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ORIGINAL ARTICLE

Comparison between Diabetes Incidence Using Different Cut Points of IFG in Tehran

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In 2003, the American diabetes Association (ADA) recommended that the definition of impaired fasting glucose (IFG) be changed from 110-125 to 100-125 mg/dL . This study examined the effect of different cut points for IFG on the incidence of diabetes in Tehran's urban population. Materials and Methods: From among the participants of the Tehran Lipid Glucose Study, after excluding subjects aged < 20 years, those with known or newly diagnosed type 2 diabetes, and those with missing values of weight, height, or other variables or lost to follow-up , data of 4728 subjects was used in this cohort study. They were followed for diabetes incidence (based on fasting plasma glucose (FPG) and glucose tolerance test) for 3.6 years. Participants were divided into different groups: Normoglycemia <100, original-IFG 110-125, added IFG 100-110 and the new IFG 100-125 mg/dL, groups. Odds ratios of diabetes incidence after adjustment for relevant confounders were calculated. Results: The median age of participants was 42.9±13.7y and 59.1% (n=2916) were female. The prevalence of original-IFG, added IFG and new IFG were 3.7% (n=183), 11.8 %(n=584), and 15.5% (n=767), respectively. After a mean follow-up duration of 3.6 years, 188 cases (3.8%) of incident diabetes were diagnosed. Diabetes incidence in the normoglycemia, original-IFG, added IFG and new IFG groups, were 1.8% (n=76), 26.2% (n=48), 11% (n=64), 14.6 %(n=112), respectively. Odds ratio for diabetes incidence after adjustment for age, sex and other relevant confounders for the original-IFG, added IFG and new IFG groups, compared to the normoglycemia group as the reference, were 11.45[95% confidence interval (CI), 7.45-17.57], 4.73 (95% CI, 3.28-6.8), 6.32 (95% CI, 4.51-8.5), respectively. Conclusion: The new IFG (100-125 mg/dL) is not superior to the original IFG (110-125 mg/dL) in terms of predicting forthcoming diabetes in Tehranian adults.

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Introduction

Originally introduced by American Diabetes Association (ADA) in 1997, impaired fasting glucose (IFG) is considered as intermediate plasma glucose concentrations that do not meet the diagnostic criteria of type 2 diabetes mellitus, and are yet too high to be considered as normal plasma glucose level. The original definition of IFG includes fasting plasma glucose (FPG) level ≥110 mg/dL and <126 mg/dL[1,2]. The main

rationale to define IFG was to create a fasting category analogous to impaired glucose tolerance (IGT). However, controversy still exists regarding IFG and IGT prevalence in diverse populations[3]. In 2003, ADA recommended that the threshold for IFG diagnosis should be lowered to 100 mg/dL[4] which was justified by the need to identify similar proportions of the populations with IFG and IGT, and to produce equivalent predictive power for progression to diabetes from both the IFG and IGT categories[5]. This recommendation was a result of some studies that used receiver operating characteristics (ROC) curve analysis in some high risk populations such as Pima Indians and concluded that FPG of approximately 100 mg/dL has the best sensitivity and specificity in predicting incidence of future diabetes [6].

However, it is still not accepted worldwide that the cutoff point of 100 mg/dL for FPG is appropriate to predict the risk of diabetes incidence and there are studies in different populations, comparing the predicting values of the original IFG (i.e. 110≤ FPG<126 mg/dL) and the new-IFG (i.e. 100≤FPG<126 mg/dL)[6-8]. In a 10-year follow-up study from England, conducted on 1040 non-diabetic adults, aged 40 years and older, the sex- and age- adjusted hazard ratio (HR) for incident diabetes was greatest in the IFG-original category, compared to the new IFG one. When adjusted for other confounding factors, the magnitude of associations persisted with HRs of 4.4 and 2.9 for the IFG-original and the new-IFG (100-125 mg/dL) categories respectively[9].

Given the aforementioned controversy in various studies and in diverse populations, in terms of predicting values of different definitions of IFG, and also assuming that, the association between IFG and incident diabetes can differ, depending on the metabolic syndrome prevalence in different populations[10,11], in the current epidemiological study, we aimed to compare the predicting power of original-IFG and new IFG in predicting type 2 diabetes in an urban population, with a mean follow-up 3.6 years.

Materials and Methods

Subjects and Design

The Tehran Lipid and Glucose Study (TLGS) is a large ongoing, population-based study, underway since 1999, to determine the prevalence and incidence of non-communicable diseases and the risk factors of atherosclerosis among Tehran's urban population and to develop population-based measures and lifestyle modifications to decrease the prevalence and prevent the rising trend of diabetes mellitus and dyslipidemia [12,13]. The design of this study includes two major components, a cross-sectional prevalence study of cardiovascular disease and associated risk factors and a prospective 20-year follow-up in several phases, at approximately 3.6-year intervals. A multi-stage stratified cluster random sampling technique was used to select 15005 people, aged 3 years and over, from urban district 13 of Tehran, the capital of the Iran; this district is located in the center of Tehran and the age distribution of its population is representative of the overall population of Tehran. During sampling, the list of all households under the coverage of the district's three healthcare centers (the official bodies responsible for vaccination programs and collection of health-related statistics in a district) was used. A random sample of households, stratified according to healthcare centers to achieve a distribution similar to the original population, was chosen, and from each household, all members above the age of three were recruited. The study began in December 1997 and the cross-sectional phase was completed in 2000; the first follow-up survey began in 2001 and was completed in 2004. After excluding subjects aged<20 years (n=4642), those with known or newly diagnosed type 2 diabetes (n=1164), and those with missed values of weight, height, or other variables (n=349), or those lost to follow-up

(n=4122), data of 4728 subjects with a complete 3.6-year follow-up was used in this cohort study. This population was divided into 4 groups; normoglycemic (<100 mg/dL), original IFG (110-125 mg/dL), added IFG (100-110 mg/dL) and the new IFG (100-125 mg/dL).New cases of diabetes were defined as OGTT≥200 mg/dL or FBS ≥126 mg/dL and individuals who developed diabetes during the follow up. In comparison to those who completed the follow-up, individuals lost to follow-up had lower values of baseline systolic blood pressure (119 vs. 117 mm-Hg), BMI (26.9 vs. 26.2 Kg/m2), waist circumference (88.2 vs. 86.5 cm), triglycerides (1.88 vs. 1.78 mmol/L), fasting plasma glucose (89.12 vs. 93.17 mg/dL) and 2-h postchallenge plasma glucose (106.13 vs. 104.12 mg/dL).

At the beginning of the cross-sectional phase, all participants provided written informed consent for the study, which was approved by the institutional ethics committee (Research Institute for Endocrine Sciences) and was conducted in accordance with the principles of the Declaration of Helsinki. Thereafter, collection of demographic data and anthropometric examinations were undertaken by trained general physicians. Weight and height were measured with subjects wearing normal indoor clothing, but no shoes. Weight was recorded using a Seca 707 weighing machine (range: 0.1–150 kg) with an accuracy of up to 100 gr. The machine was regularly checked for precision after every 10 measurements. Height was measured without shoes using a tape stadiometer with a minimum measurement of 1mm. The waist circumference was measured. Body mass index (BMI) was calculated by dividing weight (in kilograms) by height squared (in meters). To measure systolic blood pressure (SBP) and diastolic blood pressure (DBP), participants were initially made to rest for 15 min; then a qualified physician measured blood pressure twice in a seated position using a standard mercury sphygmomanometer on the right arm; the mean of the two measurements was considered as the participant's blood pressure. Fasting Plasma Glucose (FPG), 2-hour post-challenge plasma glucose (2h-PG) and serum lipids were measured at the TLGS research laboratory on the day of blood collection. Details of the biochemical measurements are published elsewhere.

Statistical Methods

Data are presented as means ± SD for continuous data and percentages for categorical data. Statistical analyses used the ANOVA and Turkey's post hoc test for comparing continuous variables and the Chi-square test for comparing categorical variables among groups. To examine incident diabetes among different fasting glucose groups, logistic regression model with diabetes incidence as the dependent variable was developed. There was no interaction between age, gender, triglycerides (TG), HDL, weight, height, waist circumference, blood pressure and family history of diabetes. Thus age, gender, TG, HDL, weight, height, waist circumference, blood pressure and family history of diabetes were entered into the model as independent variables. P values <0.05were considered statistically significant. All statistical analyses were performed using SPSS version 13 software.

Results

Table 1 shows the general characteristics and metabolic profiles of the study participants in the three groups of fasting glucose. Of the participants, 59.1% subjects were female (n=2916). The mean age of participants was 42.9±13.7 years. The prevalence of original IFG and new IFG were 3.7% and 15.5%, respectively. Serum cholesterol level, LDL, HDL, BMI, systolic and diastolic BP differed significantly between the groups. BMI, TG and waist circumference were significantly higher in the original IFG group than in the added IFG group (Table1).

Table 1. Comparison of CVD risk factors between normoglycemic, added-IFG and new-IFG groups at the beginning of the study

	Normoglycemia*(A)	Added-IFG† (B)	Original-IFG‡ (C)	P-value		
				B vs. A	C vs. A	C vs. B
n (%)	4175(84.5%)	584(11.8%)	183(3.7%)	-	-	-
Cholestrol (mg/dL)	208±44	222± 46	277±49	0.0001	0.0001	0.27
TG (mg/dL)	160±49	191±110	225±180	0.0001	0.0001	0.0001
HDL (mg/dL)	42±11	41±10	40±10	0.021	0.043	0.731
LDL (mg/dL)	133±37	142±38	143±41	0.0001	0.001	0.92
BMI (kg/m2)	27±4	28±4	29±4	0.0001	0.0001	0.04
Systolic Blood Pressure (mmHg)	117±17	126±19	128±21	0.0001	0.0001	0.27
Diastolic BP(mmHg)	77±10	80±10	81±10	0.0001	0.0001	0.57
Waist circumference (cm)	87±11	93±11	95±11	0.0001	0.0001	0.032
Family history of diabetes (%)	25	28.1	43.2	0.104	0.0001	0.0001
Current smoker (%) §	18.5	20.7	18.5	0.26	0.26	0.26

*normoglycemia: FBS<100mg/dL; †addedIFG: 100<FBS<110mg/dL; ‡original-IFG: 110<FBS<125mg/dL; §individuals who are smoking right now or had smoked before

During the 3.6-year follow-up period, 188 participants developed diabetes, of whom 182 participants had FPG ≥126 mg/dL and/or 2h-PG ≥200 mg/dL; six more cases were diagnosed as diabetic by other physicians and underwent treatment.

After adjustment for age, sex, family history of diabetes, systolic BP, waist circumference, TG, HDL and BMI, the odds ratios (OR) for original IFG, added IFG, and new IFG were 11.45 (95% CI, 7.45-17.57), 4.73(95% CI, 3.28-6.81), 6.32(95% CI, 4.51-8.51), respectively, with FPG of 100 mg/dL as the reference category (Table 2).

Table 2. Diabetes incidence risk after a 3.6-year follow-up in the normoglycemic, added-IFG, original-IFG and new-IFG categories/groups

	At the beginning	New cases of diabetes After 3.6 years follow-up n (%)	Odds ratio (CI=95%)-model 1*	Odds ratio (CI=95%) Model 2†
Number of cases	4942	188 (3.8)	-	-
Normoglycemia	4175	76 (1.8)	1	1
Original-IFG	183	48 (26.2)	17.1 (11.4-25.8)	11.4 (7.4-17.6)
Added-IFG	584	64 (11)	6.0 (4.3-8.6)	4.7 (3.3-6.8)
New-IFG	767	112 (14.6)	8.4 (6.0-11.2)	6.3 (4.5-8.5)

*model 1: After age/sex adjustment; model 2: after adjustment for age, sex, BMI, waist circumference, familial history, TG, HDL-C, systolic BP; ‡All p values were <0.05

Considering FPG of 110 mg/dL as the reference category, after adjustment for sex and age, the odds ratio was 10 by original-IFG and after further adjustment, it decreased to 6.86. Sensitivity and specificity of original-IFG for prediction of diabetes were 23% and 97%, respectively, and were 59% and 86% for new-IFG, respectively.

Discussion

Our study findings show that the original-IFG has enhanced ability to predict diabetes incidence compared to the new-IFG (OR: 11.45 vs. 6.32). Assuming FPG <110 mg/dL as the cutoff and the reference point for original IFG, our findings showed no preference for new-IFG application compared to the original-IFG (OR; 6.32 vs. 6.86).

The ADA recommendation for changing the diagnostic criteria of IFG was justified by the desire to identify similar proportions of the population with IFG and IGT and to produce an equivalent predictive power for progression to diabetes from IGT and IFG. This recommendation was based on some studies using the ROC analysis method, where plasma glucose of 100 mg/dL was found to be the best diagnostic criteria of IFG[5]. But it seems that these findings do not justify decreasing the diagnostic criteria of IFG.

In the present study, we used a different analysis method to compare different predictive power of IFG thresholds. We compared odds ratios between new-IFG and original-IFG after adjusting for confounding factors by logistic regression model. Our findings confirm results of previous studies which used the same analytic methods. Differences between these studies were follow-up durations, ages and adjustment of confounding factors. In the Ely cohort study from England, after a ten year follow up of 1040 non-diabetic adults>40y, the sex/age adjusted risk (Hazard Ratio) for incident diabetes was greatest in the IFG-original category. When adjusted for confounding factors, the magnitude and directions of associations persisted with HR 4.4 for original IFG with FPG of 100 mg/dL as reference and 2.9 for the categories of new-IFG(14); methods of this study were similar to ours; However Ely study had an older population (40-79y) than our study and, in addition, in the their study, physical activity was adjusted as a confounding factor, whereas it was not considered in our study; in our study population, the mean BMI was considerably higher theirs. In the Finish Monica study of 2592 adults, aged ≥ 45 years, after 10 years follow-up, the relative risk for diabetes incidence was 1.9, being 6.4 for added-IFG and original-IFG, respectively; in their study, gender distribution and BMI were similar to ours, but some confounding factors like blood pressure, TG and familiar history were not considered.[10]

Some other studies concluded that lowering the cutoff point for IFG optimizes its ability to predict diabetes in certain/definite populations.[15-18] Most studies have compared added-IFG with original-IFG whereas we compared new-IFG with original-IFG [5;19;20]. In addition to considering an FBG of 100 mg/dL, we also considered an FBG of 110 mg/dL as the reference category for estimating odds ratios.[5]

Another rationale behind lowering the IFG threshold was to improve sensitivity and specificity of IFG in predicting diabetes incidence; this was based on some studies using ROC analysis methods that found best sensitivity and specificity with an FPG of 100 mg/dL [5]. In the current study, sensitivity and specificity of original-IFG were 23% and 97%, respectively, as compared to sensitivity of 59% and specificity of 86% for new-IFG, similar to the results reported by some other studies [10,21,22]. In a study, Qia et al calculated sensitivity of 21% and specificity of 95% for original-IFG in predicting diabetes incidence and the sensitivity and specificity for new-IFG were 51% and 77% , respectively [10]. Therefore, sensitivity increases at cost of specificity and with the new criteria, a lot of individuals currently not diabetic, will in the future, be labeled as the "prediabetes group", although they may never become diabetic. This measure that will affect the psychological and economical aspects of societies.

Why does the specificity decrease when lowering the IFG threshold? We speculate that in contrast to increase of IGT percentage by new IFG, and the coincidence of IGT and IFG will diminish (not mentioned in the article) and because of association between IGT and CHD (coronary heart disease) risk

and diabetes incidence risk, it can be predicted that a wide spectrum of the new-IFG population will not be affected by diabetes in the future. This has been considered in some studies [5,23]; for instance, in the Inter 99 study, 60% of cases with IGT were diagnosed with new criteria of IFG, and although sensitivity improved two-fold, the proportion of the IFG group, who also had IGT, decreased from 28% to 19% [5].

Some limitations in our study merit consideration. First, the short duration of follow-up, second, we did not adjust some confounding factors like physical activity and finally the dropping out of some subjects from the study. However this population-based study, the first cohort study in Iran to predict the incidence of diabetes, can be helpful in defining the correct FPG range.

In conclusion, the results of our survey in a large population-based cohort study in the Middle East region show that the new-IFG definition is not superior to the original-IFG in terms of predicting incident diabetes. To understand the efficacy of plasma glucose lowering measures and earlier diagnosis of IFG, it would be better to design a study to treat individuals considered as IFG and follow them up to observe diabetes and CHD incidences, to enhance decision making in the future.

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