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People with Impaired Glucose Tolerance and Impaired Fasting Glucose Are Similarly Susceptible to Cardiovascular Disease: A Study in First-Degree Relatives of Type 2 Diabetic Patients

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Key Words
Cardiovascular disease · Risk factors · Impaired glucose tolerance · Impaired fasting glucose · First-degree relatives · Type 2 diabetes

Abstract
Background/Aims: To compare the cardiovascular disease (CVD) risk factors between subjects with impaired fasting glucose (IFG) and those with impaired glucose tolerance (IGT) in the first-degree relatives (FDR) of type 2 diabetic patients. ***Methods:*** A cross-sectional study, conducted between 2004 and 2006 in 1,893 (1,412 females and 481 males) FDR of type 2 diabetic outpatients of the Isfahan Endocrine and Metabolism Research Center. In all participants, blood pressure, weight, height, waist circumference, serum lipids and HbA1c were measured and a standard 75-g 2-hour oral glucose tolerance test was performed. The diagnosis of IGT, IFG and diabetes was made according to American Diabetes Association criteria. ***Results:*** Isolated IGT and isolated IFG, and both IFG and IGT were observed in 8.8%, 17.4% and 11.2% of subjects, respectively. In comparison to subjects with normal glucose levels and tolerance (control group): the mean waist circumference was significantly higher in both IFG and IGT groups; BMI, HDL-c and LDL-c in the IFG group; and triglycerides in the IGT group. The means of all studied CVD risk factors were significantly higher in the IGT+IFG group than the control group, except for blood pressure, HDL-c and HbA1c. No significant differences were found regarding CVD risk factors between IFG and IGT groups. ***Conclusions:*** The prevalence of IFG and IGT is high in FDR of type 2 diabetic patients. CVD risk factors are similar in these 2 groups and higher than in the control group. More attention should be paid to screening and treatment of this high-risk population.

Introduction

Impaired glucose tolerance (IGT) has been known as a risk factor for the development of type 2 diabetes mellitus and cardiovascular diseases (CVD) [1–3]. In 1997, American Diabetes Association (ADA) defined a new category of borderline glucose intolerance known as impaired fasting glucose (IFG), which was defined as a fasting plasma glucose between 110 and 125 mg/dl (6.1 and 6.9 mmol/l) [4, 5]. In 2003, the same committee lowered the threshold from 110 to 100 mg/dl (6.1 to 5.6 mmol/l) [6]. Since the presentation of new criteria, several studies with different results have been performed to investigate the clinical significance of CVD progression in subjects with IFG. These

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studies have also compared IFG and IGT groups for the probability of developing CVD. Some trials have shown that individuals with IFG, like those with IGT, are predisposed to cardiovascular events [7–10], but others have claimed that IFG is not an independent risk factor for the development of CVD per se [11], unless it is accompanied by IGT [12] or being converted to diabetes [13].

In one trial in our country, Iran, it was reported that IFG is more frequent than IGT in first-degree relatives (FDR) of type 2 diabetics [14]. Recently, in another study in Iran, the risk of CVD was investigated in an urban Iranian general population in relation to their glucose tolerance status. Glucose intolerance was associated with a 56% increase in the risk of CVD in women [15].

If cardiovascular risk factors are similar in both IFG and IGT, the early detection of patients with IFG and assessment of their CVD risk factors, especially in high-risk populations such as FDR of type 2 diabetics, will be very important for scheduling prevention programs. As in patients with IGT, lifestyle modification can decrease the progression of diabetes and cardiovascular risk factors [16, 17].

The aim of this study was to compare the risk factors of CVD in patients with IFG and IGT detected during screening of diabetes in FDR of type 2 diabetics, a high-risk population, as a part of a diabetes primary prevention program.

Materials and Methods

In a cross-sectional study, 25- to 55-year-old FDR of type 2 outpatient diabetics, who were not known to suffer from diabetes, were enrolled by the consecutive sampling method. This study was a part of Isfahan Diabetes Prevention Project performed at the Isfahan Endocrine and Metabolism Research Center during 2004–2006.

Siblings and offspring of type 2 diabetic patients were considered as their FDR. During this study, men and women aged 25–55 years who were FDR of type 2 diabetic patients were recruited to participate in the study (n = 2,800, females = 1,450). The number of diabetics whose FDR were tested was 702 patients; 2,103 out of 2,800 persons responded, most of whom were female (n = 1,442). Persons who had known a history of diabetes (n = 38) and/or were taking medications which may affect glucose tolerance (n = 168) were excluded from the study. Four subjects were not able to continue the glucose tolerance test because of vomiting. In total, 1,893 participants (1,412 females and 481 males) completed the test.

The Medical Ethics Committee of the Isfahan Endocrine and Metabolism Research Center approved the study protocol, and all subjects gave their written consent. The study complied with the current version of the Declaration of Helsinki.

Basal characteristics of studied subjects were obtained and recorded. In all participants, height and weight were measured with light clothing and bare feet using a Seca scale (Seca, Hamburg, Germany) by a trained nutritionist. The weight was recorded to the nearest 100 g, and height was measured to the nearest 0.5 cm. BMI was calculated as weight divided by the square of the height (kg/m^2). Waist circumferences were measured according to a standardized method [18]. Blood pressure was measured by a physician on the right arm in the seated position twice after at least 15 min of rest with a 5-min interval between the 2 measurements. The manometer was placed at the heart level.

Participants were asked to stay on an unrestricted diet (more than 150 g of carbohydrate daily) and avoid heavy physical activity at least 3 days before laboratory tests. After an overnight fasting period of 10 h, a standard 75-g oral glucose tolerance test (OGTT) was performed [19]. Plasma glucose and lipids (total cholesterol, HDL cholesterol and triglyceride) were measured by enzymatic colorimetric techniques using an auto-analyzer (Escalon, Liasys, Italy).

Inter-assay coefficients of variation were 1.25% for triglyceride, 1.2% for cholesterol and 1.25% for glucose. The corresponding intra-assay coefficients of variation were 1.97%, 1.6% and 2.2%, respectively. HbA1c was measured by ion exchange chromatography with a DS5 set (Drew Scientific, Dallas, Tex., USA). Inter- and intra-assay variations of HbA1c were 6.7% and 5.8%, respectively. LDL-c was calculated using the Friedewald formula [20].

Undesirable levels of cardiovascular risk factors were defined as follows [21]: hypertension = blood pressure ≥130/85 mm Hg; abdominal obesity = waist circumference >88 cm in women and >102 cm in men; low HDL-c = HDL-c <50 mg/dl (1.3 mmol/l) in women and <40 mg/dl (1.03 mmol/l) in men; hypertriglyceridemia = triglycerides ≥150 mg/dl (1.7 mmol/l); overweight = BMI ≥25 kg/m^2; dyslipidemia considered as hypercholesterolemia = total cholesterol ≥200 mg/dl (5.20 mmol/l); high LDL-c = LDL-c ≥130 mg/dl (3.36 mmol/l).

Considering the reported overlap between the IFG and IGT categories [22], the classification was made based on 2003 ADA criteria as below:

Isolated IFG. FPG 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l) and 2-hour post-prandial plasma glucose (2hPG) <140 mg/dl (17.8 mmol/l).

Isolated IGT. FPG <100 mg/dl (5.6 mmol/l) and 2hPG 140 mg/dl (7.8 mmol/l) to 199 mg/dl (11 mmol/l).

IFG+IGT. FPG 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l) and 2hPG 140 mg/dl (7.8 mmol/l) to 199 mg/dl (11 mmol/l).

Diabetes. FPG ≥126 mg/dl (7 mmol/l) and/or 2hPG ≥200 mg/dl (11.1 mmol/l).

Normal. FPG <100 mg/dl (5.6 mmol/l) and 2hPG <140 mg/dl (7.8 mmol/l).

Those participants whose OGTT was normal were considered as the control group.

Statistical analysis was performed using SPSS version 13 (SPSS Inc., Chicago, Ill., USA). All variables with normal distribution data are presented as means ± SD. For variables which were not normally distributed, the median and ranges are reported (age, HDL-c, HbA1c, systolic and diastolic blood pressure). If indicated, log transformation was used in order to reduce skewness. To compare the mean concentrations of cardiovascular risk factors between IFG, IGT, IFG+IGT and normal groups, ANOVA were used. If a result was statistically significant, then Tukey's post hoc test was used to test for differences between the single subgroups.

Medians of cardiovascular risk factors between groups were compared using the Kruskal-Wallis test.

Age and sex were entered in an ANCOVA as covariates for multivariate analysis. The prevalence of undesirable level of cardiovascular risk factors was compared using the χ^2 test. Age and sex adjustment was performed by univariate general linear model. Values of $p < 0.05$ were considered statistically significant.

Results

A total of 1,893 [1,412 (74.6%) females, 481 (25.4%) males] FDR of type 2 diabetic patients aged between 25 and 55 years were examined. None of them were taking medications for hypertension or dyslipidemia. The basal characteristics of all studied FDR of type 2 diabetic patients are presented in table 1.

In total, 167 (8.8%) subjects had isolated IGT, 329 (17.4%) were categorized as having isolated IFG, and 212 (11.2%) had both IFG and IGT; 188 (9.9%) subjects with diabetes were excluded.

Table 2 shows the means and/or medians of cardiovascular risk factors in IGT, IFG, IGT+IFG and normal groups. No significant differences in the means or medians of waist circumference, BMI, HbA1c, systolic and diastolic blood pressure, total cholesterol, LDL-c or HDL-c were found between the IFG and IGT groups. Triglyceride levels were significantly higher in the IGT group than in the IFG group. Triglyceride, total cholesterol, LDL-c levels were significantly higher in the IGT+IFG than in the IFG group. Total cholesterol, LDL-c and BMI were significantly higher in the IGT+IFG than IGT group. HbA1c was significantly higher in the IGT group than in the IGT+IFG group. The comparisons of all these variables in each of the IGT, IFG and IFG+IGT groups with the control group are shown in table 2.

Table 3 shows the percentage of subjects with undesirable levels of cardiovascular risk factors in the studied groups. There were no significant differences in the prev-

Table 1. Baseline characteristics of FDR of type 2 diabetic patients

	FDR (n = 1,893; 1,412 females)
Age, years	42 (27–55)
BMI	29.2 ± 4.3
Waist circumference, cm	89.2 ± 9.5
Systolic BP, mm Hg	110 (80–190)
Diastolic BP, mm Hg	70 (50–110.5)
HbA1c, %	5 (4–11.7)
Cholesterol, mg/dl	195.7 ± 39.5
Triglycerides, mg/dl	165.5 ± 92.9
LDL-c, mg/dl	117.2 ± 31.6
HDL-c, mg/dl	45 (12–100)

Medians (ranges) reported for variables which were not normally distributed, and means ± SD for normally distributed variables.

Table 2. Comparing cardiovascular disease risk factors in IFG, IGT, IFG+IGT and control groups in FDR of type 2 diabetic patients

	IGT (n = 167)	IFG (n = 329)	IFG+IGT (n = 212)	Normal (n = 997)	p value			
					total	IGT vs. normal	IGF vs. normal	IFG+IGT vs. normal
Age, years	43 (27–55)	43 (29–55)	43 (29–55)	41.6 (28–55)	0.03	0.01	0.001	0.18
BMI	29.3 ± 4.1	29.5 ± 4.2	30.4 ± 4.5	28.3 ± 4.3	0.001	0.1	0.001	0.001
Waist, cm	89.5 ± 9.2	90.5 ± 9.3	90.9 ± 8.5	87.6 ± 9.4	0.001	0.01	0.001	0.001
Systolic BP, mm Hg	110 (90–170)	110 (80–180)	110 (80.5–180)	110 (80–180.5)	0.7	0.9	0.2	0.5
Diastolic BP, mm Hg	70 (50–110)	70 (50–110.5)	70 (50–110)	70 (50–110.5)	0.2	0.08	0.4	0.1
HbA1c, %	7 (4–6.7)	4.9 (4–7.4)	5.2 (4–6.7)	5 (4–9.9)	0.04	0.5	0.9	0.07
Cholesterol, mg/dl	193.1 ± 39.8	196.2 ± 37.4	207.1 ± 42.2	190.9 ± 37.7	0.001	0.9	0.05	0.001
Triglycerides, mg/dl	173.2 ± 93.5	155.1 ± 80.1	170.4 ± 86.9	158.7 ± 90.6	0.001	0.03	0.5	0.01
LDL-c, mg/dl	115.0 ± 34.1	119.0 ± 30.3	126.3 ± 33.7	114.3 ± 30.3	0.001	0.8	0.04	0.001
HDL-c, mg/dl	44 (28–79)	46 (24–77)	46 (34–81)	44 (25–85)	0.02	0.8	0.00	0.06

Variables without a normal distribution are presented as medians (ranges). Variables with a normal distribution are presented as means ± SD. ANOVA and Tukey's post hoc tests were used.

Table 3. Percentage of subjects with undesirable levels of cardiovascular risk factors in studied groups

	IGT (n = 167)	IFG (n = 329)	IFG+IGT (n = 212)	Normal (n = 997)	p value			
					total	IGT vs. normal	IFG vs. normal	IFG+IGT vs. normal
Overweight	88.8	87.6	90.7	81.9	0.001	0.001	0.02	0.002
Abdominal obesity	34.7	40.1	47.9	29.9	0.001	0.5	0.001	0.001
Hypertension	30.6	24.8	23.4	21.4	0.071	0.04	0.6	0.1
High cholesterol	41.3	45.8	56	37	0.001	0.5	0.01	0.001
High triglyceride	52.5	45	49.5	42.3	0.013	0.1	0.7	0.07
High LDL-c	30.1	36.8	44.3	28.8	0.013	0.9	0.01	0.001
Low HDL-c	58.9	50.2	55.6	59.1	0.05	0.9	0.01	0.2

Age and sex were entered in an ANCOVA as covariates for multivariate analysis.

alence of abdominal obesity, hypertriglyceridemia, low HDL-c, hypertension, hypercholesterolemia and overweight between the IFG and IGT groups. The prevalence of abdominal obesity, hypercholesterolemia, high LDL-c and obesity was higher in the IGT group in comparison to the IGT+IFG group. The prevalence of hypercholesterolemia was higher in the IFG group in comparison to the IGT+IFG group.

Discussion

This study showed that FDR of type 2 diabetic patients with IFG or IGT had higher cardiovascular risk factors than normal individuals, but those with both IFG and IGT had a similar level of cardiovascular risk factors, except for triglyceride levels. However, triglyceride, total cholesterol and LDL-c were significantly higher in the IGT+IFG than the IFG group. Total cholesterol, LDL-c and BMI were significantly higher in the IGT+IFG than the IGT group. Thus, it seems that the combination of IFG and IGT increases the prevalence of most CVD risk factors in this group in comparison to isolated IFG or IGT.

Undesirable levels of CVD risk factors were observed more frequently in those people who had both IFG and IGT than normal individuals. These findings are very similar to those of the Telde Study [23] and the National Health Survey of Singapore [7]. These claimed that CVD risk factors were similar in participants with IFG and those with IGT, but individuals with both IFG and IGT had a greater incidence of cardiovascular dysmetabolic syndrome and presented the most unfavorable cardiovascular risk profiles.

Considering the fact that direct comparisons between our findings and those of other studies are difficult because of differences in genetic background, environmental and cultural factors, and also different biochemical, clinical and applied research methods, the present results are in accordance with the Telde Study and others [9, 10, 23].

In our study, the BMI of the participants was much higher than for the Iranian general population [15]. However, these subjects were FDR of diabetic patients and it was expected that they would be heavier than normal general population.

Recently, in a population-based study (n = 4,025) in Tehran, subjects who were CVD-free at baseline were followed for 7.5 years. The risk of CVD was determined according to the status of glucose intolerance. They concluded that glucose intolerance (IFG or IGT) was associated with a 56% increased risk of CVD in women, but diabetes (both known or unknown) was considered a strong risk factor for the disease in both genders [15].

In the current study, the levels of HDL-c, HbA1c and systolic and diastolic blood pressure were not significantly higher in the IFG+IGT group compared to the control group (table 2). In the case of HDL-c and HbA1c, the p values showed trends towards significance. However, according to previous studies, there are controversies about the association of IFG or IGT with CVD, and it is still unclear whether the risk of CVD among patients with glucose intolerance is due to the status of IFG or IGT or to the conversion of these to diabetes during follow-up. Indeed, it seems that blood pressure would increase with a long duration of glucose intolerance [13, 15, 24].

However, the results of the present study are not similar to those of Blake et al. [25]. In this study, CVD risk factors were more prevalent in subjects with IFG or with IGT than in normal individuals, with differences more prominent for individuals with IFG than those with IGT. In this study, it was claimed that subjects with isolated IFG had similar levels of CVD risk factors as subjects with normal glucose metabolism, while the subjects with isolated IGT or IFG+IGT had a higher prevalence of CVD risk factors. They concluded that IGT was associated with increased levels of CVD risk factors, but IFG was not. Although the differences in CVD risk factors between the IFG and normal group did not reach statistical significance, waist circumferences, BMI and LDL-c levels tended to be higher in the IFG group than the normal group. In this study, with a follow-up period of 9 years, the incidence of CVD events was not significantly different between groups [25].

A Japanese cohort study [11] showed a significantly higher death rate due to CVD in subjects with IGT than in individuals with normal glucose metabolism, but the difference between IFG and subjects with normal fasting glucose was not significant. In that study, the survival rate of subjects with IFG and IGT was not directly compared, and they did not consider those subjects who had IFG+IGT. Moreover, the number of subjects with IFG and CVD-related deaths was low (3 deaths).

The Hoorn Study has shown that only individuals with IFG who had converted to diabetes had a high risk of CVD mortality, while, in participants who had not, the CVD mortality risk was similar to that of normal subjects [13]. In the DECODA study, it was concluded that unlike IGT, IFG was not an independent risk factor for CVD mortality [26].

It should be mentioned that the latter studies have focused on the CVD mortality rather than CVD risk factors [26, 27].

The DECODE study [27] pointed out that 2hPG is a better predictor of death than the FPG. In addition, a stronger effect on carotid intima media thickness has been shown for 2hPG than for FPG [12]. Therefore, it is expected that the CVD outcome of IFG and IGT groups must be different. However, both of them can be considered as predictors of CVD.

In the current study, the prevalence of IFG was 17.4% in FDR of type 2 diabetic patients, whereas in the general population it is just 0.5% [27]. The CVD risk factor profile of IFG and IGT groups was similar to that of the general population [28]. In turn, our results, which were not obtained in a community-based study and done on the FDR of type 2 diabetics, show a higher prevalence of CVD risk factors in subjects with IGT and/or IFG than in the control group. Hence, differences may have arisen from the differences in the populations studied.

One of the limitations of the current study is that we only studied people aged 25–55 years considering that CVD risk factors are more prevalent in this age group, whereas it would have been more accurate if we had included younger and older people. Especially in younger age groups, in whom the rate of CVD is increasing [29]. Another limitation is that we classified people according to the results of a single OGTT. Although, it is based on the latest definition of ADA, it is recommended to perform the test twice for more confidence.

With regard to the high prevalence of IFG in FDR of type 2 diabetic patients and higher prevalence of CVD risk factors in IFG and IGT subjects in comparison to those with normal glucose metabolism, detecting those with IFG and IGT is important to establish appropriate strategies to lower CVD risk.

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