

The product of triglycerides and glucose in comparison with fasting plasma glucose did not improve diabetes prediction

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Abstract

Aims Previous study has reported that triglycerides-glucose (TyG) index, a product of triglycerides and fasting plasma glucose (FPG), might be useful in the prediction of incident type 2 diabetes (T2D). We evaluated the ability of the TyG index compared to FPG and OGTT as possible diabetes predictor in nondiabetic first-degree relatives (FDRs) of patients with T2D.

Methods A total of 1,488 FDRs without diabetes of consecutive patients with T2D 30–70 years old (361 men and 1,127 women) were examined and followed for a mean (SD) of 6.9 (1.7) years for diabetes incidence. We examined the incidence of diabetes across quartiles of the TyG index and plotted a receiver operating characteristic (ROC) curve to assess discrimination. At baseline and through follow-up, participants underwent a standard 75-g two-hour oral glucose tolerance test.

Results During 10,124 person-years of follow-up, 41 men and 154 women developed T2D. Those in the top quartile of TyG index were 3.4 times more likely to develop T2D than those in the bottom quartile (odds ratio 3.36; 95 % CI

1.83, 6.19). On ROC curve analysis, a higher area under the ROC was found for FPG (76.2; 95 % CI 71.9, 80.6), 1-hPG (81.0, 95 % CI 77.2, 84.9) and 2-hPG (76.5; 95 % CI 72.3, 80.8) than for TyG index (65.1; 95 % CI 60.5, 69.7).

Conclusions TyG index is predicted T2D in high-risk individuals in Iran but FPG, 1-hPG and 2-hPG appeared to be more robust predictor of T2D in our study population.

Keywords Diabetes mellitus · First-degree relatives · Glucose tolerance · Incidence · Risk score · Triglycerides and glucose index · Product of fasting triglycerides and glucose

Introduction

Type 2 diabetes mellitus (T2D) is an important and growing public health problem worldwide [1]. Based on a recent report by the International Diabetes Federation (IDF), Middle East and North Africa region currently has the highest regional prevalence of T2D, and by 2030 it is expected to have the second largest proportional increase after Africa [2]. Based on available data of adults aged 20–70 years, the IDF Atlas of Diabetes [1] estimated a point prevalence of 9.33 % for T2D in 2011, and it has also predicted that this figure would rise to 13.15 % by 2030. T2D prevalence in Iran is significantly higher than its neighboring countries Pakistan (6.7 % for 2007) [3] and Turkey (7.2 %, for 1997–1998) [4]. On the other hand, our figures often fall below the prevalence rates observed in Arab communities [5]. Available reports of T2D prevalence among Middle Eastern countries vary substantially, ranging from 2.8 % in Israel [6] to 29 % in Bahrain [7]. In a 2009 systematic review, a prevalence rate of 10.5 % (95 % CI 8.6, 12.7 %) in the region was recorded [8].

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Thus, with a strong evidence base for lifestyle interventions to prevent diabetes [9, 10], there is great interest in identifying individuals at high risk of developing diabetes with the aim of prevention and proper intervention. A simple, reliable, noninvasive, effective and widely applicable tool to rapidly identify asymptomatic individuals in whom oral glucose tolerance tests (OGTT) should be measured to rule out T2D would be practical for use by the general public and in primary health care. During the past few decades, various risk factors and predictive models have been suggested to identify persons at high risk for the future development of T2D [11–13]. It is well established that the level of fasting plasma glucose (FPG) and triglycerides is associated with increased risk of T2D [14–16]. The triglycerides-glucose (TyG) index, the product of FPG and triglycerides, is a novel index that has been suggested as a surrogate of insulin resistance (IR) in healthy subjects [17–19]. It was well correlated with the homeostasis model assessment of IR (HOMA-IR) and total glucose metabolism rate during hyperinsulinemic-euglycemic clamp studies [18]. The assessment of IR is of interest because of its key role in T2D and is already present 1–2 decades before the diagnosis [20, 21], surrogate indices of IR might aid in the prediction of incidence T2D. It has been tested in a Korean population with encouraging results [22], but it may not be universally applicable among all ethnic groups and populations. No study to date has examined T2D incidence with TyG index in Iran. Moreover, nothing is known about the relationship of TyG and T2D in FDR of patients with T2D who are at higher risk of diabetes.

The objective of this study, therefore, was to evaluate the ability of TyG index compared with FPG and oral glucose tolerance test (OGTT) to predict the incidence of T2D in an Iranian population without diabetes.

Patients and methods

Data collection

This study was conducted within the framework of the Isfahan Diabetes Prevention Study (IDPS), an ongoing cohort in central Iran to assess the various potential risk factors for diabetes in subjects with family history of T2D (one of the main risk factors for diabetes). The recruitment methods and examination procedures of the IDPS have been described before [23]. Our study sample comprised 3,409 (895 men and 2,514 women) first-degree relatives (FDR) of consecutive patients with T2D. All patients were attendees at clinics at Isfahan Endocrine and Metabolism Research Center, which is affiliated to Isfahan University of Medical Sciences, Iran. The study was conducted

between the years 2003 and 2005. All participants were from Isfahan city and adjoining areas. They completed laboratory tests including a standard 75-g 2-h OGTT, a questionnaire on their health status and on various potential risk factors for diabetes. Participants received follow-up tests according to Standard of Medical Care in Diabetes [24] to update information on demographic, anthropometric and lifestyle factors and on newly diagnosed diabetes. Accordingly, if OGTT was normal at baseline, repeat testing was carried out at least at 3-year intervals. Otherwise, repeat testing was usually carried out annually. The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki [25] and has been approved by Institutional Review Board of Isfahan University of Medical Sciences, Iran, and an informed consent form was signed by each participant.

Follow-up and ascertainment of diabetes

Cases of diabetes were identified from baseline and follow-up OGTT according to American Diabetes Association criteria [26]. Pregnant women and people with type 1 diabetes were excluded. Among 3,409 persons who participated at baseline, 308 were excluded because of diagnosis of diabetes at baseline, 1,564 had no follow-up, and 49 had missing data, leaving 1,488 participants with a mean age 43.1 (6.6) (range 30–70) years for the present analysis, all of whom had at least one subsequent review during a mean [standard deviation (SD)] follow-up period of 6.9 (1.7) (range 3–10) years. Attendees at the follow-up visit did not differ significantly from non-attendees regarding most baseline characteristics: age, height, weight, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-hip ratio (WHR) and levels of HbA1c, cholesterol, low-density lipoprotein cholesterol (LDLC), triglycerides, systolic and diastolic blood pressure (BP) and obesity. However, non-attendees had slightly lower FPG (94.7 mg/dl vs. 95.7 mg/dl, $P < 0.05$) and plasma glucose (PG) at 30 min (138.7 mg/dl vs. 145.6 mg/dl, ($P < 0.001$), 60 min (141.1 mg/dl vs. 151.0 mg/dl, $P < 0.001$), 120 min (111.2 mg/dl vs. 120.6 mg/dl, $P < 0.001$) and a slightly lower TyG index (8.78 vs. 8.84, $P < 0.001$), but higher levels of high-density lipoprotein cholesterol (HDLC) (46.4 mg/dl vs. 45.0 mg/dl, $P < 0.01$).

Procedures

Information on age, gender, body size, HbA1c, cholesterol, LDLC, HDLC, triglycerides and BP, family and personal medical history was collected at baseline and through follow-up. The same methodology was used for baseline and

follow-up studies. The participants included siblings and children. Participants reported to clinics in the morning after an overnight fast. They were asked to abstain from vigorous exercise in the evening and in the morning of the investigations. Smokers were encouraged to abstain from smoking in the morning of their visit. First, on arrival at the clinic, the information provided by the participants in the questionnaire on family history was verified. Then, with the subjects in light clothing and without shoes, height, weight, WC and HC were measured using standard apparatus. Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height, WC and HC were measured to the nearest 0.5 cm with a measuring tape. The waist was measured midway between the lower rib margin and the iliac crest at the end of gentle expiration in the standing position. HC was measured over the greater trochanters directly over the underwear. Resting BP was measured at each examination by physician after the participants had been seated for 10 min with a mercury column sphygmomanometer and appropriately sized cuffs, using standard techniques. The systolic BP and diastolic BP were recorded at the first appearance (phase I) and the disappearance (phase V) of Korotkoff sounds. FPG was measured with the glucose oxidase method. Participants with FPG ≥ 200 mg/dl or pharmacological treatment were considered as persons with diabetes. If FPG was ≥ 126 mg/dl and <200 mg/dl, a second FPG was measured on another day. If the second FPG was also ≥ 126 mg/dl, participants were considered as persons with diabetes. Those with FPG < 126 mg/dl underwent a standard OGTT (75 g glucose, 2 h) at baseline and follow-up visits. Venous blood was sampled 0, 30, 60 and 120 min after oral glucose administration. Plasma samples were centrifuged and analyzed the same day.

Glycosylated hemoglobin (HbA1c) (measured by ion-exchange chromatography), total cholesterol, triglycerides, HDLC and LDLC (calculated with the Friedewald equation [27] provided total triglycerides did not exceed 400 mg/dl) were recorded. All blood sampling procedures were performed in the central laboratory of the Isfahan Endocrine and Metabolism Research Center using enzyme-linked method.

Definitions

Based on the OGTT results, participants were categorized as having either normal glucose tolerance (NGT, FPG below 100 mg/dl and the 2-h plasma glucose (2hPG) < 140 mg/dl), impaired fasting glucose (IFG, FPG in the range of 100–125 mg/dl and the 2hPG was < 140 mg/dl), impaired glucose tolerance (IGT, FPG < 126 mg/dl, but with 2hPG concentration ≥ 140 and < 200 mg/dl) or diabetes (FPG ≥ 200 mg/dl or pharmacological treatment,

FPG ≥ 126 and/or 2hPG ≥ 200 mg/dl) [28]. TyG index was computed for each participant as the natural logarithm (Ln) of [fasting triglycerides (mg/dl) \times FPG (mg/dl)/2] [18]. Metabolic syndrome was considered present when at least three of the following characteristics were observed: central obesity, defined using ethnic-specific cut points of waist (waist circumference ≥ 102 cm in men and ≥ 88 cm in women); triglycerides ≥ 150 mg/dl; HDLC < 40 mg/dl in men and < 50 mg/dl in women; BP $\geq 130/85$ mmHg or on antihypertensive medication, or raised plasma glucose, defined as FPG ≥ 100 mg/dl [29].

Determination of diabetes incidence

Incidence was expressed as the number of cases of T2D per 1,000 person-years of follow-up beginning on the date of completion of the baseline examination in 2003–2005 and continuing until the occurrence of diabetes, the date of the last completed follow-up, death or end of follow-up on September 31, 2011, whichever came first.

Analysis

Statistical methods included the Student's *t* test (for normally distributed variables), the Mann–Whitney *U* test (for not normally distributed variables), one-way ANOVA (for normally distributed variables), Kruskal–Wallis test (for not normally distributed variables), the Chi-squared test, Pearson correlation (for normally distributed variables), Spearman's rank correlation (for not normally distributed variables) and binary logistic regression. Differences between more than two groups were estimated using one-way ANOVA with Bonferroni post hoc test. Pearson correlation analysis or Spearman's rank correlation was used to examine the linear relationships between the TyG index and other variables. Univariate and multivariate binary logistic regression equations were fitted to identify predictors of new-onset diabetes using the SPSS version 18 for Windows [SPSS Inc., Chicago, IL, USA]. Diastolic BP was not included in multivariate analysis to avoid co-linearity between systolic and diastolic BP. The TyG index was recoded into quartiles and compared the risk of developing diabetes in each quartile with the lowest category of risk (reference group). The ability of TyG index, triglyceride, FPG, 1-hPG, 2-hPG and HbA1c values to predict the incidence diabetes was examined with receiver operating characteristic (ROC) curves and their respective areas under the curve, in which sensitivity was plotted as a function of 1-specificity. The area under the ROC curve is a global summary statistic of the discriminative value of a model, describing the probability that the score will be higher in an individual developing than in an individual not developing T2D. Areas under the ROC curves were

compared by the algorithm developed by DeLong et al. [30]. Age-adjusted means were calculated and compared using general linear models. All tests for statistical significance were two-tailed, and all were done assuming a type I error probability of <0.05.

Results

Baseline characteristics of the 1,294 (87.0 %) participants without and 195 (13.0 %) with diabetes are shown in Table 1. As expected, those who developed diabetes were older and had higher mean BMI, WC, HC, follow-up, FPG and PG at 30, 60 and 120 min, higher HbA1c, triglyceride, cholesterol, LDLC and TyG index at baseline, and a higher proportion of overweight, metabolic syndrome, IFG and IGT. The mean (SD) age was 44.5 (7.0) years for those with and 42.9 (6.5) years for those without diabetes. The mean (SD) TyG index was 9.1 (0.5) for those with and 8.8 (0.5) for those without diabetes.

The baseline characteristics of the study participants by TyG index quartile are shown in Table 2. In comparison with variables at baseline, all variables were more likely to increase. HDLC, NGT and follow-up duration were more likely to decrease across all four subject groups.

During 10,124 (2,448 men and 7,676 women) person-years of follow-up, 195 (13.0 %) (41 men and 154 women) incident cases of T2D occurred. The overall incidence of subsequent T2D was 19.2 (95 % CI 16.6, 21.9) per 1,000 person-years. Incidence rates were slightly higher in women (20.1; 95 % CI 16.9, 23.2 per 1,000 person-years) than men (16.7; 95 % CI 12.0, 22.6), but the difference was not statistically significant. The TyG index was associated with T2D incidence. The incidence of T2D was 30.9 per 1,000 person-years (95 % CI 24.5, 38.5) for participants in the highest quartile of TyG index, and 7.9 per 1,000 person-years (95 % CI 4.9, 12.0) for the lowest quartile. The risk of T2D increased with increasing quartiles of TyG index. Compared with participants in the lowest quartile,

Table 1 Age and age-adjusted means (SE) and proportional frequencies of selected baseline characteristics in 194 first-degree relatives of patients with type 2 diabetes who did and 1,294 who did not develop diabetes

Variables	Developed diabetes Mean (SE)	No diabetes Mean (SE)	Difference (95 % CI)
Age (year)	44.5 (0.47)	42.9 (0.18)	1.6 (0.61, 2.59)**
Height (cm)	158.5 (0.59)	159.6 (0.22)	-1.1 (-2.43, 0.03)
Weight (kg)	76.5 (0.84)	73.0 (0.32)	3.5 (1.56, 5.04)***
Body mass index (kg/m ²)	30.5 (0.30)	28.7 (0.11)	1.8 (1.18, 2.42)***
Waist circumference (cm)	91.8 (0.66)	88.4 (0.25)	3.4 (2.31, 5.09)***
Waist-to-hip ratio	0.83 (0.005)	0.83 (0.002)	0.0 (0.00, 0.03)
Hip circumferences (cm)	110.3 (0.63)	107.2 (0.24)	3.1 (1.67, 4.33)***
Follow-up duration (year)	7.2 (0.12)	6.8 (0.05)	0.4 (0.04, 0.56)**
Systolic BP (mmHg)	116.7 (1.16)	115.0 (0.44)	1.7 (0.28, 5.32)
Diastolic BP (mmHg)	76.2 (0.86)	74.9 (0.33)	1.3 (-0.04, 3.64)
Baseline fasting glucose (mg/dl)	105.6 (0.82)	94.2 (0.31)	11.4 (10.10, 13.50)***
Plasma glucose 30 min (mg/dl)	169.2 (2.27)	142.3 (0.84)	26.9 (23.10, 32.70)***
Plasma glucose 60 min (mg/dl)	194.5 (2.88)	144.5 (1.09)	50.0 (45.40, 57.60)***
Plasma glucose 120 min (mg/dl)	150.7 (2.31)	116.2 (0.88)	34.5 (30.30, 39.90)***
HbA1c (%)	5.5 (0.06)	5.0 (0.02)	0.5 (0.38, 0.62)***
Triglyceride (mg/dl)	193.5 (7.22)	162.7 (2.73)	30.8 (17.40, 47.80)***
Cholesterol (mg/dl)	205.4 (2.94)	195.0 (1.10)	10.4 (6.12, 18.70)**
HDL cholesterol (mg/dl)	45.1 (0.88)	45.0 (0.33)	0.1 (-1.73, 1.93)
LDL cholesterol (mg/dl)	123.8 (2.66)	118.5 (0.98)	5.3 (1.44, 12.80)*
TyG index	9.1 (0.04)	8.8 (0.01)	0.3 (0.22, 0.38)***
	%	%	
Men	21.0	24.9	-3.9 (-10.10, 2.29)
Overweight (BMI ≥ 25)	91.2	83.5	7.7 (3.24, 12.20)**
Normal glucose tolerance	11.8	55.4	-43.6 (-48.8, -38.3)***
Impaired fasting glucose	69.7	32.5	37.2 (30.30, 44.20)***
Impaired glucose tolerance	18.5	12.1	6.4 (0.60, 12.00)***
Metabolic syndrome	55.4	36.0	19.4 (12.00, 26.80)***

TyG index: Ln [fasting triglyceride (mg/dl) × FPG (mg/dl)/2]. Differences in mean or percentage values of variables between diabetes and no diabetes

CI confidence interval, BP blood pressure, HDL high-density lipoprotein, LDL low-density lipoprotein

* $P < 0.05$, ** $P < 0.01$,

*** $P < 0.001$

Table 2 Age and age-adjusted mean (SE) and proportion of first-degree relatives of patients with type 2 diabetes by triglycerides and glucose (TyG) index quartile in the Isfahan Diabetes Prevention Study

Characteristic	Total	TyG index at baseline			
		1st quartile (<8.50)	2nd quartile (8.50–8.83)	3rd quartile (8.84–9.17)	4th quartile (>9.17)
Number (%)	1,477 (100)	367 (25.0)	370 (25.0)	370 (25.0)	370 (25.0)
TyG index	8.8 (0.01)	8.2 (0.01)	8.7 (0.01)	9.0 (0.01)	9.5 (0.01)*
Age (year)	43.0 (0.03)	41.5 (0.33)	42.6 (0.33)	43.7 (0.33)	44.4 (0.33)*
Height (cm)	159.4 (0.21)	158.5 (0.43)	158.6 (0.42)	159.8 (0.42)	160.8 (0.43)*
Weight (kg)	73.5 (0.30)	69.8 (0.60)	72.3 (0.59)	74.7 (0.59)	77.1 (0.59)*
Waist circumference (cm)	88.9 (0.24)	85.0 (0.46)	88.0 (0.46)	90.1 (0.46)	92.4 (0.46)*
Hip circumference (cm)	107.6 (0.23)	105.8 (0.46)	107.4 (0.45)	108.5 (0.45)	108.9 (0.46)*
Waist-to-hip ratio	0.83 (0.002)	0.81 (0.003)	0.82 (0.003)	0.83 (0.003)	0.85 (0.003)*
Body mass index (kg/m ²)	28.9 (0.11)	27.8 (0.22)	28.8 (0.21)	29.3 (0.21)	29.8 (0.21)*
Follow-up duration (year)	6.8 (0.04)	8.1 (0.09)	6.8 (0.09)	6.7 (0.09)	6.6 (0.09)**
FPG (mg/dl)	95.8 (0.32)	90.6 (0.61)	94.8 (0.60)	97.4 (0.60)	100.1 (0.60)*
PG 30 min (mg/dl)	145.9 (0.84)	135.8 (1.64)	144.0 (1.63)	148.2 (1.61)	155.5 (1.65)*
PG 60 min (mg/dl)	151.3 (1.14)	134.6 (2.19)	146.5 (2.17)	157.8 (2.17)	166.4 (2.19)*
PG 120 min (mg/dl)	120.8 (0.89)	112.3 (1.76)	118.6 (1.74)	121.7 (1.75)	130.2 (1.75)*
HbA1c (%)	5.1 (0.02)	5.0 (0.4)	5.0 (0.4)	5.1 (0.4)	5.2 (0.4)**
Cholesterol (mg/dl)	196.6 (1.07)	177.8 (1.99)	193.5 (1.97)	201.3 (1.97)	213.6 (1.99)*
LDL (mg/dl)	119.2 (0.94)	113.1 (1.81)	122.5 (1.81)	123.3 (1.82)	117.7 (1.92)*
HDL (mg/dl)	45.1 (0.31)	48.3 (0.60)	46.5 (0.60)	44.2 (0.61)	41.2 (0.60)*
Triglyceride (mg/dl)	166.2 (2.55)	83.3 (3.30)	125.7 (3.27)	168.3 (3.27)	286.8 (3.28)*
Systolic BP (mm Hg)	115.2 (0.42)	111.6 (0.83)	113.5 (0.82)	116.3 (0.82)	119.3 (0.81)*
Diastolic BP (mm Hg)	75.0 (0.32)	72.3 (0.62)	74.0 (0.61)	75.7 (0.61)	78.0 (0.61)*
Women, no. (%)	1,126 (75.7)	310 (83.3)	290 (78.2)	279 (75.0)	247 (66.4)*
Overweight, no. (%)	1,243 (84.6)	275 (74.9)	307 (83.6)	322 (87.7)	339 (91.9)*
Normal glucose tolerance, no. (%)	740 (49.7)	246 (66.1)	204 (54.8)	160 (43.0)	130 (34.9)*
Impaired fasting glucose, no. (%)	557 (37.4)	81 (21.8)	115 (30.9)	165 (44.4)	196 (52.7)*
Impaired glucose tolerance, no. (%)	191 (12.8)	45 (12.1)	53 (14.2)	47 (12.6)	46 (12.4)*
Metabolic syndrome, no. (%)	585 (39.3)	32 (8.6)	68 (18.3)	203 (54.6)	282 (75.8)*

Data are expressed as mean (SE) or number (%). TyG index: $\text{Ln} [\text{fasting triglyceride (mg/dl)} \times \text{FPG (mg/dl)} / 2]$

* $P < 0.001$, ** $P < 0.01$ comparison across all four groups

the risk of T2D was 4.3 times higher in those in the highest quartile at baseline (odds ratio (OR) 4.29; 95 % CI 2.58, 7.13) and 2.7 times higher in those in the third quartile (OR 2.7; 95 % CI 1.60, 4.61) and 1.9 times higher in those in the second quartile (OR 1.85; 95 % CI 1.06, 3.22) in unadjusted models. Controlling for age and gender did not appreciably alter the OR compared to the unadjusted model. Further controlling for BMI, WC, BP and HbA1c attenuated associations. Further controlling for HDLC, LDLC and cholesterol slightly increased the ORs (Table 3).

The TyG index showed significant correlations ($P < 0.001$) with age ($r = 0.157$), weight ($r = 0.202$), BMI ($r = 0.157$), WC ($r = 0.295$), HC ($r = 0.107$), systolic BP ($r = 0.204$), diastolic BP ($r = 0.188$), levels of FPG ($r = 0.339$), 30 min PG ($r = 0.259$), 60 min PG

($r = 0.303$), 120 min PG ($r = 0.219$), HbA1c ($r = 0.101$), triglyceride ($r = 0.882$), cholesterol ($r = 0.380$), HDLC ($r = -0.210$), LDLC ($r = 0.084$).

The ROC curves for the incidence of T2D for TyG index, triglyceride, FPG, 1-hPG, 2-hPG and HbA1c are shown in Fig. 1. The areas under the ROC curves (95 % CI) were 0.651 (0.605, 0.695) for TyG index, 0.762 (0.719, 0.806) for FPG, 0.811 (0.772, 0.849) for 1-hPG, 0.765 (0.723, 0.808) for 2-hPG, 0.655 (0.610, 0.701) for HbA1c and 0.591 (0.542, 0.639) for triglyceride. All parameters were significant predictors for future risk of T2D ($P < 0.001$). The areas under the curve were higher for 1-hPG, 2-hPG and FPG than for TyG index. The area for HbA1c was almost similar for TyG index. However, it is apparent that in this population of FDR of patients with

Table 3 Incidence rates and odds ratios (OR) of diabetes by triglycerides and glucose (TyG) index quartile at baseline and type 2 diabetes, the Isfahan Diabetes Prevention Study

	TyG index at baseline			
	1st quartile (<8.5)	2nd quartile (8.50–8.83)	3rd quartile (8.84–9.17)	4th quartile (>9.17)
Number of cases (%)	21 (11.3)	37 (19.9)	52 (28.0)	76 (40.9)
Person-years	2,652	2,527	2,487	2,458
Incidence/1,000 person-year (95 % CI)	7.9 (4.9, 12.0)	14.6 (10.3, 20.1)	20.9 (15.7, 27.3)	30.9 (24.5, 38.5)
Odds ratio (95 % CI)				
Unadjusted	1.00	1.85 (1.06, 3.22)*	2.72 (1.60, 4.61)***	4.29 (2.58, 7.13)***
Gender adjusted	1.00	1.89 (1.08, 3.30)*	2.81 (1.65, 4.78)***	4.61 (2.76, 7.69)***
Age and gender adjusted	1.00	1.87 (1.07, 3.27)*	2.79 (1.64, 4.74)***	4.50 (2.69, 7.51)***
Age, gender and BMI adjusted	1.00	1.82 (1.04, 3.23)*	2.57 (1.49, 4.41)**	3.81 (2.26, 6.43)***
Age, gender, BMI and WC adjusted	1.00	1.77 (.00, 3.12)	2.40 (1.39, 4.14)**	3.47 (2.05, 5.89)***
Age, gender, BMI, WC and BP adjusted	1.00	1.59 (0.89, 2.83)	2.24 (1.29, 3.88)**	3.36 (1.98, 5.71)***
Age, gender, BMI, WC, BP, HbA1c and cholesterol adjusted	1.00	1.51 (0.80, 2.83)	2.02 (1.11, 3.68)*	2.88 (1.63, 5.11)***
Multiple adjusted ^a	1.00	1.72 (0.90, 3.27)	2.21 (1.19, 4.11)*	3.36 (1.83, 6.19)***

TyG index: $\text{Ln} [\text{fasting triglyceride (mg/dl)} \times \text{FPG (mg/dl)} / 2]$. Odds ratio (with 95 % CI) calculated by binary logistic regression

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. CI confidence interval

^a Adjusted for age, gender, BMI, waist circumference, systolic blood pressure, HbA1c, HDLC, LDLC and total cholesterol

T2D, the 1-hPG, 2-hPG and FPG were better than TyG index in predicting future risk of T2D ($p < 0.001$; areas under the ROC curves were compared with TyG index by the algorithm developed by DeLong et al. [30]).

When we re-analyzed the data with exclusion of subjects with prediabetes, the results did not appreciably alter compared to the analyses that include participants with IFG and IGT at baseline. This suggests that TyG index may uniformly predict T2D in both normal and individuals with IFG/IGT.

Discussion

The present study showed that elevated TyG index is a strong predictor of incident T2D independent of several known or suspected risk factors for T2D, in a large cohort of FDR of patients with T2D in Iran. Among participant without T2D at baseline, those in the top quartile of TyG index were 3.4 times more likely to develop T2D than those in the bottom quartile after full adjustment. Although TyG index could be an alternative test to predict T2D, 1-hPG, 2-hPG and FPG appeared to be more robust predictor of T2D in our study population. However, the association between TyG index and T2D was relatively similar to that observed with HbA1c and fasting triglyceride level. This observation was confirmed by the results from ROC curve analysis. Additionally, 1-hPG, 2-hPG and FPG outperformed HbA1c, TyG index and fasting triglyceride in predicting T2D. Fasting glucose, 1-hPG and

2-hPG had been also advocated in literature as valuable T2D prediction tools [31–34].

Only one Korean cohort study has assessed the risk of diabetes based on the TyG index [22], and some other studies assessed TyG index as surrogate for IR [17, 18, 35, 36]. In the Chungju Metabolic Disease Cohort Study of 5,354 nondiabetic individuals followed for median 4.6 years, Lee et al. [22] showed that TyG index was a strong predictor of T2D after full adjustment. Our data are in agreement with this study. In contrast to this study, we showed 1-hPG, 2-hPG and FPG appeared to be more robust predictor of T2D than TyG index. While they reported that TyG index is better than the triglyceride/HDL ratio or the HOMA-IR, they did not measure the effect of parameters of OGTT on development of T2D. However, the baseline characteristics, such as age, BMI, waist and HC, BP, ethnicity, the prevalence of family history of diabetes, differ somewhat between the study by Lee et al. [22] and current analysis. In the Montreal-Ottawa New Emerging Team (MONET) population database, Bastard et al. [35] reported that TyG and insulin sensitivity/resistance indices were only relatively modestly related to hyperinsulinemia-euglycemic clamp and both fasting- and OGTT-derived surrogate indices appear to be more accurate in estimating insulin sensitivity/resistance. Guerrero-Romero et al. [17, 18] proposed the TyG index as a surrogate of IR and reported that the TyG index has high sensitivity and specificity to recognize IR. In a Brazilian study, Vasques et al. [36] reported that the TyG index correlated with adiposity, metabolic and atherosclerosis markers related to

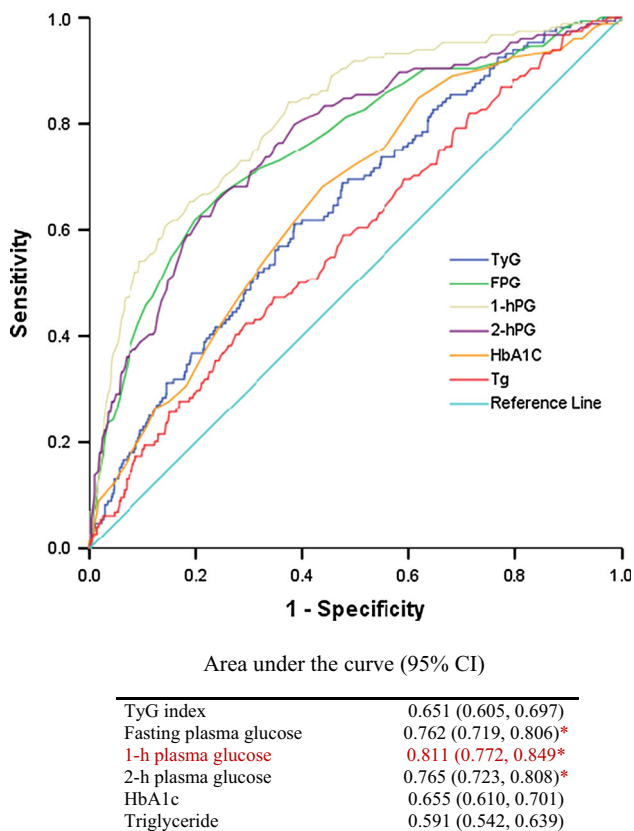


Fig. 1 Receiver operating characteristic curves for triglyceride and glucose (TyG) index, fasting plasma glucose (FPG), HbA1c, 1-h plasma glucose (1-hPG), 2-h plasma glucose (2-hPG) and triglyceride (Tg) to predict type 2 diabetes in first-degree relatives without diabetes of patients with type 2 diabetes. Sensitivity represents true-positive results and 1-specificity, the false-positive results. The estimates of the area under the ROC curves and their 95 % confidence intervals (CI) are shown. * $P < 0.001$; areas under the ROC curves were compared with TyG index by the algorithm developed by DeLong et al. [30]

IR and presented a moderate degree of agreement with hyperinsulinemic-euglycemic clamp test. Abbasi and Reaven [19] showed that the TyG index was weakly correlated with insulin-stimulated glucose uptake measured as the steady-state plasma glucose concentration during insulin suppression testing. They also conclude that although the TyG index was not better than other indices, such as the triglyceride/HDL ratio and HOMA-IR, for assessing IR, the TyG index might be of value for screening because of its low cost, being derived from routine clinical measurement.

Our study has several strengths and limitations. The strengths include use of a sample consisting of both men and women, diagnosis of diabetes based on standard OGTT and information on potential determinants of glucose intolerance. Selection and information bias were unlikely because of the prospective design. At follow-up, non-

attendees in the entire population did not differ from attendees according to major risk factors for progression to diabetes, although a difference too small to explain the high progression rate to diabetes in our study was seen in the mean levels of HDL and PG. Our database is one of the few that followed FDR of patients with T2D, thereby enabling us to simultaneously control the genetic factors that may predict glucose tolerance status. Our study was limited to a cohort of individuals who are at increased risk of developing T2D, because they had a FDR with the disease. This group of individuals will only increase further with time, as the prevalence of diabetes is expected to increase worldwide [1]. In term of our definition of incidence T2D, some selection bias may be present as participants who attended for screening may have been more likely to be tested and consequently diagnosed as having T2D. Thus, participants with T2D who had low risk score may have been missed through lack of testing. Another limitation is lack of information on the use of lipid-lowering agents which might have influenced the results. Finally, given the variability of triglycerides levels according to ethnicity, further research is needed to evaluate the TyG index in different populations.

In conclusion, these data provide further evidence that TyG index is predicted T2D, but 1-hPG, 2-hPG and FPG appeared to be more robust predictor of T2D in our study population.

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Conflict of interest Janghorbani M, Almasi SZ and Amini M declare that they have no conflict of interest.

Ethical standard This study was approved by the Institutional Ethics Committee of the Isfahan University of Medical Sciences, Iran.

Human and Animal Rights disclosure All procedures followed were in accordance with the ethical standards of the Institutional Review Board of Isfahan University of Medical Sciences, Iran and with the Helsinki Declaration of 1975, as revised in 2009 [25].

Informed consent disclosure Informed consent was obtained from all patients for being included in the study.

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