of follow-up [30]. The threshold values used to define the MetS criteria were higher than those indicated by NCEP/ATP III for lipids (triglyceride ≥ 200 mg/dL, HDL < 35 mg/dL in men and < 45 mg/dL in women) and BP (BP ≥ 140/90 mm Hg for systolic and diastolic, respectively). However, our findings indicate that patients with T2DM appearing to be at higher risk for developing MetS do not actually develop it. A possible explanation is that these patients may adjust their habits toward a healthier lifestyle, besides receiving appropriate treatment for hypertension and hyperlipidaemia.

Several risk factors predicted the incidence of MetS in our study. Univariate analysis (Table III) shows

Table III. *Incidence rates and relative risks (RR) for metabolic syndrome by baseline variables*

Tabela III. *Wskaźniki zapadalności na zespół metaboliczny i ryzyko względne (RR) rozwoju zespołu metabolicznego zależnie od wyjściowych wartości badanych parametrów*

Variables	At risk (n)	Cases (n)	Person--year	Incidence/1,000 person-years	Crude RR (95% CI)	Age-adjusted RR (95% CI)†
All	3,047	1,017	35,677	28.5	–	–
Gender						
Men	1,461	446	17,205	25.9	1.00	1.00
Women	1,586	571	18,472	30.9	1.19 (1.06, 1.35)**	0.99 (0.84, 1.70)
Age (yr.)						
< 40	485	133	5,552	23.9	1.00	–
40–49	946	321	10,603	30.3	1.27 (1.04, 1.54)**	–
50–59	946	351	10,732	32.7	1.37 (1.12, 1.66)**	–
60–69	508	165	6,700	24.6	1.03 (0.82, 1.29)	–
≥ 70	160	47	2,134	22.0	0.92 (0.66, 1.28)	–
Age at diagnosis (yr.)						
< 30	198	58	2,333	24.9	1.00	–
30–59	2,584	874	30,116	29.0	1.16 (0.90, 1.52)	–
≥ 60	251	80	3,126	25.6	1.03 (0.74, 1.44)	–
Duration of diabetes (yr.)						
< 5	1,551	522	17,101	30.5	1.00	1.00
5–7	540	173	6,450	26.8	0.88 (0.74, 1.04)	0.85 (0.77, 0.94)**
8–11	422	143	5,104	28.0	0.92 (0.77, 1.10)	0.79 (0.71, 0.88)***
≥ 12	522	174	6,927	25.1	0.82 (0.70, 0.98)	0.71 (0.65, 0.80)***
Fasting glucose [mg/dL]						
< 100	139	51	1,428	35.7	1.00	1.00
≥ 100	2,809	951	33,258	28.6	0.80 (0.61, 1.06)	0.78 (0.66, 0.93)**
HbA_{1c} (%)						
< 6.5	258	99	1,407	70.4	1.00	1.00
≥ 6.5	1,034	423	8,667	48.8	0.69 (0.56, 0.86)*	0.51 (0.45, 0.59)***
Systolic BP [mm Hg]						
< 130	2,556	919	28,892	31.8	1.00	1.00
≥ 130	348	96	4,410	21.8	0.69 (0.56, 0.84)**	0.90 (0.80, 1.01)
Diastolic BP [mm Hg]						
< 85	2,709	966	30,796	31.4	1.00	1.00
≥ 85	189	49	2,413	20.3	0.65 (0.49, 0.86)**	0.88 (0.76, 1.02)
Cholesterol [mg/dL]						
< 200	1,332	429	14,494	29.6	1.00	1.00
200–219	512	182	6,038	30.1	1.02 (0.86, 1.21)	0.84 (0.76, 0.93)
≥ 220	1,010	373	12,892	28.9	0.98 (0.85, 1.12)	0.75 (0.69, 0.81)***
HDL [mg/dL]						
Men ≥ 40 & women ≥ 50	438	210	3,883	54.0	1.00	1.00
Men < 40 & women < 50	106	39	989	39.4	0.73 (0.52, 1.02)	0.85 (0.68, 1.05)
LDL [mg/dL]						
< 100	144	57	1,226	46.5	1.00	1.00
≥ 100	388	186	3,533	52.6	1.13 (0.85, 1.51)	0.86 (0.71, 1.05)

Table III. cont. *Incidence rates and relative risks (RR) for metabolic syndrome by baseline variables*

Tabela III. cd. *Wskaźniki zapadalności na zespół metaboliczny i ryzyko względne (RR) rozwoju zespołu metabolicznego zależnie od wyjściowych wartości badanych parametrów*

Variables	At risk (n)	Cases (n)	Person--year	Incidence/1,000 person-years	Crude RR (95% CI)	Age-adjusted RR (95% CI)†
Triglycerides [mg/dL]						
< 150	1,951	693	21,754	31.9	1.00	1.00
≥ 150	878	292	11,276	25.9	0.81 (0.71, 0.93)**	0.73 (0.67, 0.79)***
BMI [kg/m^2]						
< 25	1,688	511	20,077	25.5	1.00	1.00
25–29.9	644	300	6,739	44.5	1.75 (1.52, 2.01)***	1.24 (1.12, 1.35)***
≥ 30	293	153	2,803	54.6	2.14 (1.80, 2.56)***	1.47 (1.29, 1.67)***
Smoking						
Never smoker	1,979	677	25,960	26.1	1.00	1.00
Current smoker	416	100	5,820	17.2	0.66 (0.54, 0.81)***	0.87 (0.74, 0.98)*
Education						
Primary or below	1,718	621	21,273	29.2	1.00	1.00
Secondary	778	246	8,142	30.2	1.03 (0.89, 1.20)	1.25 (1.14, 1.36)***
Matriculation or above	374	100	3,782	26.4	0.90 (0.74, 1.12)	1.37 (1.23, 1.54)***
Creatinine [mg/dL]						
≤ 1.5	2,159	823	22,669	36.3	1.00	1.00
> 1.5	61	21	841	25.0	0.69 (0.45, 1.05)	0.60 (0.47, 0.77)***
Therapeutic regimen						
Diet	687	211	8,471	24.9	1.00	1.00
Oral agent	1,860	632	21,480	29.4	1.18 (1.01, 1.38)***	1.25 (1.11, 1.40)***
Insulin	500	174	5,777	30.1	1.21 (0.99, 1.49)	1.20 (1.10, 1.32)***

Total number of patient–years and at risk is not the same for each variable because of missing values; *p < 0.5, **p < 0.01, ***p < 0.001,†relative risks (with 95% CI) calculated by Cox's proportional hazards model; CI — confidence interval; RR — relative risk; BP — blood pressure; HDL — high-density lipoprotein cholesterol; LDL — low-density lipoprotein cholesterol

an expected pattern of association for many variables with the development of MetS. Participants who subsequently developed MetS had greater obesity and higher triglycerides, lower smoking and had a higher proportion of insulin- or oral agent-treated at baseline than those who did not develop MetS. In multivariate analysis, fewer remain independently associated. The people with T2DM who were insulin- or oral agent-treated were at higher risk of MetS than those treated with diet and exercise. Insulin or oral agent treatment may indicate a more severe disease process. A higher incidence of MetS among insulin- or oral agent-treated patients could be attributable to their longer duration of diabetes, younger age at onset, and poorer metabolic control than in non-insulin-treated diabetes. Other longitudinal studies have documented the pivotal role of obesity in the pathogenesis of MetS in different populations, although the definition of MetS adopted varied from study to study [28, 30].

The lack of correlation between the incidence of MetS and elevated BP at baseline in our patients is not surprising. In fact, this sort of 'dissociation' may affect the decision-making process in a clinical setting tailored to prevent MetS and cardiovascular events.

The role of gender as a risk factor for MetS remains unsettled. There have been conflicting reports about the relationship between gender and MetS incidence in general populations; in some studies, MetS incidence was higher in women [27, 30], whereas in other studies it was higher in men [34, 35]. Similar to our results, some other cohorts from different ethnic backgrounds have reported no significant differences regarding gender [29, 32, 33].

The higher MetS incidence found in lower values of HbA_{1c} was probably related to the fact that patients with higher values of HbA_{1c} probably are more deficient

in insulin and less insulin resistant, which could have reduced their probability to present MetS. However, this warrants further study.

Some limitations warrant consideration. The Isfahan clinical information system for diabetes provides one of the largest clinic-based data sets of its kind in the developing world. Although we have not carried out any special studies of the validity or reliability of data for this analysis, a clerk was employed to check consistency and, where possible, to ensure completeness of data. Previous studies have shown that these patients are a representative sample of the known diabetic patients of Isfahan [38]. Our experience with other parts of the data set gives us some confidence that data quality is sufficient for this type of study and that our results provide useful additional evidence on the incidence of, and risk factors for, MetS. The study was clinic-based, rather than population-based, and so may not contain a clinical spectrum representative of diabetic patients in the community. Many patients requiring only oral or dietary treatment may never attend the clinic. Clinic-based estimates of the incidence or prevalence of complications are most likely to be affected by referral patterns. Selection bias is less likely to affect incidence rates and associations between risk factors and complications as investigated in this study. The study was performed according to the modified NCEP/ATP III criteria [14]. We used BMI instead of waist circumference due to the unavailability of data regarding waist circumference in our database. The central pattern of distribution, with its higher weighting of waist circumference, is associated with more insulin resistance than is the peripheral pattern of distribution [37, 38]. Nevertheless, although waist measurement is easy and not time-consuming, the waist is not routinely measured in clinical practice. A number of studies have also shown that BMI is as effective as waist circumference for predicting the development of T2DM and other metabolic disturbances [5, 8, 15, 16]. In addition, the Japan Society for the Study of Obesity has reported that BMI can estimate visceral fat measured by computed tomography as robustly as waist circumference, and that obesity-related complications increase for a BMI of 25 [39]. An additional limitation of the present study is represented by the lack of information on the effect of medications (lipids lowering and antihypertensive) on the trajectory of MetS components. Despite the above limitations, the findings here add to our understanding of the incidence, prevalence, risk factors and the natural course of MetS in patients with T2DM in Iran. Furthermore, this study provides new data from Iran, a developing country that has been under-represented in past studies.

Conclusions

In conclusion, this longitudinal study provides information on the high prevalence, but low incidence rate, of MetS in patients with T2DM in Isfahan, Iran. Our study shows that in routine practice the natural course of MetS in patients with T2DM is dynamic. The clinical management of patients with T2DM will contribute significantly to MetS prevention.

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