ORIGINAL ARTICLE

Developing risk models for predicting incidence of diabetes and prediabetes in the first-degree relatives of Iranian patients with type 2 diabetes and comparison with the finnish diabetes risk score

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Background: We aimed to develop risk models for predicting the onset of developing diabetes and prediabetes in the first-degree relatives (FDRs) of patients with type 2 diabetes, who have normal glucose tolerance (NGT). **Materials and Methods:** In this study, 1765 FDRs of patients with type 2 diabetes mellitus, who had NGT, were subjected to the statistical analysis. Diabetes risk factors, including anthropometric indices, physical activity, fast plasma glucose, plasma glucose concentrations 2-h after oral glucose administration, glycosylated hemoglobin (HbA1c), blood pressure, and lipid profile at the baseline were considered as independent variables. Kaplan–Meier, log-rank test, univariate, and multivariable proportional hazard Cox regression were used for the data analysis. The optimal cutoff value for risk score was created according to the receiver operating characteristic curve analysis. **Results:** The best diabetes predictability was achieved by a model in which waist-to-hip ratio, HbA1c, oral glucose tolerance test-area under the curve (OGTT-AUC), and the lipid profile were included. The best prediabetes risk model included HbA1c, OGTT-AUC, systolic blood pressure, and the lipid profile. The predictive ability of multivariable risk models was compared with fasting plasma glucose (FPG), HbA1c, and OGTT. The predictive ability of developed models was higher than FPG and HbA1c; however, it was comparable with OGTT-AUC alone. In addition, our study showed that the developed models predicted diabetes and OGTT-AUC better than the Finnish Diabetes Risk Score (FINDRISC). **Conclusion:** We recommend regular monitoring of risk factors for the FDRs of patients with type 2 diabetes as an efficient approach for predicting and prevention of the occurrence of diabetes and prediabetes in future. Our developed diabetes risk score models showed precise prediction ability compared to the FINDRISC in Iranian population.

Key words: First degree relative, prediabetes, risk factor, risk model, type 2 diabetes

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) has high morbidity and mortality worldwide. In addition, diabetes is responsible for microvascular (blindness, nephropathy, and neuropathy)[1,2] and macrovascular (cardiovascular and stroke) degenerative complications.[3] Iran is one of 19 countries of the International Diabetes Federation-Middle East and North Africa region and has been ranked the third in the prevalence of diabetes among them.[4] National Program for the Prevention and

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Control of Diabetes 2016 reported the prevalence of type 1, types 2, and other types of diabetes were, respectively, 11.4%, 85.5%, and 1.3% in Iran.[5]

Different modifiable and unmodifiable risk factors have been identified for the onset of diabetes, counting obesity, unhealthy lifestyle behaviors including smoking and alcohol consumption, poor nutrition, high lipids profile, hypertension, low level of physical activities, and family history of diabetes.[6-8] Various risk prediction models have been developed worldwide by incorporating noninvasive tests and blood-based metabolic parameters to identify individuals at high risk of developing diabetes.[9-14] For instance, different studies in Western populations have constructed risk models using these factors could identify individuals with higher incident of diabetes. Although these models have been proven to be efficient, due to the large differences in diabetes risk factors across different ethnics, the suitability of each risk score model may differ in terms of ethnicity.[15-17]

The risk of diabetes incidence in the first-degree relatives (FDRs) of patients with T2DM is 2–8 times higher than general population; therefore, it is important to establish appropriate predictive strategies for this "at-risk" sub-population.[6-8]

Few risk models have been developed specifically to identify individuals at high risk of type 2 diabetes in Iran and almost all have been developed from the cross-sectional data.[18,19] In the present study, we aimed to develop the models and evaluate their predictabilities by using simple risk scores based on self-assessed and noninvasive measures, low-cost laboratory tests, and easily accessible anthropometric measures in a long-term prospective cohort of 13 ± 2.3 years for the Iranian population at increased risk of developing type 2 diabetes. We focused on the FDRs of T2DM patients with normal glucose for the first time in Iranian population. This study is among rarely conducted studies worldwide on developing risk score models for this high-risk population. We have also developed risk models to predict prediabetes in the FDRs of T2DM patients with normal glucose for the first time worldwide. Furthermore, we have compared the performance of our model for predicting diabetes incidence in our population with a widely practiced prediction model of the Finnish Diabetes Risk Score (FINDRISC).

MATERIALS AND METHODS

Study design and participants

Subjects of the present study are participants of the Isfahan diabetes prevention study (IDPS), an ongoing cohort study in the center of Iran. The current study was conducted as a secondary data analysis of the IDPS. The IDPS was initiated between 2003 and 2005 for 3483 FDRs of patients with type 2 diabetes at the Isfahan Endocrine and Metabolism Research Center affiliated to Isfahan University of Medical Sciences. Those FDRs of patients with T2DM with normal glucose tolerance (NGT) test or were diagnosed with prediabetes included into the cohort study based on a consecutive sampling method. The IDPS is a prospective cohort study in Isfahan, the largest city in center of Iran. The IDPS was established to evaluate various potential risk factors of T2DM in subjects with a family history of T2DM as a high-risk population. The sample of IDPS was recruited ongoingly from 2003 to date; therefore, each considered individual was followed from entrance to the cohort study until they experienced a typical proposed outcome, depending on objectives of a specific secondary study on main cohort. Recruitment methods and examination procedures have been described in detail elsewhere.[20]

For the current secondary study, we included a total of 1765 FDRs of patients with type 2 diabetes who had NGT at the entrance to the cohort, as the baseline, and followed them up to 2021. Although we observed a total of 31.8% loss to follow-up during the study period, we have included their data until the date they were followed. We excluded prediabetic patients and those who had any acute illness <2 weeks prior to the clinic review and also participants with previously diagnosed diabetes, documented anemia, pregnancy, and chronic kidney disease, which could interfere with the glycosylated hemoglobin (HbA1c) testing accuracy. In the IDPS, those participants who were diagnosed as prediabetic at the baseline with 75-g oral glucose tolerance test (OGTT) were examined annually while individuals with normal OGTT (NGT) were evaluated at 3-year interval. The Ethics Committee of the Isfahan University of Medical Sciences approved the protocol of the current secondary study (IR.MUI.MED.REC.1398.525) and the main IDPS study was conducted according to the Declaration of Helsinki. All participants provided written informed consents.

Data collection and definition of variables

Demographic information, anthropometric measures, biochemical, and clinical data were obtained from the registry of the IDPS at the Isfahan Endocrine and Metabolism Research Center. Anthropometric indices at the baseline (weight, height, waist circumference, and hip circumference) were measured by trained examiners. Waist to hip ratio (WHR) is another anthropometric variable used in the present study. Body mass index (BMI) was considered as weight in kilogram divided by height in meter squared.

A blood sample was collected from all participants after 10 h overnight fasting for biochemical tests, including fasting plasma glucose (FPG), 2 h blood glucose levels at 30, 60, and 120 min after oral glucose administration

(2 h-OGTT), HbA1c, total cholesterol, triglyceride (TG), high density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol. All biochemical tests were measured using standard procedures in the central laboratory of the Isfahan Endocrine and Metabolism Research Center.[20] The individual was diagnosed by impaired fasting glucose (IFG), if the FPG was between 100 mg/dL and 125 mg/dl, and 2-h post 75 g glucose load was <140 mg/dl. When the 2-h post glucose load was between 140 mg/dL and 199 mg/dL with normal fasting glucose (FPG <100 mg/dl), the patient was diagnosed by impaired glucose tolerance (IGT). Prediabetes were defined as either IFG or IGT or both.[21] Participants were diagnosed with diabetes, if the FPG was ≥126 mg/dl and/or the 2-h post glucose load was ≥200 mg/dl.[21] The FPG <100 mg/dl and the 2-h post glucose load <140 mg/dl were considered as NGT.[21]

Blood pressure was measured using a mercury sphygmomanometer twice, while participants were in seated position, and the mean was recorded as the final value of blood pressure. Hypertension was defined as systolic blood pressure (SBP) ≥130 mmHg, Diastolic blood pressure ≥85 mmHg and/or taking anti-hypertensive medications, according to the Joint National Committee criteria.[22]

The overall physical activity level was assessed by using the short form of International Physical Activity Questionnaire and scored as a continuous variable, metabolic equivalent minutes (MET min/week). We considered resting energy expenditure to be 1 MET min, walking to be 3.3 MET min, moderate physical activity to be 4 MET min and vigorous physical activity to be 8 MET min.[23]

Demographic information including age, gender, educational level (illiterate, under-diploma, diploma (formal 12-year education), university graduate), and smoking status was recorded through survey questions.

Statistical analysis

Statistical analyses were performed by the Statistical Package for Social Science (version 16; SPSS Inc., Chicago, IL, USA). Continuous normally distributed data and categorical data were presented as mean ± standard deviations and percentage, respectively. Normality of quantitative data was evaluated using Kolmogorov–Smirnov test and Q-Q plot. To evaluate the association between categorical data, Chi-squared test was used. Comparisons of normally distributed quantitative data between groups were conducted using analysis of variance followed by Bonferroni *post hoc* test. A two-tailed $P < 0.05$ was considered to be statistically significant.

The area under the curve (AUC) of OGTT was derived from the OGTT curve, using the trapezoidal method between 0 and 120 min according to our previous study.[24] The lipid index is introduced as a combined continuous measure, which was constructed from lipid profiles including TG, cholesterol, HDL, and LDL by using exploratory analysis factor. The OGTT-AUC and lipid index have been used as independent variables in our models.

The optimal cutoff values of each risk factor at the time of entrance to the cohort for predicting incidence of T2DM and prediabetes were calculated by using the receiver operating characteristics curve (ROC), and these variables were categorized according to the determined cutoff values. We used categorical variables instead of continuous variables to develop a simple model. Then the association of each risk factor with the incidence of T2DM and prediabetes was evaluated in univariate analysis and those with significant *P* values were entered into multivariable analysis. Kaplan–Meier and log Rank test were conducted to determine the incidence rates of diabetes and prediabetes in the follow up period until 2021, according to the determined cutoff points of risk factors at the baseline. The corresponding hazard ratio was calculated using univariate and multivariable Cox proportional hazard regression. During this process we developed a prediction model containing only significant risk factor of developing T2DM and prediabetes in future. Then individuals, whose values were higher than the determined optimal cutoff values, were coded as 1 and others were coded as 0. Then each risk factor's weight was determined by its corresponding Cox regression coefficient. Finally, all scores associated with significant risk factors for each participant were summed up to consider risk score for each participant. Then the predictive values of our models, based on computed sum of scores of risk factors, were evaluated using the ROC analysis and the optimal cutoff values for risk score for each model were determined. The AUC and its 95% confidence interval (CI) were reported and the optimal cutoff points and overall effectiveness of risk score models were determined when the maximum value of Youden's index was archived.

The performance of our risk models was compared with each glucose indices (FPG, HbA1c and OGTT-AUC) separately, based on the AUC of related ROC curves. We also compared the performance of our models for predicting incidence of diabetes with the FINDRISC. The risk score for variables of the concise FINDRISC model was determined for each participant and the overall risk score was calculated as the sum of the individual scores. The performance of all competitive models based on the AUC of relevant ROC curve was compared by the Delong test.[25]

RESULTS

The cumulative incidence rate of diabetes was 7.4% in the patients with NGT during the follow-up period. In addition,

the incidence rate of developing prediabetes was 32.6% and 59.7% of them remained NGT. The characteristics of participants at the baseline were reported at the categories of final status of participants in Table 1. Individuals in whom diabetes were developed after 13 ± 2.3 years, compared to those who remained with NGT, had higher WHR, cholesterol, TG, cholesterol, and the OGTT-AUC at the baseline (all $P < 0.05$). Participants who became prediabetes during the follow up period were older and had higher mean waist circumference, OGTT-AUC, HbA1c, cholesterol, TG, and cholesterol at the baseline compared to those who remained NGT (all $P < 0.05$) [Table 1].

We categorized these potential risk factor variables for developing diabetes and prediabetes based on their optimal cutoff values obtained from the ROC analysis [Tables 2 and 3]. The incidence of diabetes and prediabetes were significantly high in upper categories of all studied risk factors. These variables were examined in various combinations and several Cox's proportional hazard models were developed. Finally, the best predictive models were selected [Tables 4 and 5]. The final models to predict the risk of developing diabetes were created by 4 variables. Diabetes risk model 1 included WHR, HbA1c, lipid index, and OGTT-AUC with AUC of 0.71 (95% CI: 0.66–0.77). Diabetes risk model 2 was created by considering WHR, HbA1c, lipid index, and FPG, as predictors, with AUC of 0.69 (95% CI: 0.63–0.74). The total diabetes risk score was calculated as the sum of the individual's scores ranged 0–11 and 0–9 for future incidence of diabetes in models of 1 and 2, respectively. The performance of our risk models was evaluated by the ROC analysis and the appropriate risk score cut-points (sensitivity, specificity, accuracy) were 6 (78%, 52%, 54%) and 4 (77%, 52%, 53%) for predicting diabetes risk models 1 and 2, respectively ($P > 0.1$) [Table 4].

Prediabetes risk model 1 was developed based on HbA1c, SBP, lipid index, and OGTT-AUC and the respective AUC was 0.63 (95% CI: 0.59–0.67). In the case of model 2, the best predictive ability was observed when age, waist circumferences, FPG, HbA1c, and lipid index were included,

Table 1: Comparison of participant's characteristics at entrance to the cohort in their final status categories during follow-up

Variables	Final status			P^a (prediabetes)	P^b (diabetes)
	Normal (%)	Prediabetes (%)	Diabetes (%)		
Age	41.89±6	43.29±6.42	43.04±6.12	0.001*	0.094
Sex					
Male	25.4	28.2	33	0.342	0.124
Female	74.6	71.8	67		
Education					
Illiterate	3.2	4.4	3.3	0.778	0.142
Under-diploma	46.8	47.2	53.3		
Diploma	32.6	32.2	35.6		
University graduate	17.4	16.2	7.8		
Smoker	9.10	6.10	9.10	0.363	0.995
BMI (kg/m^2)	28.10±4.20	29.09±4.30	28.65±4.9	0.051*	0.037*
Waist (cm)	86.91±9.69	90.53±9.47	88.75±9.57	0.005*	0.001*
Hip (cm)	106.18±8.59	17.57±8.94	106.88±8.56	0.228	0.153
WHR	0.82±0.07	0.84±0.06	0.83±0.07	0.011*	0.005*
FPG (mg/dL)	87.31±7.67	89.70±7.22	90.35±9.94	<0.001*	<0.001*
OGTT 30 (mg/dL)	126.20±24.59	138.04±26.04	142.13±25.93	<0.001*	<0.001*
OGTT 60 (mg/dL)	121.58±31.40	137.48±31.08	149.312±34.97	<0.001*	<0.001*
OGTT1 20 (mg/dL)	98.32±20.94	103.21±21.83	107.62±20.05	0.001*	<0.001*
OGTT-AUC	749.70±124.26	817.49±122.32	863.11±131.03	<0.001*	<0.001*
TG (mg/dL)	145.75±80.76	159.83±84.42	179.13±98.52	<0.001*	<0.001*
Cholesterol (mg/dL)	189.14±38.12	196.00±38.63	201.09±42.84	0.008*	0.007*
HDL (mg/dL)	45.20±11.48	44.85±11.45	44.14±10.22	0.660	0.415
LDL (mg/dL)	115.63±33.12	119.97±34.26	121.94±43.32	0.064	0.115
SBP (mmHg)	11.29±1.50	11.68±1.63	11.52±1.60	<0.001*	0.177
DBP (mmHg)	7.45±7.50	7.58±1.14	7.45±1.23	0.086	0.996
HbA1c (mg/dL)	4.93±0.78	5.07±0.70	5.16±0.70	0.006*	0.012
Physical activity (MET in/week)	86.93±108.5	86.59±87.78	180.149±421.93	0.979	0.018*

[a]Comparison between prediabetes and the NGT (healthy population); [b]Comparison between diabetes and normal, resulted from ANOVA followed by Bonferroni *post hoc* test. TG=Triglyceride; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; BMI=Body mass index; WHR=Waist-to-hip ratio; FPG=Fasting plasma glucose; OGTT 30, 60, 120=Oral glucose tolerance test after 30 min, 60 min, 120 min; HbA1c=Glycosylated hemoglobin; OGTT-AUC=Oral glucose tolerance test-area under the curve; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; MET=Metabolic equivalent; NGT=Normal glucose tolerance; ANOVA=Analysis of variance. **p*-value obtained from Independent samples t-test or Mann-Whitney U test for quantitative and Chi-squared test for categorical variables

with the corresponding AUC of 0.60 (95% CI: 0.57–0.64). The total prediabetes risk score was calculated as the sum of the individual's scores ranged 0–6 for prediabetes model 1 and 0–7 for prediabetes model 2. The corresponding risk score cutoff values were 3 (71%, 52.5%, 55%) and 3.99 (65%, 50%, 52%) for prediabetes risk model 1 and 2, respectively [Table 5].

Table 2: The derived cutoff values of risk factors for developing type 2 diabetes (final status) during the follow-up period

Variables	Optimal cutoff-value	Final status (%)		*P*
		Normal	Diabetes	
WHR	≥0.795	58.8	77.5	0.001*
	<0.795	41.2	22.5	
Cholesterol (mg/dL)	≥185	52.5	67	0.010*
	<185	47.5	33	
TG (mg/dL)	≥120	53.6	67	0.010*
	<120	46.4	33	
FPG (mg/dL)	≥88.5	49.9	34.1	0.004*
	<88	50.1	65.9	
OGTT-AUC	≥773	59.1	25	<0.001*
	<773	40.9	75	
HbA1c (mg/dL)	≥4.8	48.1	37.2	0.068
	<4.8	51.9	62.8	
Lipid index	≥0.04	55	38.1	0.040*
	<0.04	45	61.9	

Lipid index: A combined measure of lipid profiles including; TG, cholesterol, HDL, and LDL. TG=Triglyceride; WHR=Waist-to-hip ratio; FPG=Fasting plasma glucose; HbA1c=Glycosylated hemoglobin; OGTT-AUC=Oral glucose tolerance test-area under the curve; HDL=High-density lipoprotein; LDL=Low-density lipoprotein. *p-value obtained from Chi-squared test for categorical variables

Table 3: The derived cutoff value of risk factors for developing prediabetes (final status) during the follow-up period

Variables	Optimal cutoff-value	Final status (%)		*P*
		Normal	Prediabetes	
Age	≥41	52.9	41.2	0.001*
	<41	47.1	58.8	
Waist (cm)	≥85.9	46.6	39	0.025*
	<85.9	53.4	61	
Cholesterol (mg/dL)	≥185.5	48.5	39.6	0.008*
	<185.5	51.5	60.4	
TG (mg/dL)	≥121	47.6	38.2	0.005*
	<121	52.4	61.8	
FPG (mg/dL)	≥88	44.8	33	<0.001*
	<88	55.2	67	
OGTT-AUC	≥746	50.3	29.9	<0.001*
	<746	49.7	70.1	
HbA1c (mg/dL)	≥4.8	48.1	40.9	0.038*
	<4.8	51.9	59.1	
Lipid index	≥0.04	48.9	41.3	0.030*
	<0.04	51.1	58.7	
SBP (mmg)	≥11	55	45.8	0.007*
	<11	45	54.2	

Lipid index: A combined measure of lipid profiles including TG, cholesterol, HDL, and LDL; *P* values were obtained from the Chi-squared test. TG=Triglyceride; FPG=Fasting plasma glucose; HbA1c=Glycosylated hemoglobin; OGTT-AUC=Oral glucose tolerance test-area under the curve; SBP=Systolic blood pressure; HDL=High-density lipoprotein; LDL=Low-density lipoprotein. *p-value obtained from Chi-squared test for categorical variables

We compared the predictability of our models with other blood glucose indices: FPG, HbA1c, and OGTT-AUC [Figure 1]. Both diabetes risk models surpassed FPG and HbA1c risk factors at predicting diabetes (FPG-AUC: 0.61 [95% CI: 0.54–0.68] and HbA1c-AUC: 0.57 [95% CI: 0.50–0.64]). No significant difference was detected between the AUC of diabetes risk model 1 and OGTT-AUC (0.71 [95% CI: 0.66–0.77] vs. 0.73 [95% CI: 0.67–0.80]) ($P > 0.1$) [Figure 1].

The predictive efficiency of both prediabetes risk models was slightly better than FPG, and HbA1c risk factors individually (FPG-AUC: 0.59 [0.55–0.63] and HbA1c-AUC: 0.56 [0.52–0.60]). There was no significant difference observed between OGTT-AUC and prediabetes risk model 1 (0.65 [95% CI: 0.61–0.69] vs. 0.63 [95% CI: 0.59–0.67]) [Figure 2].

We compared the ability of the FINDRISC to predict developing of diabetes in our population with the current study models. The predictive performance of our diabetes risk models was more precise than the FINDRISC and the corresponding *P* values were 0.003 for the FINDRISC against the model 1, and 0.005 for FINDRISC versus the model 2 [Figure 3].

DISCUSSION

There are strong evidences that people with the family history of diabetes are 2–8 fold more likely to develop diabetes.[26] This association was independent of other risk factors, such as obesity, insulin resistance, and lifestyle factors which means this risk factor solely is strong enough to predict diabetes in individuals with family history.[7] Therefore, in the present study we focused on this at-risk subgroup of population and developed a reliable risk score for future development of diabetes and prediabetes.

In this study, higher WHR, Cholesterol, TG, Lipid index (combined variable based on lipid profile), and the OGTT-AUC at the baseline in those FDRs who developed diabetes during follow up period were significantly associated with the increased risk of developing diabetes. Clinical and demographic significant risk factors for developing prediabetes were age, waist circumferences, OGTT-AUC, HbA1c, cholesterol, TG, and the lipid index.

According to these risk factors that showed significant associations with diabetes in univariate analysis, we developed two risk score models to predict the risks of developing diabetes and prediabetes. Diabetes risk model 1 included WHR, HbA1c, lipid index and OGTT-AUC and diabetes risk model 2 included WHR, HbA1c, lipid profile

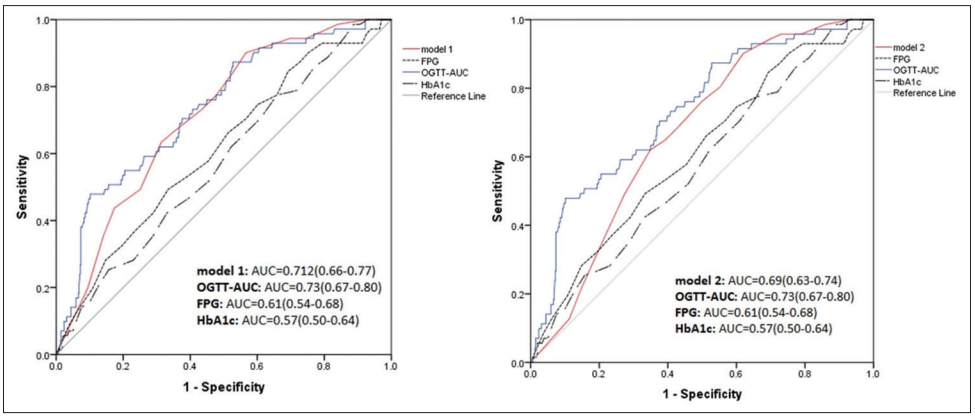

Figure 1: ROC curves and corresponding areas under the curves for model 1, model 2, FPG, 2-h PG, and HbA1c for predicting diabetes. The optimal cutoff value of the model 1 is 6 (Sensitivity: 78%, specificity: 52%, and accuracy: 54%). The optimal cutoff value of model 2 is 4 (77%, 52%, and 53%). ROC: Receiver operating characteristic curve, HbA1c: Glycosylated hemoglobin

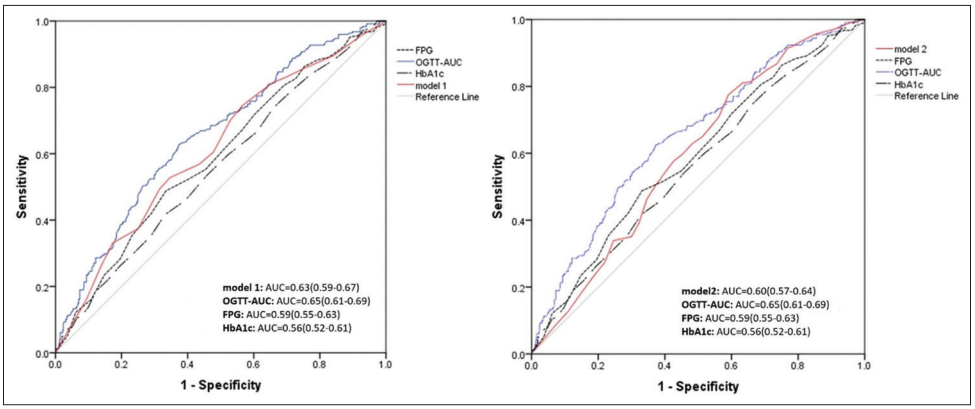

Figure 2: ROC curves and corresponding areas under the curves for model 1, model 2, FPG, 2-h PG, and HbA1c for predicting prediabetes. The optimal cutoff value of the model 1 is 3 (Sensitivity: 71%, specificity: 52.5%, and accuracy: 55%). The optimal cutoff value of the model 2 is 4 (65%, 50%, 52%). ROC: Receiver operating characteristic curve, HbA1c: Glycosylated hemoglobin

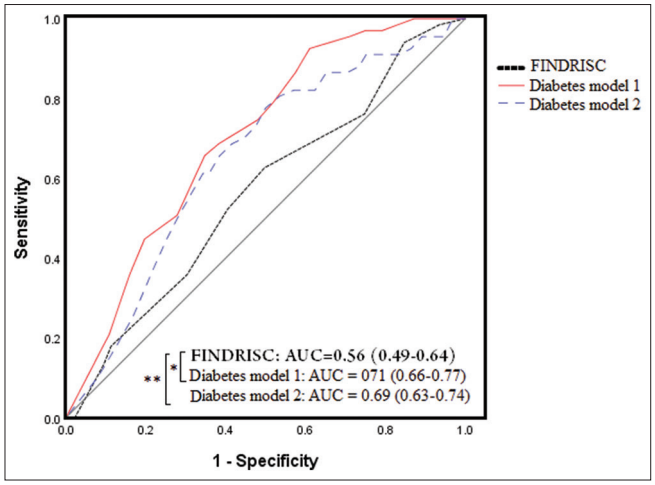

Figure 3: The performance of diabetes models 1 and 2, compared with FINDRISC for predicting diabetes. *P = 0.005 **P = 0.003. FINDRISC: Finnish Diabetes Risk Score

and FPG. The best diabetes predictability was obtained by a model which included OGTT-AUC. The AUC of this model was 0.71 (0.66–0.77). The other model included FPG instead OGTT-AUC showed an AUC of 0.69 (0.63–0.74). According to diabetes risk model 1, individuals with score values more than 6 were determined as high-risk for developing diabetes. Although, the predictive efficiencies of both models were higher than other plasma glucose indices, the predictability of the OGTT-AUC alone was comparable to the multifactorial developed predictive models in our study. The OGTT-AUC cutoff value for diabetes prediction is blood glucose more than 7.8 and 7.2 mmol/L at 30 and 60 min, respectively. Therefore, we recommend a univariate and simple OGTT test for screening the FDRs for predicting the risk of developing diabetes. Same scenario is true about prediabetes risk prediction.

Prediabetes risk model 1 included HbA1c, SBP, lipid index, and OGTT-AUC with the AUC of 0.63 (0.59–0.67). Prediabetes risk model 2 was developed based on age, waist circumferences, HbA1c, lipid index, and FPG with the AUC of 0.60 (0.57–0.64). Based on prediabetes risk model 1, the score value more than 3 is a critical score for the onset of prediabetes in the FDRs of patients with T2DM. The AUC of all prediabetes risk models were significantly higher than FPG and HbA1c. However, there was no significant

Table 4: Univariate and multivariable analyses of risk factors for diabetes and the performance of the risk score: Two predictive models for developing diabetes

	Univariate analysis HR (95%CI)	Multivariable analysis HR (95%CI)	AUC (95% CI) of model	Risk scores, mean±SD	Risk scores, median (maximum–minimum)	Risk scores cutoff-values (sensitivity, specificity, accuracy) (%)	*P*
Model 1							
WHR	2.47 (1.50–4.07)	1.93 (1.11–3.37)	0.71 (0.66–0.77)	5.89±3.22	5.61 (0–11.14)	6 (78, 52, 54)	<0.001*
HbA1c	1.90 (1.20–3.02)	1.90 (1.17–3.09)					
OGTT-AUC	4.12 (2.54–6.68)	3.68 (2.17–6.25)					
Lipid index	2.43 (1.56–3.78)	2.25 (1.37–3.72)					
Model 2							
WHR	2.47 (1.50–4.07)	1.91 (1.10–3.32)	0.69 (0.63–0.74)	4.70±2.30	7.50 (0–8.53)	4 (77, 52, 53)	<0.001*
HbA1c	1.90 (1.20–3.02)	1.97 (1.22–3.16)					
FPG	2.29 (1.48–3.54)	2.06 (1.26–3.37)					
Lipid index	2.43 (1.56–3.78)	2.59 (1.58–4.25)					

Lipid index: A combined measure of lipid profiles, including TG, cholesterol, HDL, and LDL. TG=Triglyceride; WHR: Waist-to-hip ratio; FPG=Fasting plasma glucose; HbA1c=Glycosylated hemoglobin; OGTT-AUC=Oral glucose tolerance test-area under the curve; SD=Standard deviation; HDL=High-density lipoprotein; LDL=Low-density lipoprotein, HR=Hazard ratio; CI=Confidence interval. *significant level for AUC

Table 5: Univariate and multivariable analyses of risk factors for prediabetes and the performance of the risk score: two predictive models for developing prediabetes

	Univariate analysis HR (95%CI)	Multivariable analysis HR (95%CI)	AUC (95% CI) of model	Risk scores, mean±SD	Risk scores, median (maximum–minimum)	Cutoff-values for risk scores (sensitivity, specificity, accuracy) (%)	*P*
Model 1							
OGTT-AUC	1.88 (1.47–2.40)	1.80 (1.37–2.37)	0.63 (0.59–0.67)	3.20±1.65	3.07 (0–5.92)	3 (71, 52.5, 55)	<0.001*
SBP	1.46 (1.17–1.81)	1.27 (0.97–1.66)					
HbA1c	1.28 (1.01–1.61)	1.25 (0.97–1.62)					
Lipid index	1.64 (1.30–2.07)	1.48 (1.14–1.93)					
Model 2							
FPG	1.79 (1.42–2.26)	1.88 (1.45–2.43)	0.60 (0.57–0.64)	4.11±1.87	4.31 (0–7.37)	4 (65, 50,52)	<0.001*
Age	1.46 (1.17–1.82)	1.18 (0.92–1.52)					
Waist	1.40 (1.11–175)	1.34 (1.05–1.72)					
HbA1c	1.28 (1.01–1.61)	1.30 (1.01–1.66)					
Lipid index	1.64 (1.30–2.07)	1.67 (1.30–2.15)					

Lipid index: A combined measure of lipid profiles including TG, cholesterol, HDL, and LDL. TG: Triglyceride; FPG=Fasting plasma glucose; HbA1c=Glycosylated hemoglobin; OGTT-AUC=Oral glucose tolerance test-area under the curve; SBP=Systolic blood pressure; SD=Standard deviation; CI=Confidence interval; HR=Hazard ratio; HDL=High-density lipoprotein; LDL=Low-density lipoprotein. *significant level for AUC

difference in predictability of the OGTT-AUC alone with prediabetes risk model 1.

Similarly, in previous studies,[27,28] no further improvement was achieved in predictability of the model by adding other clinical factors. For instance, in the Framingham Offspring study,[27] the initial model was based on age, gender, parental history of diabetes, BMI, waist circumference blood pressure, HDL, TG, FPG; and no further improvement was observed in predictability of diabetes by adding 2 h-OGTT, fasting insulin level, log Gutt insulin sensitivity index, HOMA index, and C-reactive protein level to the models. Moreover, the ARIC's model[28] for predicting diabetes, based on noninvasive parameters including waist, height, hypertension, blood pressure, family history of diabetes, ethnicity, and age, performed similar to fasting glucose alone (AUCs were 0.71 and 0.74, respectively). On the other hand, another model composed of the noninvasive parameter plus FPG (AUC 0.78) and a model included FPG, TG, and HDL (AUC 0.80), showed better predictabilities. This mix in influential risk factors in the final models might result from the diversity in population. Diabetes risk scores demonstrated good predictability in the original populations in which they were derived. However, their predictive values were usually reduced in external populations.[29] Therefore, it was suggested to develop population-specific risk prediction models.[29]

The FINDRISC[14] is one of the most efficient and widely used screening tools to detect new cases of T2DM. However, the FINDRISC needs to be validated in populations other than the original Finnish population for which it was developed, to determine performance attributes. The FINDRISC was developed based on age, BMI, waist circumference, antihypertensive drug therapy, and history of high blood glucose levels. According to this model, the diabetes risk score value ranked from 0 to 20 years. The predictive value

of the model was the AUC of 85% with 77% sensitivity and 66% specificity at the score 9.[14]

In a previous study,[28] we evaluated the validity of the concise FINDRISC to predict type 2 diabetes in our population (i.e. the FDRs of patients with type 2 diabetes who had NGT).[30] The predictability of the FINDRISC in our population was lower than finish population. In this study, we compared the ability of the FINDRISC and our diabetes models to predict the onset of diabetes and results confirm that the predictability of our diabetes models is higher than the FINDRISC in our population. However, the FINDRISC model is developed based on the data collected from a questionnaire with totally noninvasive screening method in the general population while we have developed models for a more specific high risk population of the FDR of type 2 diabetes patients. This justifies the utilization of more sophisticated anthropometric measurements as well as invasive tedious OGTT.

The results of this study need to be interpreted in light of its strengths and weaknesses. The advantages of our study are as follows: (1) the large sample size (n = 1765), (2) long-term follow-up, and (3) valid diagnose of diabetes and prediabetes diagnosed by FPG and OGTT criteria. The limitation of our study is that it was conducted in a single urban city in Iran. As risk factors, prevalence, and progression to diabetes may well differ in other cities and rural areas, so the results should be handled with caution before they can be generalized to the rest of the country. Moreover, although we considered majority of easily measurable and accessible risk factors to predict diabetes and prediabetes, we did not have valid data on nutrition habits and intakes, and accordingly, these variables are not included in the developed models.

CONCLUSION

We developed risk score models for predicting the incidence of diabetes and prediabetes in the FDRs of T2DM patients with NGT in a long follow-up cohort. Our developed model showed good predictability for both conditions in this high-risk population and they are barely based on noninvasive, low cost, and easily measurable risk factors. On the other hand, we showed that the OGTT-AUC is the strong predictor alone for predicting the risk of diabetes and prediabetes. We recommend regular evaluation for the FDRs of patients with type 2 diabetes to predict the risk of diabetes and prediabetes by using OGTT-AUC that is a simple and univariate test.

Ethics approval and consent to participate

The Ethics Committee of the Isfahan University of Medical Sciences approved the protocol of this study (IR.MUI.MED.REC.1398.525) and the tenants of the Declaration of Helsinki were followed. All participants had provided written informed consents.

Availability of supporting data

The data that support the findings of this study are available on request from the corresponding author, AA. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Authors contributions

AA, MA (Massoud) and AF had a substantial contribution to the conception and design of the current secondary study. AF, contributed to acquisition and analysis of data. PKH, AF, and AA contributed to drafting of study's manuscript. AF and SA substantially revised the work. SA contributed in English editing. MA (Majid) contributed in data analysis as technical assistant. All authors read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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