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RESEARCH ARTICLE

Progression to impaired glucose metabolism in first-degree relatives of patients with type 2 diabetes in Isfahan, Iran

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Abstract

Background The aim of this study was to estimate the progression rates from normal glucose tolerance (NGT) to impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes, and from IFG and IGT to diabetes in first-degree relatives (FDRs) of individuals with type 2 diabetes mellitus.

Methods A total of 701 non-diabetic FDRs of consecutive patients with type 2 diabetes aged 20–70 years in 2003–2005 were followed through 2007 for the occurrence of IGT, IFG and type 2 diabetes. Glucose tolerance classification was based on the criteria of the American Diabetes Association and standard 75 g 2-h oral glucose tolerance test (OGTT).

Results The progression rate from NGT to IFG, IGT and diabetes were 8.6% (95% confidence interval (CI) 6.8–10.6), 3.7% (95% CI: 2.5–5.1) and 0.5% (95% CI: 0.1–1.2) per year after an average of 27.6 months, respectively. Progression rates from IFG and IGT to diabetes were 5.1% (95% CI: 2.1–10.2) and 9.9% (95% CI: 7.7–12.6) per year.

Conclusions To our knowledge, these are the first estimate of progression rates from NGT to IFG, IGT and diabetes in FDRs of individuals with type 2 diabetes in Iran. The progression rates to diabetes in these participants are high, and intensive follow-up and intervention strategies are recommended for these high-risk individuals. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords first-degree relatives; diabetes mellitus; impaired glucose tolerance; impaired fasting glucose; impaired glucose regulation; progression rate

Introduction

First-degree relatives (FDRs) of individuals with diabetes are at higher risk of developing glucose intolerance and diabetes [1,2]. Due to the silent nature of diabetes, diagnosis is often delayed with many patients presenting complications [3]. With the increasing prevalence of diabetes mellitus worldwide [4], particularly in Asia and Africa, and the number of FDRs of individuals with type 2 diabetes, as well as an increase in the risk of developing diabetes, identifying these high-risk individuals becomes increasingly important. Information on the risk of progression to diabetes, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) in these high-risk individuals is highly relevant as progression to diabetes is preventable or delayed with lifestyle changes or pharmacological interventions [5–10].

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Despite the high risk of diabetes in FDRs of patients with diabetes, there is a paucity of prospective data on the progression rate from normal glucose tolerance (NGT) or IGT to diabetes in this population. Some studies have estimated progression rates from NGT or IGT to diabetes in general or selected populations [11–19] and none of them have undertaken in developing countries or in FDRs of individuals with type 2 diabetes. Because of the heterogeneity of type 2 diabetes and its recognized polygenic basis and dependence on environmental factors, there is a need for ethnically focused, and country/continent-specific studies of progression to diabetes [20].

The objective of this study therefore was to estimate the progression rates from NGT to IFG, IGT and diabetes, as well as from IFG and IGT to diabetes, and to conduct a preliminary investigation of the determinants of progression to more advanced stage of impaired glucose metabolism in FDRs of patients with type 2 diabetes.

Materials and methods

Data collection

The Isfahan Diabetes Prevention Study (IDPS) is an ongoing cohort study in central Iran to assess the efficacy of intensive diet and exercise to prevent or delay the onset of type 2 diabetes mellitus in FDRs of patients with type 2 diabetes. The study was established in 2003–2005 when 2368 (614 men and 1754 women) FDRs of a consecutive sample of patients with type 2 diabetes attending clinics in Isfahan Endocrine and Metabolism Research Center, which is affiliated to Isfahan University of Medical Sciences, Iran, completed laboratory tests including standard 75 g 2-h oral glucose tolerance test (OGTT) and 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 [21] to update information on demographic, anthropometric and lifestyle factors, and on newly diagnosed diabetes, IGT and IFG. Accordingly, if OGTT was normal at baseline, repeat testing was carried out at least at 3-year interval. Otherwise, repeat testing was carried out annually. The Isfahan Diabetes Prevention Study baseline methods have been described in detail elsewhere [22]. The participants included siblings and children of patients with type 2 diabetes. All participants were referred for nutritional and weight management program after the start of the study by qualified nutritionists to give detailed information and education about diabetes risk factors and prevention and if necessary recommend weight management program.

Ascertainment of diabetes

Cases of IGT, IFG and diabetes were identified from baseline and follow-up OGTTs according to American Diabetes Association criteria [23]. Individuals who were not diabetic at baseline and who had at least one subsequent examination were included. Pregnant women were excluded. For the present study, analyses were limited to the 701 participants [150 men and 551 women, mean (SD) age 42.7 (6.4) years] in the average 27.6 months (2.3-year) follow-up for whom complete data were available. 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, waist-to-hip ratio (WHR) and levels of FPG (Fasting plasma glucose), cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, systolic blood pressure (BP) and obesity. However, non-attendees had slightly lower diastolic BP (73.5 mmHg *versus* 74.6 mmHg $p < 0.05$), HbA_{1c} (5.0% *versus* 5.1%, $p < 0.05$), and plasma glucose (PG) at 30 min (142.2 mg/dL *versus* 147.0 mg/dL ($p < 0.01$), 60 min (145.1 *versus* 155.5, $p < 0.01$) and 120 min (115.0 mg/dL *versus* 127.8 mg/dL $p < 0.01$), but higher levels of low-density lipoprotein (LDL) cholesterol (118.5 mg/dL *versus* 115.3 mg/dL, $p < 0.05$).

Procedures

Information on age, gender, body size, HbA_{1c}, cholesterol, LDL, HDL, triglyceride, BP, and family and personal medical history was collected at the baseline and through follow-ups. The same methodology was used for both the prevalence and incidence studies. Participants reported to clinics in the morning after an overnight fast. Subjects were asked to abstain from vigorous exercise in the evening before and on the morning of the investigations. Smokers were encouraged to abstain from smoking on the morning of the investigations. On arrival at the clinic, the information given by the participants in the questionnaire on family history was verified. Then, with the subjects in light clothes and without shoes, height, weight, waist and hip circumference were measured using standard apparatus. Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height, waist, and hip circumference were measured to the nearest 0.5 cm with a measuring tape. Waist was measured midway between the lower rib margin and the iliac-crest at the end of a gentle expiration. Hip circumference was measured over the greater trochanters directly over the underwear. Using standard techniques, resting BP was measured after subjects had been seated for 10 min by using a mercury sphygmomanometer and appropriately sized cuffs. FPG was measured using the glucose oxidase method. Subjects with FPG <126 mg/dL underwent a standard OGTT (75 g glucose 2-h) at baseline and the follow-ups. Venous blood was sampled at fasting, 30, 60, and 120 min after oral glucose administration. Plasma samples obtained after centrifuge were analysed on the same day.

HbA_{1c} (measured by ion-exchange chromatography), total cholesterol, triglyceride, HDL and LDL (calculated by

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the Friedewald equation [24] provided total triglycerides did not exceed 400 mg/dL) were also assessed. All the blood sampling procedures were performed in the central laboratory of the Isfahan Endocrine and Metabolism Research Center using enzyme-linked method. Tenets of the Declaration of Helsinki were followed, Institutional Ethical Committee approval was granted and an informed consent form was signed by each participant.

Definitions

We calculated BMI as the ratio of weight (kg) to squared height (m^2), the latter being assessed at baseline only. Those participants with FPG ≥200 mg/dL or pharmacological treatment were considered as diabetic. If FPG was ≥126 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 diabetic. FPG ≥126 mg/dL or 2-h PG ≥200 mg/dL defined diabetes mellitus. IGT was defined as FPG <126 mg/dL, but with 2-h PG concentration ≥140 and <200 mg/dL. If FPG was in the range of 100–126 mg/dL and 2-h PG was <140 mg/dL, it was considered as IFG. If the FPG was below 100 mg/dL and 2-h PG smaller than 140 mg/dL, it was considered as a sign of NGT [23]. The NCEP-ATP III [25] definition was used for the metabolic syndrome (MetS) by the presence of three or more of the following abnormalities: BP ≥130/85 mm Hg or a history of hypertension and current use of antihypertensive treatment; waist girth >102 cm for men and >88 cm for women, serum triglyceride ≥150 mg/dL (≥1.7 mmol/lL and/or HDL-cholesterol [<40 mg/dL (<0.9 mmol/L) for men and <50 mg/dL (<1.0 mmol/L) for women]; and FPG levels ≥126 mg/dL (6.1 mmol/L).

Analysis

Progression rates were estimated as the number of cases progressed to more advanced stage of impaired glucose metabolism per 100 person-years of follow-up. The relevant period was considered to start on the date when the baseline examination was performed sometime between 2003–2005 until either *i*) the onset of more advanced stage of impaired glucose metabolism, *ii*) the date of the last completed follow-up, *iii*) death, or *iv*) end of follow-up on December 31, 2007, whichever came first. For ease of interpretability, we report the progression rates in terms of percent per year. Statistical methods used included the Student's t-test, chi-squared test, and Cox's proportional hazards model. Within-group comparisons were done by paired student's t-test. We considered the following covariates in the multivariate-adjusted analyses: age, gender, BMI, WC, triglyceride, LDL, HDL, total cholesterol and diastolic BP. Variables such as age, BMI, WC, triglyceride, LDL, HDL, total cholesterol and BP were entered in models as continuous variables, while gender was categorical. Age-adjusted means were calculated and compared using general linear models. Analysis was performed using software SPSS for Windows (SPSS Inc., Chicago, Illinois, IL). All tests for statistical significance were two-tailed, and performed assuming a type I error probability of <0.05.

Results

Characteristics

Baseline characteristics of the 331 (47.2%) participants with NGT, 315 (44.9%) with IGT and 55 (7.8%) with IFG are shown in Table 1. As expected, those with IGT or IFG were older at baseline than NGT, and had higher age-adjusted mean BMI, WC, hip circumference, waist-to-hip ratio, FPG, PG at 30, 60 and 120 min., cholesterol, LDL, HDL, triglyceride and higher proportion of obesity. There was a tendency towards lower follow-up for IGT than for NGT or IFG group. The mean (SD) age was 43.5 (6.7) years for those with IGT, 42.9 (6.6.) years for those with IFG and 41.8 (5.8) years for those with NGT. MetS was present in over a quarter of the participants (25.2%; 95% confidence interval (CI): 22.0–28.4).

Worsening glucose tolerance over time

The progression rates from NGT, IGT or IFG to more advanced stage of impaired glucose metabolism are presented in Table 2. During 1630 (354 men and 1276 women) person-years of follow-up, 74 (10.6%) (12 men and 62 women) incident cases of type 2 diabetes occurred. The overall progression rate to diabetes was 4.5% (95% CI: 3.6–5.7) per year. Progression rates to diabetes were higher in women (4.9%, 95% CI: 3.7–6.2 per year) than in men (3.4%, 95% CI: 1.8–5.8). This difference was not statistically significant. Of the 331 participants with NGT at baseline, 111 (12.7% per year) subsequently progressed to diabetes, IGT or IFG at a rate of 0.5, 3.7, and 8.6%, per year, respectively. Of the 315 participants who had IGT at initial registration, 61 subsequently developed diabetes, giving a progression of 9.9% (95% CI: 7.7–12.6) per year. This was much higher than the progression rates seen for NGT, 0.5% per year (95% CI: 0.1–1.2) ($p < 0.001$). Of the 55 participants who had IFG at initial registration, 7 subsequently developed diabetes, giving a progression of 5.1% (95% CI: 2.1–10.2) per year. Progression to diabetes was 6.0% (95% CI: 3.9–8.8) per year in those with MetS. This was higher than the progression rates seen for those without MetS, 4.0% per year (95% CI: 3.0–5.3). This difference was not statistically significant. As shown in Table 3, the progression to diabetes increased across the five subject groups, from 0.6% per year in the NGT and no MetS group, to 13.9% per year in the IGT and MetS group. In addition, Table 3 demonstrates how multivariate-adjusted relative risk (RR) of progression to diabetes in subjects with NGT and MetS, IFG and MetS and IGT with and without MetS

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Table 1. Age, age-adjusted mean (SE) and proportion characteristics† of first-degree relatives of patients with type 2 diabetes by glucose tolerance status in the Isfahan Diabetes Prevention Study

Baseline characteristic	NGT ($n = 331$)	IGT ($n = 315$)	IFG ($n = 55$)
Age (year)	41.8 (0.3)	43.5 (0.4)	42.9 (0.9)**
Height (cm)	159.7 (0.4)	158.3 (0.4)	159.8 (1.0)
Waist circumference (cm)	87.0 (0.5)	90.0 (0.5)	90.9 (1.2)***
Hip circumference (cm)	107.1 (0.5)	108.6 (0.5)	111.0 (1.2)**
Waist-to-hip ratio	0.81 (0.003)	0.83 (0.004)	0.82 (0.009)**
BMI (kg/m^2)	28.4 (0.2)	29.5 (0.2)	30.5 (0.5)***
Follow-up duration (year)	2.6 (0.04)	1.9 (0.05)	2.5 (0.1)***
Fasting glucose baseline (mg/dL)	86.6 (0.5)	100.9 (0.5)	106.7 (1.3)***
Plasma glucose 30 min (mg/dL)	131.6 (1.5)	160.7 (1.6)	164.6 (3.8)***
Plasma glucose 60 min (mg/dL)	128.9 (1.9)	183.9 (2.0)	156.7 (4.6)***
Plasma glucose 120 min (mg/dL)	99.5 (1.1)	161.1 (1.1)	106.7 (2.7)***
HbA_{1c} (%)	5.1 (0.05)	5.1 (0.05)	5.3 (0.1)
Cholesterol (mg/dL)	184.9 (2.2)	200.0 (2.3)	207.9 (5.5)***
LDL-cholesterol (mg/dL)	110.8 (2.1)	118.6 (2.0)	123.3 (5.2)**
HDL-cholesterol (mg/dL)	43.9 (0.7)	46.1 (0.7)	49.2 (1.7)**
Triglyceride (mg/dL)	155.9 (5.8)	181.6 (5.9)	173.2 (14.2)**
Systolic BP (mm Hg)	114.5 (0.9)	115.4 (0.9)	117.4 (2.2)
Diastolic BP (mm Hg)	74.5 (0.7)	74.5 (0.7)	76.3 (1.7)
Men, no. (%)	77 (23.1)	58 (18.4)	13 (23.6)
Obesity (BMI $\geq$30), no. (%)	103 (31.7)	128 (40.9)	29 (53.7)**
Metabolic syndrome, no. (%)	74 (22.2)	90 (28.6)	13 (23.6)

CI, confidence interval; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure.
†Age-adjusted means were calculated using general linear models. Data are expressed as mean (SE) or number (%). The difference in the mean or percentage of the variables between normal, impaired glucose tolerance and impaired fasting glucose: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

increased relative to those with NGT and without MetS. Participants with IGT with and without MetS tended to have a significantly higher risk of diabetes than did participants with NGT ($p < 0.001$). Controlling for other time-dependent covariates did not appreciably alter the relationship between IGT and diabetes compared to the model adjusted for age alone. The age- and multivariate-adjusted risk for diabetes among those with IGT and MetS was higher than those without MetS.

On the other hand, of the 315 participants with IGT at baseline 59 (18.7%) reverted to NGT and 64 (20.3%) to IFG at a rate of 9.6% and 10.5% per year, respectively. Of the 55 participants, who had IFG at initial registration, 15 (27.3%) improved to NGT, giving an improvement rate of 10.9% (95% CI: 5.7–16.1) per year.

The BMI, WC, hip circumference and weight decreased among participants who improved from IGT to NGT or IFG. Participants who progressed to more advanced stage of impaired glucose metabolism consistently showed higher PG levels through the follow-up. Those who did not progress showed lower PG levels. Between baseline and the end of follow-up the cholesterol increased among participants, whether they progressed or not from NGT to more advanced stage of impaired glucose metabolism (Table 4).

Table 2. Progression rates to impaired glucose tolerance, impaired fasting glucose and diabetes from baseline to mean 2.3-year follow-up period

Glucose tolerance status at baseline	Glucose tolerance status at follow-up: Outcome	Person-year	Rate/100 person-year (95% CI)
	Diabetes mellitus		
Normal glucose tolerance	4	876	0.5 (0.13, 1.17)
Impaired fasting glucose	7	138	5.1 (2.10, 10.20)
Impaired glucose tolerance	61	612	9.9 (7.71, 12.60)
	Impaired glucose tolerance		
Normal glucose tolerance	32	876	3.7 (2.51, 5.12)
Impaired fasting glucose	8	238	3.4 (1.46, 6.51)
Impaired glucose tolerance	93	612	15.2 (12.40, 18.00)
	Impaired fasting glucose		
Normal glucose tolerance	75	876	8.6 (6.79, 10.60)
Impaired fasting glucose	25	238	10.5 (6.61, 14.49)
Impaired glucose tolerance	64	612	10.5 (8.03, 12.90)
	Normal glucose tolerance		
Normal glucose tolerance	222	876	25.3 (22.50, 28.20)
Impaired fasting glucose	15	238	6.3 (3.57, 10.20)
Impaired glucose tolerance	99	612	16.2 (13.30, 19.10)

CI, confidence interval.
Due to missing data, number of incident diabetes = 72.

Discussion

In this cohort study, FDRs of patients with type 2 diabetes with NGT at baseline show 0.5, 3.7, and 8.6%, per year progression to diabetes, IGT or IFG. Among participants with IGT, 9.9% per year progressed

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Table 3. Incidence rates and relative risks (95% CI) of type 2 diabetes by metabolic syndrome status, the Isfahan Diabetes Prevention Study, 2003–2008

Variables	Metabolic syndrome	Cases (No.)	Incidence/100 person-year	Age-adjusted relative risk (95% CI)	Multivariate-adjusted relative risk (95% CI)[a]
Normal glucose tolerance	No	4	0.6	1.00 (reference)	1.00 (reference)
Impaired fasting glucose	No	6	5.6	1.07 (0.77, 1.48)	0.98 (0.67, 1.44)
Impaired fasting glucose	Yes	1	3.2	1.19 (0.68, 2.08)	1.29 (0.66, 1.21)
Impaired glucose tolerance	No	38	8.5	1.59 (1.32, 1.91) ***	1.59 (1.30, 1.94)***
Impaired glucose tolerance	Yes	23	13.9	1.89 (1.47, 2.42) ***	1.72 (1.21, 2.44)**

CI, confidence interval; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure; BMI, body mass index; WC, waist circumference. Due to missing data, number of incident diabetes = 72.
[a]Relative risks (with 95% CI) calculated by Cox's proportional hazards model, adjusted for age, gender, BMI, WC, triglyceride, LDL, HDL, total cholesterol and BP.
$^{**}p < 0.01$, $^{***}p < 0.001$.

Table 4. Changes over time in subjects who did or did not progress to more advanced stage of impaired glucose metabolism during mean 2.3 years follow-up period

	Change from baseline to final assessment		
Characteristic	Not progressed ($n = 519$)	Progressed ($n = 182$)	Difference (95% CI)
Waist circumference (cm)	−0.5 (4.4)	0.5 (4.5)	−1.0 (−1.69, −0.17)*
Hip circumference (cm)	−0.6 (4.7)	0.2 (4.4)	−0.8 (−1.62, −0.05)*
Waist-to-hip ratio	0.0 (0.04)	0.0 (0.04)	0.0 (−0.01, 0.04)
Weight (kg)	−1.1 (5.4)	0.2 (4.0)	−1.3 (−2.16, −0.44)**
Body mass index (kg/m^2)	−0.4 (2.0)	0.07 (1.6)	−0.5 (−0.83, −0.19)**
PG baseline (mg/dL)	−0.6 (12.3)	17.2 (17.2)	−17.8 (−20.02, −15.40)***
PG 30 min (mg/dL)	−10.8 (33.4)	14.1 (35.6)	−24.9 (−31.43, −18.37)***
PG 60 min (mg/dL)	−7.3 (39.5)	17.8 (38.6)	−25.1 (−32.43, −17.85)***
PG 120 min (mg/dL)	−15.6 (34.8)	26.5 (36.0)	−42.1 (−48.43, −35.80)***
HbA_{1c} (%)	−0.07 (0.8)	−0.1 (0.8)	0.03 (−0.11, 0.23)
Cholesterol (mg/dL)	9.3 (35.6)	23.1 (33.3)	−13.8 (−19.87, −7.83)***
LDL-cholesterol (mg/dL)	7.9 (35.8)	16.7 (32.7)	−8.8 (−15.21, −2.43)**
HDL-cholesterol (mg/dL)	1.0 (11.6)	4.6 (12.4)	−3.6 (−5.69, −1.48)**
Triglyceride (mg/dL)	−1.8 (84.8)	5.8 (85.9)	−7.6 (−22.33, 7.00)
Systolic BP (mm Hg)	2.3 (48.1)	−4.2 (16.1)	6.5 (−1.22, 14.23)
Diastolic BP (mm Hg)	1.4 (14.4)	−4.9 (14.7)	6.3 (3.62, 8.85)***

CI, confidence interval; PG, plasma glucose; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure.
Data are expressed as mean (SD). The difference in the means of the variables between not progressed and progressed:
$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

to diabetes. Of the participants with IGT at baseline, 9.6% per year improved to NGT and 10.5% to IFG and of the individuals who had IFG at initial registration, 10.9% per year improved to NGT. To the best of our knowledge, this is the first study to report on progression rates from NGT to more advanced stage of impaired glucose metabolism in FDRs of individuals with type 2 diabetes. Progression rates to IFG, IGT and type 2 diabetes in general populations in various studies from around the world show considerable variation. Estimates of progression to IFG, IGT and diabetes will depend upon the methodological factors, the definition of the diabetes, IGT and IFG used, unknown time spent with IFG and IGT, and the composition of the community examined by age and gender, making comparisons between studies of limited values. In population-based studies the annual progression rates were 1–5% for IFG and 3–11% for IGT [11,13,26,27]. In control groups of randomized clinical trials the progression rates from IGT were up to 12% per year [5,8,28]. The Hoorn study [11] estimated that 33% of individuals with IFG but not IGT and 64.5% of individuals with IFG and IGT developed diabetes over a follow-up of 5.8–6.5 years, an annual rate of approximately 5.5 and 10.8%, respectively. The Paris Prospective Study [12] reported much lower proportions: 2.7% among patients with NGT or isolated IFG and 14.9% among patients with IFG and IGT over 2.5 years of follow-up, an annual rate of about 1.1 and 6%, respectively. The Inter99 study [28] reported annual progression rate of 2.1% in low- and high-risk patients with NGT. Among high-risk individuals, 5.8% per year with NGT progressed to IGT, IFG or diabetes, and 4.9% per year progressed from IFG or IGT to diabetes over 1-, 3- and 5-year of follow-up. An Italian study [13] spanning 11.5 years found that 9.1% of patients with isolated IFG and 44.4% of subjects with IFG and IGT developed diabetes, an annual rate of around 0.8 and 3.9%, respectively. Studies of non-White populations have reported diabetes development proportions ranging from 21.6% over 5 years (4.3% per year) among Mauritians with isolated IFG [14] to 41.2% over 5 years (8.2% per year) among Pima Indians with IFG and IGT [15]. The highest proportion of diabetes development, 72.7%

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over 7 years among subjects with IGT and IFG, was found in a Brazilian-Japanese population, annual rate of about 10.4% [29]. The Baltimore Longitudinal Study of Aging [30] found that diabetes occurred in 25% of 216 subjects over 10 years (2.5% per year), following their progression from NGT to IFG or IGT. Nichols *et al*. [31] in a retrospective cohort study of real-world patients with incidence of IFG found that diabetes occurred in 8.1% subjects over a mean follow-up of 6.3 years, an annual rate of 1.34%. The ADDITION Study, Denmark, [32] found that the annual progression rate to diabetes in high-risk individuals identified in a pragmatic diabetes screening program in general practice was 17.6% for IFG and 18.8% for IGT. The annual progression rates from IFG or IGT to diabetes in our FDRs of patients with type 2 diabetes is higher than the values reported in Paris Prospective Study [12], the Inter99 study [28], Italian study [13], studies of non-White populations [14,15] and other population-based studies [26,27], but lower than the ADDITION Study [32]. Our progression rates were comparable to those of Hoorn study [11] and Brazilian-Japanese population study [29], whose annual changes from IFG and IGT to diabetes were about 5 and 10%, respectively. FDRs likely carry a predisposing genetic factor. Unfortunately, the data used here do not allow for an empirical test of this speculation. Further research would be useful to examine what factors play a role in the higher progression rate of FDRs of patients with type 2 diabetes.

All studies [11–16], as well as our study, agreed that the risk of developing diabetes was higher in individuals with either IFG or IGT as compared with individuals with NGT. Most of these studies agreed with our studies that IGT defined a larger number of individuals who are at risk of developing diabetes than IFG [12–16]. Both IFG and IGT have a heterogeneous pathogenesis, and this may contribute to different rates of progression to diabetes.

The natural history of both IFG and IGT is variable, with ~25% progressing to diabetes, 50% remaining in their abnormal glycemic state, and 25% reverting to NGT over an observational period of 3–5 years [14,15]. Individuals who are older and overweight, have higher level of blood glucose and other diabetes risk factors are more likely to progress to diabetes. Moreover, low insulin secretion and severe insulin resistance help in identifying individuals more likely to progress to diabetes [33]. With longer observation, the majority of individuals with IFG or IGT appear to develop diabetes. It seems likely that the high improvement rates or remaining in their baseline glycemic state within a short time in our high-risk population may be due to the awareness about diabetes prevention as part of the Isfahan Diabetes Prevention Study, and this may have influenced our reported findings. The improvement in glucose tolerance with lifestyle change may be the result of improved β-cell function along with enhanced insulin sensitivity.

The risk of diabetes was amplified in the presence of MetS in participants with IGT. The participants who had MetS and IGT were at higher risk of diabetes than individuals without MetS. This suggests that obesity, BP and dyslipidemia make a significant contribution to the subsequent development of diabetes.

The high risk of developing type 2 diabetes in FDRs with MetS underlines the importance of prevention of type 2 diabetes in these individuals. Clinical trials demonstrate that lifestyle [5,6,10] and pharmaceutical interventions [7–9] in high risk individuals can prevent the development of diabetes. This highlights the importance of identifying high-risk subjects so as to institute early lifestyle or pharmacological intervention but also reduce the number of cases of undiagnosed diabetes who should received treatment.

The mechanisms underlying the increased risk of type 2 diabetes in FDRs of patients with type 2 diabetes are not entirely clear. Putative mechanisms include the evidence of abnormalities in insulin sensitivity and β-cell function in this population. The relative importance of insulin resistance and β-cell dysfunction in the development of type 2 diabetes has been a long-standing debate [32–40]. Evidence that a decline in β-cell function is a critical determinant of deteriorating glucose tolerance comes from two longitudinal studies in Pima Indians [32] and in post-menopausal women [35] and from the UK Prospective Diabetes Study [36], as well as other studies [33,37,38]. The mechanisms underlying the progressive decline in β-cell function are not fully understood. It may be related to a genetic predisposition compounded by environmental exposure such as increased caloric intake and the development of obesity. Recently Cnop *et al*. [39] found that the development of central obesity was associated with loss of β-cell function, suggesting that changes in central or visceral fat-derived factors may predispose to β-cell dysfunction in high-risk individuals. Similarly, others have found that central body fatness and the increase in fat over time were the major predictors of a decline in the homeostasis model assessment insulin secretion index in women with a family history of diabetes [40]. Insulin resistance is also likely to be involved in the pathogenesis of type 2 diabetes, but the progressive loss of β-cell function appears to be the critical determinant for progression from NGT to IFG or IGT and to type 2 diabetes.

The strengths of present study include the prospective cohort design, the sample consisting of both men and women of a wide age range, diagnosis of diabetes based on standard OGTT, and information on potential determinants of diabetes. Selection and information bias is considered unlikely by virtue of the prospective design. Our study addressed individuals at increased risk of developing type 2 diabetes, because they had FDRs with the disease. The multiple examinations with OGTTs make the progression rates very accurate. This study could draw criticism because of the short follow-up. The short follow-up time in our study implies that the risk of diabetes is imminent. Other limitations include the use of a relatively small sample of FDRs. Assessing the prediction in a larger sample and longer-term period are therefore warranted. Furthermore, those at greatest diabetes risk may have been tested more frequently,

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therefore increasing the likelihood of detection, causing an overestimation of progression rates. At follow-up, non-attendees of the entire population did not differ from attendees by major risk factors for progression, although a difference too small to explain the high progression rates in our study was seen in the mean levels of LDL, HbA_{1c} and PG. Despite the above limitations, the findings here add to our understanding of the progression rate to more advanced stage of impaired glucose metabolism in FDRs of individuals with type 2 diabetes in Iran. Furthermore, this study provides new data from Iran, a developing country that has been under-represented in past studies.

In conclusion, the findings of this study illustrate for the first time the progression rates from NGT, IGT and IFG to diabetes in FDRs of patients with type 2 diabetes in Iran. These findings strongly support the regular screening and follow-up of FDRs of patients with type 2 diabetes, and intervention strategies are recommended for these high-risk subjects.

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Conflict of interest

None declared.

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