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Triglyceride- Glucose Index Strongly Predicts Dysglycemia in First-Degree Relatives of People with Type 2 Diabetes Mellitus: A Retrospective Cohort Study

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Abstract

Background: First-degree relatives (FDRs) of people with type 2 diabetes mellitus (T2DM) are at substantially increased risk of dysglycemia. However, practical approaches for early risk stratification to dysglycemia remain limited. To determine the long-term incidence of dysglycemia and identify baseline metabolic predictors of progression to dysglycemia among normoglycemic FDRs of people with T2DM.

Methods: A total of 169 normoglycemic first-degree relatives of patients with type 2 diabetes mellitus were included in this retrospective cohort study. All participants were recruited through the Clinical Research Unit of the Endocrine Research Center, Institute of Endocrinology and Metabolism, Tehran, Iran. Baseline evaluation included anthropometric measures, fasting and 2-hour post-load plasma glucose, HbA1c, lipid profile, insulin-related indices, renal parameters, and lifestyle factors. Dysglycemia was defined as progression to prediabetes or diabetes during follow-up. Independent predictors were identified using multivariable logistic regression, and predictive performance was assessed by receiver operating characteristic analysis.

Results: The study included 169 participants with a mean age of 42.94±10.46 years at baseline. During a median follow-up of 7.1 years, 144 (85.2%) participants developed dysglycemia, including 129 (76.3%) who progressed to prediabetes and 15 (8.9%) who developed diabetes. In adjusted analyses, baseline triglyceride-glucose index and 2-hour post-load plasma glucose were independently associated with progression to dysglycemia. One standard deviation (0.25) increase in the triglyceride-glucose index was associated with 84% higher odds of dysglycemia (standardized odds ratio 1.84 (1.10-3.09); $P = 0.020$), while a comparable increase in 2-hour glucose was associated with 70 % higher odds (standardized odds ratio 1.70 (1.05-2.76); $P = 0.031$). The triglyceride-glucose index demonstrated modest discriminative ability, with an optimal cut-off value of 4.42.

Conclusion: Normoglycemic first-degree relatives of people with type 2 diabetes mellitus experience a high incidence of early glycemic deterioration. Triglyceride–glucose index and 2-hour post-load glucose are the main risk factors, supporting their integration into risk-based screening strategies in order to enable earlier, targeted prevention in high-risk populations.

Keywords: First-degree relatives, Dysglycemia, Triglyceride–glucose index, 2-hour post-load glucose

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Key Messages:

↑What is "already known" in this topic:

Type 2 diabetes risk is substantially increased in individuals with a first-degree family history, who have a higher prevalence of prediabetes and diabetes. The triglyceride–glucose (TyG) index and OGTT-derived measures have been validated as predictors of progression to dysglycemia in high-risk populations.

→What this article adds:

This study shows that normoglycemic first-degree relatives of individuals with diabetes remain at high long-term risk of glycemic deterioration. The TyG index and 2-hour OGTT glucose may serve as complementary, accessible markers for early risk detection, supporting proactive, and targeted prevention in this high-risk population.

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Introduction

Diabetes mellitus represents a major global public health challenge, currently affecting approximately 37 million adults in the United States and an estimated 537 million individuals worldwide. As such, it remains a leading cause of disabling and life-threatening complications, including blindness, lower-limb amputation, and chronic kidney disease (1-3).

The development of T2DM is multifactorial, reflecting the interaction of both modifiable and non-modifiable determinants. Established risk factors include overweight or obesity, insufficient physical activity, ethnic predisposition, hypertension, dyslipidemia, and having a first-degree relative with diabetes (4, 5). Among these, family history reflects both genetic susceptibility and shared environmental exposures (6-8).

First-degree relatives (FDRs) of individuals with T2DM constitute a particularly high-risk population for dysglycemia and/or overt diabetes. Prospective cohort studies have demonstrated that up to half of FDRs, especially those with a family history of young-onset diabetes, may develop diabetes over long-term follow-up (9). Large population-based analyses further indicate that a first-degree family history confers an approximately two- to three-fold increased risk of incident type 2 diabetes, independent of adiposity and lifestyle factors (8, 10, 11). These findings are supported by cross-sectional studies showing a markedly higher prevalence of diabetes and prediabetes among first-degree relatives compared with individuals without a family history (12, 13).

In parallel, several metabolic markers have been identified as predictors of progression from normoglycemia or prediabetes to overt diabetes. Notably, the triglyceride–glucose (TyG) index has consistently emerged as an independent predictor of incident prediabetes and type 2 diabetes across large prospective cohorts and meta-analyses, even among individuals with normal baseline glucose levels (14-17). TyG-based composite indices, such as TyG–BMI and TyG–waist circumference, further improve risk stratification beyond traditional metabolic measures (18). Additionally, higher fasting plasma glucose, elevated 2-hour oral glucose tolerance test values, increased HbA1c, greater body mass index, hypertension, dyslipidemia, and family history have been repeatedly validated as predictors in longitudinal studies and multivariable prediction models (19, 20). Importantly, evidence from studies focused on first-degree relatives supports the relevance of these predictors, particularly TyG- and OGTT-derived measures, in identifying individuals at highest risk (21).

In this retrospective cohort study, we aimed to evaluate the long-term incidence of dysglycemia among normoglycemic first-degree relatives of people with T2DM. We further sought to identify baseline metabolic and clinical predictors associated with progression to dysglycemia in this high-risk population.

Methods

Study Design and Setting

The present investigation employed a retrospective cohort design using data obtained from an ethically approved parent study, "Survey of the Prevalence of Diabetes, Prediabetes, and Metabolic Syndrome in First-Degree Relatives of Patients with Type 2 Diabetes" (Project Code: 27463). The baseline assessments were performed around 4 to 8 years prior to the present analysis at the Endocrine Research Center, Institute of Endocrinology and Metabolism, Tehran, Iran. For the current investigation, historical baseline data were linked to follow-up clinical and laboratory evaluations to determine the incidence of dysglycemia and baseline predictors.

Study Population and Eligibility Criteria

The study population consisted of 169 FDRs of people with T2DM. Inclusion criteria were: participation in the original cohort, absence of diabetes or prediabetes at baseline, and availability of complete clinical and laboratory data at follow-up. Eligible participants were invited for a scheduled morning visit to the study center.

Ethical Considerations

Approval for this investigation was obtained from the Ethics Committee of Iran University of Medical Sciences (Approval No. IR.IUMS.FMD.REC.1403.208). The study was carried out in accordance with the ethical principles of the Declaration of Helsinki. All participant data were anonymized and handled confidentially. No additional invasive procedures were performed beyond standard clinical assessments.

Clinical and Anthropometric Assessments

Follow-up evaluations were conducted during scheduled morning clinic visits by trained personnel using standardized protocols. Anthropometric measurements included height, weight, waist circumference, and hip circumference. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured after at least 15 minutes of rest using a calibrated automated sphygmomanometer, and the mean of two measurements was recorded.

Laboratory Assessments

Participants attended the clinic after an overnight fast of at least 8 hours. A morning spot urine sample was collected prior to blood sampling to assess renal indices. Venous blood samples were then obtained for biochemical analyses, followed by the administration of a standard 75-g oral glucose tolerance test (OGTT), with plasma glucose measured at baseline and 2 hours post-load.

Blood samples were analyzed to determine fasting plasma glucose (FPG), 2-hour plasma glucose (2h-PG), fasting insulin, glycated hemoglobin (HbA1c), serum creatinine, and lipid parameters, including total cholesterol, triglycerides, HDL-C, and LDL-C. Insulin resistance was evaluated using two surrogate indices: the Homeostatic

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Model Assessment for Insulin Resistance (HOMA-IR) and the triglyceride-glucose (TyG) index, the latter being calculated from fasting plasma glucose and triglyceride levels (22). Renal function was evaluated using the urinary albumin-to-creatinine ratio (Alb/Cr) and the estimated glomerular filtration rate (eGFR) derived from serum creatinine.

Baseline laboratory, anthropometric, and metabolic data were retrieved from the original study database to enable longitudinal comparison.

Covariates and Lifestyle Assessment

Demographic characteristics, smoking status, medication use, and medical history (including cardiovascular disease) were obtained through structured interviews. Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) and expressed as metabolic equivalent task (MET) minutes per week. Dietary intake was evaluated using a validated food frequency questionnaire.

Outcome Definitions

Glycemic Status

Glycemic status at baseline and follow-up was categorized as normoglycemia, prediabetes, or diabetes based on fasting plasma glucose, 2-hour plasma glucose, and HbA1c values, according to the diagnostic criteria recommended by the American Diabetes Association (ADA).[4] Prediabetes was defined as FPG 100–125 mg/dL, 2-h PG (OGTT) 140–199 mg/dL, or an HbA1c level of 5.7–6.4%. Diabetes was defined as FPG ≥126 mg/dL, 2-h PG (OGTT) ≥200 mg/dL, or an HbA1c level ≥6.5%.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA; released in 2017). The normality of continuous variables was evaluated with the Shapiro–Wilk test. Data with a normal distribution are expressed as mean ± standard deviation (SD), whereas non-normally distributed variables are summarized as median with interquartile range (IQR). Within-participant changes between baseline and follow-up were evaluated using paired t-tests or Wilcoxon signed-rank tests, as appropriate. Between-group comparisons across glycemic conversion categories were conducted using analysis of variance (ANOVA) or Kruskal–Wallis tests.

Logistic regression analyses were used to identify significant predictors of hyperglycemic conversion. Univariate models were first fitted, and variables with a p-value ≤0.1 were entered into the multivariate model. To avoid multicollinearity, variance inflation factors (VIFs), tolerance statistics, and a correlation matrix were assessed for all candidate predictors (systolic blood pressure, fasting plasma glucose, 2h-PG, HbA1C, triglyceride, TyG index, Alb/Cr). Subsequently, triglyceride was removed from the model due to the strong correlation with TyG (correlation coefficient = 0.975), while VIF values for other variables were well below 10, tolerance values > 0.2, and correlation coefficients <0.6.

The predictive performance of the baseline TyG index was evaluated using receiver operating characteristic (ROC) analysis, and the optimal cut-off value was determined using the Youden index. A two-sided *P*-value < 0.05 was considered statistically significant.

Results

Study Population and Longitudinal Characteristics

A total of 169 normoglycemic first-degree relatives of individuals with diabetes were included at baseline, with outcomes ascertained retrospectively over a median follow-up of 7.08 years (IQR, 5.50–7.50; range, 3.58–9.25 years). As presented in Table 1, participants had a mean age of 42.9 ± 10.5 years, and 74% were female. Most were overweight or obese (median BMI 27.8 kg/m², IQR 25.0–30.5; 74% with BMI ≥25 kg/m²). Blood pressure, glycemic, and lipid profiles were generally within normal ranges, and renal function was preserved (mean eGFR 96.2 ± 13.2 mL/min/1.73 m²). Hypertension was present in 27.8% of participants, and 7.7% were current smokers. Medication use was modest, with 14.2% on statins and 14.8% on antihypertensives, and only 0.6% reported a history of cardiovascular disease.

Over follow-up, median FPG increased from 85.0 (80.0–89.0) to 106.0 (99.0–113.0) mg/dL, and median 2h-PG increased from 102.0 (91.0–117.0) to 126.0 (109.0–152.0) mg/dL (both $P < 0.001$). HbA1c increased from 5.30% (5.10–5.50) to 5.40% (5.20–5.70) ($P < 0.001$). HOMA-IR did not change significantly ($P = 0.225$), while the TyG index increased from 4.47 (4.31–4.68) to 4.71 (4.54–4.87) ($P < 0.001$). Lipid parameters demonstrated significant longitudinal changes, with increases in total cholesterol and triglyceride levels (both $P < 0.001$). Renal indices showed a significant rise in serum creatinine, accompanied by a meaningful decline in eGFR (both $P < 0.001$), while the urinary Alb/Cr ratio remained unchanged ($P = 0.963$).

Glycemic Conversion During Follow-up

Changes in glycemic status during follow-up are illustrated in Figure 1. Overall, 144 participants (85.2%) developed dysglycemia, including 129 individuals (76.3%) who progressed to prediabetes and 15 individuals (8.9%) who developed diabetes, while 25 participants (14.8%) remained normoglycemic. Baseline characteristics stratified by glycemic conversion status are summarized in Table 2, with participants categorized as remaining normoglycemic (N→N, n = 25), progressing to prediabetes (N→Pre-DM, n = 129), or progressing to diabetes (N→DM, n = 15). The three groups differed significantly in terms of 2-hour plasma glucose ($P = 0.038$) and HbA1c levels ($P = 0.01$) at baseline, increasing stepwise from the N→N group to the N→Pre-DM and N→DM groups. Triglyceride concentrations and the TyG index also differed significantly across groups, with progressively higher values observed in participants who developed prediabetes or diabetes (both $P = 0.002$). In contrast, fasting plasma glucose, fasting serum insulin, HOMA-IR, and renal indices did not differ significantly between groups.

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Table 1. Characteristics of the study participants (n=169)

Characteristic	Baseline	End of the study	*P*-value†
Age (years)	42.94±10.46	49.62±10.41	<0.001
Gender (Female, %)	125 (74.0%)	125 (74.0%)	1.00
BMI (kg/m^2)	27.76 (24.96-30.51)	28.70 (25.80-31.80)	<0.001
BMI≥25 kg/m^2, n (%)	125 (74.0%)	137 (81.1%)	0.012
WC (cm)	96.66±11.73	96.12±12.80	0.446
WC/HC ratio	0.91±0.07	0.89±0.07	<0.001
SBP (mmHg)	112.00 (105.00-122.00)	113.00 (107.00-123.00)	0.006
DBP (mm Hg)	71.00 (65.66-77.00)	71.00 (67.00-78.00)	0.068
FPG (mg/dL)	85.00 (80.00-89.00)	106.00 (99.00-113.00)	<0.001
2h-PG (mg/dL)	102.00 (91.00-117.00)	126.00 (109.00-152.00)	<0.001
Hb A1c (%)	5.30 (5.10-5.50)	5.40 (5.20-5.70)	<0.001
Total cholesterol (mg/dL)	163.00 (138.00-179.00)	182.00 (161.00-211.00)	<0.001
Triglyceride (mg/dL)	90.00 (66.00-135.00)	115.00 (86.00-155.00)	<0.001
HDL.chol (mg/dL)	45.00 (39.00-53.00)	58.00 (51.00-68.00)	<0.001
LDL.chol (mg/dL)	93.00 (77.00-109.00)	83.00 (68.00-98.00)	<0.001
Insulin (µIU/mL)	7.40 (5.06-10.30)	5.70 (3.20-10.80)	0.001
HOMA-IR	1.54 (1.04-2.16)	1.46 (0.81-2.85)	0.225
TyG	4.47 (4.31-4.68)	4.71 (4.54-4.87)	<0.001
Serum Cr (mg/dL)	0.83 (0.76-0.90)	0.88 (0.81-0.98)	<0.001
eGFR (mL/min/1.73m^2)	96.21±13.24	85.89±14.16	<0.001
U. Alb/Cr ratio (mg/g)	7.18 (4.24-11.25)	6.32 (3.95-10.11)	0.963
Medication, n (%)			
Statin	24 (14.2%)	27 (16.0%)	0.250
Anti-hypertensive	25 (14.8%)	27 (16.0%)	0.500
Anti-platelet	6 (3.6%)	15 (8.9%)	0.035
History of CVD, n (%)	1 (0.6%)	6 (3.6%)	0.125
Hypertension, n (%)	47 (27.8%)	58 (34.3%)	0.035
Smoking, n (%)	13 (7.7%)	26 (15.4%)	0.002
Physical activity (MET-min/week)	967.50 (421.50-2155.50)	834.00 (297.00-2199.00)	0.473

Characteristics of participants at the end of the study were compared with those at the baseline using paired t-test [for age, waist circumference (WC), WC/HC ratio, and eGFR], Wilcoxon signed-rank test (for body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), 2h-PG, Hb A1c, cholesterol, triglyceride, HDL.chol, LDL.chol, Insulin, HOMA-IR, TyG, serum Cr, U. Alb/Cr ratio, and physical activity), or McNemar's chi-square test [for statin medication, antihypertensive medication, anti-platelet medication, history of CVD, hypertension, and smoking].

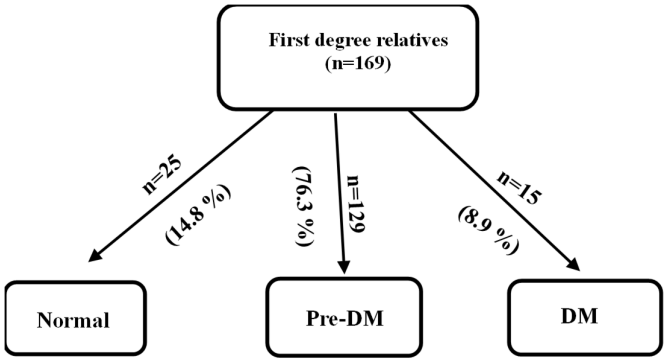

Figure 1. Changes in glycemic status over 7 years of follow-up

Independent Predictors of dysglycemia

In univariate analyses, the odds of progression to dysglycemia increased with higher 2h-PG (OR 1.033, 95% CI 1.008–1.059; *P* = 0.009), TyG index (OR 16.476, 95% CI 2.224–122.051; *P* = 0.006), FPG (OR 1.069, 95% CI 1.001-1.142, *P* = 0.048) and HbA1c (OR 8.714, 95% CI 1.550-48.996, *P* = 0.014). The urinary Alb/Cr ratio showed a borderline association (OR 1.090, 95% CI 0.997–1.192; *P* = 0.059).

In the fully adjusted multivariable model, only the baseline TyG index (OR 11.329, 95% CI 1.463–87.718; *P* = 0.020) and 2h-PG (OR 1.029 per 1 mg/dL, 95% CI 1.003–1.057; *P* = 0.031) remained significant predictors of dysglycemia progression, with the TyG index showing the strongest association (standardized OR 1.844). The urinary Alb/Cr ratio was not statistically significant in the adjusted model (*P* = 0.088). Detailed logistic regression analyses of baseline predictors for progression from normoglycemia to dysglycemia are presented in Table 3.

Predictive Performance of the TyG Index

Receiver operating characteristic (ROC) analysis for baseline TyG index is shown in Figure 2. An optimal cut-off value of 4.42 yielded a sensitivity of 65.3% and specificity of 72.0%, with an area under the curve (AUC) of 0.685 (95% CI, 0.575–0.795; *P* = 0.003).

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Table 2. Characteristics of the study participants at the baseline, stratified by the conversion status

Characteristic	N to N (n=25)	N to Pre-DM (n=129)	N to DM (n=15)	*P*-value†
Age (years)	41.52±9.18	43.40±10.71	41.40±10.60	0.600
Gender (F, %)	21 (84.0%)	95 (73.6%)	9 (60.0%)	0.268
BMI (kg/m^2)	26.87 (22.68-32.89)	27.67 (25.38-30.36)	29.14 (27.34-31.05)	0.435
WC (cm)	93.68±17.46	96.92±10.27	99.42±11.86	0.288
SBP (mmHg)	109.00 (103.33-119.66)	112.33 (106.33-122.66)	118.66 (108.33-123.67	0.160
DBP (mm Hg)	68.66 (64.00-74.66)	71.66 (66.00-77.66)	72.66 (64.83-77.67)	0.238
FPG (mg/dl)	83.00 (78.00-85.00)	85.00 (80.00-90.00)	85.00 (81.00-88.00)	0.083
2h-PG (mg/dl)	92.00 (75.00-115.00)	103.00 (93.00-119.00)	110.00 (102.00-116.50)	0.038
Hb A1c (%)	5.10 (5.00-5.35)	5.30 (5.10-5.50)	5.40 (5.20-5.50)	0.010
Cholesterol (mg/dl)	149.00(131.00-176.00)	165.00 (140.00-181.00)	164.00 (147.00-171.50)	0.318
TG (mg/dl)	73.00 (57.00-89.00)	91.00 (68.00-138.00)	134.00 (98.50-150.00)	0.002
HDL.chol (mg/dl)	47.00 (41.00-58.00)	45.00 (39.00-53.00)	41.00 (37.00-47.00)	0.156
LDL. chol (mg/dl)	90.00 (71.00-102.00)	95.00 (78.00-112.00)	91.00 (76.00-103.00)	0.349
Insulin (µIU/ml)	7.90 (4.20-10.34)	7.20 (5.10-9.60)	10.40 (6.19-12.00)	0.125
HOMA-IR	1.54 (0.84-2.12)	1.49 (1.05-2.11)	2.16 (1.20-2.51)	0.175
TyG	4.36 (4.22-4.47)	4.48 (4.32-4.68)	4.68 (4.46-4.76)	0.002
Serum Cr (mg/dl)	0.83±0.10	0.84± 0.12	0.85± 0.12	0.948
eGFR (mL/min/1.73m^2)	95.39±13.62	96.12±13.54	98.47±9.96	0.778
U.Alb/Cr ratio (mg/g)	4.52 (2.66-7.63)	7.68 (4.41-11.54)	6.85 (4.58-10.76)	0.051
Medication, n (%)				
Statin	3 (12.0%)	19 (14.7%)	2 (13.3%)	1.000
Anti-hypertensive	4 (16.0%)	19 (14.7%)	2 (13.3%)	1.000
Anti-platelet	1 (4.0%)	4 (3.1%)	1 (6.7%)	0.575
History of CVD, n (%)	0 (0.0%)	1 (0.80%)	0 (0.0%)	1.000
Hypertension, n (%)	5 (20.0%)	39 (30.2%)	3 (20.0%)	0.551
Smoking, n (%)	1 (4.0%)	10 (7.8%)	2 (13.3%)	0.535
Physical activity (MET-min/week)	1368.00 (495.00-2604.00)	951.00 (421.00-2082.00)	813.00 (396.00-2619.00)	0.919
Follow-up period (y)	7.08 (6.00-7.67)	7.25 (6.83-7.67)	7.25 (6.17-7.63)	0.674

†, Between-group comparisons across glycemic conversion categories were conducted using analysis of variance (ANOVA) test for: age, waist circumference (WC), eGFR, and serum creatinine (Cr); Kruskal–Wallis test for: BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), 2h-PG, Hb A1c, cholesterol, triglyceride (TG), HDL.chol, LDL. chol, Insulin, HOMA-IR, TyG, U. Alb/Cr ratio, Physical activity, and Follow-up period; or Fisher's exact test for gender (value: 2.79), statin medication (value: 0.119), antihypertensive medication (value: 0.158), anti-platelet medication (value: 1.354), history of CVD (value: 1.479), hypertension (value: 1.360), smoking (value: 1.266).

Discussion

In this cohort of normoglycemic FDRs of patients with diabetes, we observed a high cumulative incidence of dysglycemia over 7 years, with over three-quarters progressing to prediabetes and nearly 9% developing T2DM. These results emphasize the marked predisposition to dysglycemia conferred by familial risk, independent of baseline glycemic status. Importantly, the baseline TyG index and 2h-PG were the main predictors of glycemic progression among initially normoglycemic individuals. Specifically, each standard deviation increase in the TyG index and 2h-PG was independently associated with approximately 1.8-fold and 1.7-fold higher risks, respectively, of progression to hyperglycemia after multivariable adjustment. Finally, according to the ROC analysis, the baseline TyG index demonstrated modest but statistically significant discriminative ability for predicting progression to prediabetes or diabetes, with an optimal cut-off value of 4.42.

There is growing literature affirming the TyG index as an early predictor of glycemic progression (23). In this cohort, the TyG index emerged as a significant predictor of conversion from normoglycemia to pre-DM or T2DM among FDRs. The TyG index is widely used as a surrogate marker of insulin resistance and has proven utility in predicting metabolic disease risk, even outperforming HOMA-IR in identifying insulin resistance among children and adolescents (24-28). Importantly, the TyG index outperformed HOMA-IR in our study, highlighting its ability to integrate both lipid and glucose dysregulation and thereby reflect glucolipotoxicity rather than isolated hepatic insulin resistance. Accumulating evidence indicates that elevated TyG levels are related to a higher risk of T2DM, non-alcoholic fatty liver disease (NAFLD), and cardiovascular disease (29-32). Notably, Zhang et al. demonstrated a metabolic saturation effect, whereby diabetes risk accelerates sharply beyond a critical TyG threshold (> 8.00), reflecting the failure of compensatory insulin secretion in the setting of escalating insulin resistance (33). Similarly, long-term data from the Tehran Lipid and Glucose Study demonstrated that the TyG index is a strong independent predictor of incident T2DM, with cumulative exposure capturing chronic metabolic stress more effectively than single-point measurements (34). In line with our results, a comprehensive meta-analysis of cohort studies reported that elevated TyG index levels were strongly associated with an increased risk of incident T2DM, reinforcing its potential utility as a predictive metabolic marker (35). Moreover, elevated TyG index levels have been shown to be significantly associated with an increased risk of pre-DM (23). Additionally, evidence has shown that the TyG index demonstrates strong discriminatory ability for identifying individuals with pre-DM or T2DM (36). Together, these findings position the TyG index as a cost-effective, accessible, and biologically grounded early warning tool for identifying individuals at a metabolic tipping point, enabling timely intervention before the onset of overt diabetes.

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Table 3. Predictors of converting to dysglycemia after median follow-up period of 7 years among normoglycemic participants at the baseline

Baseline characteristics	Univariate			Multivariate†				
	B	OR (95% CI)	*P*-value	B	OR (95% CI)	Standardized B	Standardized OR (95% CI)	*P*-value
Age	0.016	1.016 (0.974-1.059)	0.461					
Gender	-0.703	0.495 (0.160-1.533)	0.223					
SBP	0.036	1.037 (0.994-1.081)	0.091					
DBP	0.041	1.042 (0.989-1.098)	0.125					
FPG	0.067	1.069 (1.001-1.142)	0.048					
2h-PG	0.033	1.033 (1.008-1.059)	0.009	0.029	1.029 (1.003-1.057)	0.530	1.700 (1.049-2.755)	0.031
HbA1c	2.165	8.714 (1.550-48.996)	0.014					
HOMA-IR	0.086	1.090 (0.737-1.612	0.666					
TyG	2.802	16.476 (2.224-122.051)	0.006	2.427	11.329(1.463-87.718)	0.612	1.844 (1.101-3.088)	0.020
TG	0.013	1.014 (1.002-1.025)	0.022					
Cholesterol	0.012	1.012 (0.997-1.028)	0.116					
HDL.chol	-0.023	0.977 (0.940-1.016)	0.243					
LDL.chol	0.012	1.012 (0.993-1.032)	0.200					
eGFR	0.006	1.006 (0.974-1.038)	0.736					
Alb/Cr	0.086	1.090 (0.997-1.192)	0.059	0.076	1.079 (0.989-1.178)	1.436	4.204 (0.808-21.869)	0.088
Smoking	0.780	2.182 (0.271-17.567)	0.464					
Physical activity	0.000	1.000 (1.000-1.000)	0.681					
Follow-up period	0.239	1.270 (0.823-1.961)	0.281					

†, Baseline variables with $p \leq 0.1$ in univariate analysis (SBP, FPG, 2h-PG, HbA1c, TyG index, triglycerides, Alb/Cr) were considered as the potential predictors for the multivariable model. Triglycerides were then excluded for collinearity with TyG index. SBP, FPG, HbA1c, and Alb/Cr were removed from the final model due to $p > 0.1$. The final adjusted model includes only variables with $P \leq 0.1$.

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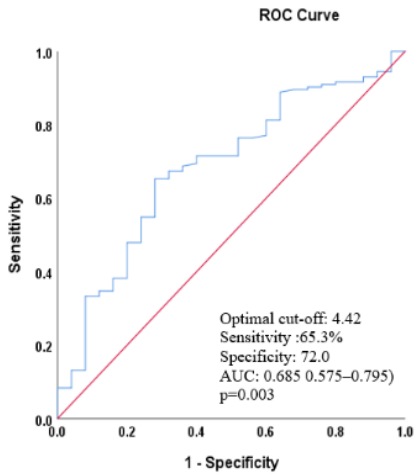

Figure 2. ROC analysis of baseline TyG index as a predictor of dysglycemia

From a pathophysiological standpoint, an elevated TyG index reflects metabolic disturbances that contribute to hyperglycemia, most notably pancreatic β-cell dysfunction and reduced insulin sensitivity in peripheral tissues (37). Evidence suggests that nutrient excess and disrupted lipid metabolism promote the accumulation of glucolipid byproducts and triglycerides within pancreatic islets, leading to β-cell dysfunction (38, 39). Concurrently, elevated circulating triglycerides increase plasma free fatty acid (FFA) levels, which impair insulin-mediated glucose uptake in skeletal muscle through inhibition of glucose oxidation (the Randles cycle) and disruption of insulin receptor signaling pathways. This dual metabolic burden fosters peripheral insulin resistance while exacerbating β-cell stress, ultimately accelerating β-cell apoptosis in the setting of chronic hyperglycemia (40, 41). Emerging evidence suggests that the TyG index may preferentially capture muscle-related insulin resistance, a key early abnormality in the progression from normoglycemia to pre-DM and T2DM (42). Since the TyG index incorporates both lipid and glucose components, it effectively reflects this cumulative metabolic stress, which HOMA-IR alone may fail to capture in the early stages of disease progression.

Beyond insulin resistance–related markers, our findings underscore the importance of post-challenge glucose. Baseline 2h-PG emerged as a powerful and independent predictor of incident prediabetes and T2DM, highlighting the limitations of relying solely on fasting plasma glucose for risk stratification. The predictive value of OGTT-derived measures in FDRs is well documented. Feizi et al. followed normoglycemic FDRs in Iran and showed that an exaggerated glycemic response during OGTT was highly predictive of progression to prediabetes/diabetes (43). Our observation that baseline 2h-PG independently predicts conversion corroborates these findings, reinforcing that even within normoglycemic ranges, higher post-load glucose indicates latent β-cell insufficiency. Indeed, large analyses have shown that an elevated 1-hour OGTT glucose (around 155–180 mg/dL) identifies individuals at high diabetes risk earlier than fasting or 2h glucose criteria (44). Although we did not measure 1-h glucose, the significance of 2h-PG in our model suggests that any degree of impaired glucose tolerance in FDRs is clinically important. Of note, our data resonate with a recent 20-year study in older Chinese men where the TyG index was also an independent predictor, though in that elderly cohort OGTT 1-h and 2-h glucose values provided even stronger predictive power, and support a complementary role for insulin resistance markers and OGTT in diabetes prediction (45).

Our findings have important implications for risk stratification and early intervention among FDRs of individuals with T2DM. The high prevalence of dysglycemia in this group justifies the routine use of the TyG index as a simple, low-cost tool derived from standard fasting tests. In our cohort, a TyG value above approximately 4.4 identified FDRs at elevated risk despite fasting glucose and triglyceride levels remaining within conventional ranges, indicating that standard thresholds may underestimate risk in genetically predisposed individuals. Early detection of elevated TyG may prompt timely lifestyle interventions to improve insulin sensitivity before overt hyperglycemia develops. However, the modest discriminative performance observed in our ROC analyses indicates that TyG should not be considered a standalone diagnostic marker or used in isolation for individualized clinical decision-making without external validation and demonstration of added predictive value beyond established risk factors. Our results also reinforce the value of OGTT, particularly in FDRs with high-normal fasting glucose or HbA1c, as post-challenge hyperglycemia reflects early β-cell dysfunction at a potentially reversible stage. Additionally, the observed association between baseline microalbuminuria and glycemic progression, while not independent, aligns with prior data linking microalbuminuria to an increased risk of developing diabetes and may further inform holistic risk assessment in selected individuals (46,47). Collectively, these findings support integrating TyG assessment and selective OGTT into risk-based screening strategies for FDRs to enable earlier, individualized diabetes prevention.

Strengths, Limitations, and Future Directions

Strengths of this study include the cohort of FDRs, the longitudinal design with extended follow-up, and the simultaneous evaluation of OGTT-derived measures and emerging metabolic indices such as the TyG index. By focusing on a high-risk group, we were able to identify early predictors of dysglycemia often underrepresented in the general population. Importantly, this study adds novel evidence from a Middle Eastern population, extending the generalizability of prior findings largely derived from East Asian and Western cohorts.

Nonetheless, limitations should be acknowledged. The modest sample size and limited number of incident diabetes cases constrained statistical power to evaluate predictors of T2DM separately from prediabetes, necessitating a composite dysglycemic outcome. Baseline-only assessment of predictors, combined with the fact that the exact timing of

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conversion to dysglycemia was unknown due to assessments being limited to scheduled visits, precluded evaluation of dynamic changes over time and the use of time-to-event analyses. Furthermore, the predominantly female, ethnically homogeneous, single-center cohort may limit generalizability. As with all observational studies, residual confounding and selection bias cannot be fully excluded. The outcome was imbalanced (144 converters vs. 25 non-converters), which may have affected the precision of logistic regression estimates. These results should therefore be interpreted with caution.

Our findings open several avenues for future research. First, larger prospective studies in first-degree relatives should be conducted to validate the TyG index as a risk stratifier and to establish optimal cut-off values in various populations (48). Another important direction is investigating the role of non-glycemic factors in this high-risk group. For instance, fat distribution (visceral adiposity by imaging), NAFLD, inflammatory markers, and gut microbiome differences might modulate risk among FDRs with similar clinical profiles. Incorporating polygenic risk scores alongside phenotypic markers such as TyG and 2h-PG represents a promising strategy to advance precision prevention (49). Ultimately, translating these predictors into targeted lifestyle or pharmacologic intervention trials will be critical to determining whether early identification can meaningfully alter disease trajectories in high-risk families.

Conclusion

In conclusion, normoglycemic individuals with a first-degree family history of diabetes are at substantial risk of developing dysglycemia. Our findings identify the TyG index and 2-hour OGTT glucose as accessible and complementary markers that unmask early insulin resistance and impaired glucose tolerance before overt dysglycemia. These results support a shift toward more aggressive, risk-based metabolic screening in FDRs to enable timely, targeted preventive interventions. Recognizing family history as an indicator for early evaluation, rather than a passive risk factor, may help reduce the incidence of diabetes in high-risk families.

Acknowledgment

We acknowledge the study participants.

Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contributions

N.B. and M.E.K. contributed to the study design. N.B., Z.E., and F.A. contributed to the data acquisition and analysis. F.A., M.M., and M.E.K. contributed to the data interpretation. F.A. cleaned and analyzed the data. S.R., N.B., F.A., and M.E.K. drafted or substantially contributed to revising the work. All authors read and approved the manuscript.

Ethical Considerations

All participants provided written informed consent, and the study procedures were approved by the Committee on Iran University of Medical Sciences (IR.IUMS.REC.1403.208).

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Data Availability

The data analyzed in this study are available from the corresponding author upon reasonable request.

AI Use Statement

The manuscript was written by the authors. AI tools were used to assist with grammar, Language editing, and improving readability. All content, interpretation, and conclusions were developed, reviewed, and approved by the authors.

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