Title

~~Should t~~The threshold for definition of impaired fasting glucose ~~be lowered~~should be preserved~~?~~

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Running title
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Abstract

Aims

We examined whether the cut-off value of fasting plasma glucose (FPG) for diagnosing impaired fasting glucose (IFG) should be lowered or not, using data from a large Japanese population.

Methods

A retrospective cohort study was conducted from 1998 to 2006. Follow-up (2002-2006) data were merged with baseline (1998-2002) data, yielding 11,129 persons who had been evaluated during both time periods. Among these, 10,475 persons who had neither diabetes (known diabetes or defined as FPG >=7.0~~0~~ mmol/l) or suspected diabetes (hemoglobin A1c >=6.4%) were analyzed.

Results

During follow-up of an average of 5.4 years, 279 (5.2%) out of 5,372 men and 98 (1.9 %) out of 5,103 women developed diabetes. According to the three baseline FPG categories (<5.~~5~~6, 5.~~5~~6-6.1~~06~~, and 6.1~~1~~-6.9~~4~~ mmol/l), 28/3,401 (0.8%), 91/1,456(6.3%) and 160/515 (31.1%) respectively in men and 13/4,218 (0.3%), 30/695(4.3%) and 55/177 (31.1%) respectively in women developed diabetes. The optimal cut-off FPG value to predict diabetes was 5.7~~2~~ mmol/l both for men (sensitivity;84.2%, specificity; 76.9%) and women (81.6%, 91.0%). However, lowering the cut-off from 6.11 to 5.7~~2~~ mmol/l increased the prevalence of IFG 2.7 fold in men and 3.0 fold in women. Lowering the value further to 5.6~~56~~ mmol/l increased the prevalence of IFG 3.8 fold in men and 4.9 fold in women.

Conclusions

It may be reasonable to retain the conventional lower FPG limit for IFG and treat FPG values of 5.6~~56~~-6.1~~06~~ mmol/l as non-diabetic hyperglycemia, considering the four to five fold increase in individuals classified as IFG when the new cut-off is applied.

Keywords

Epidemiology, Type-2 diabetes, Diagnosis

Introduction

The lower limit of impaired fasting glucose (IFG) was lowered from 6.11 mmol/l to 5.56 mmol/l by the American Diabetes Association (ADA) in 2003[1], whereas the European Diabetes Epidemiology Group (EDEG) recommended retaining the original cut-off point (6.11 mmol/l) in 2006[2]. Recently in 2008, the Japan Diabetes Association (JDA) declared that fasting plasma glucose (FPG) values between 5.656 and 6.106 mmol/l should be considered as 'high-normal' but stating the range for IFG to be unchanged [3]. We examine the optimal cut-off point of FPG for predicting diabetes in a Japanese population and discuss whether the conventional IFG criteria should be lowered.

Participants and Methods

The data set was obtained from the health screening program performed by the Yuport Medical Checkup Center in Tokyo, whose details were described previously[4]. As the previous study, we set a 4-year baseline period between April 1998 and March 2002 and the 4-year follow-up period between April 2002 and March 2006. During the baseline period, 21,885 persons underwent checkups at least once. If subjects underwent more than one checkup, the initial checkup data were used. During the follow-up period, 23,547 persons underwent checkups. If subjects underwent more than one checkup during the follow-up period, all the data were used to identify incident diabetes. Follow-up data were merged with baseline data, yielding 11,129 persons evaluated during both time periods.

Among them, 129 with known diabetes at baseline were excluded, leaving 11,000 persons. Of these, 411 who had baseline FPG levels >= 7.00 mmol/l were further excluded. Then 114 who had baseline hemoglobin A1c levels greater than 6.4 percent were excluded, since a hemoglobin A1c level of 6.4% corresponds to a FPG level of diagnosed diabetes (7.00 mmol/l) [5]. Thus the remaining 10,475 persons were analyzed as study subjects and comprised 5,372 men (age, 51.8±12.0 years; BMI, 23.5±2.8) and 5,103 women (age, 54.0±11.2 years; BMI, 22.3±3.0). Informed consent for anonymous participation in epidemiological research was obtained at every checkup [4]. All the blood samples were obtained after overnight fasting and measured at the Center's laboratory. Plasma glucose levels were measured using the hexokinase-G6PD method.

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All the checkup procedures were performed in the same manner, both during the baseline and follow-up periods, including blood measurements. In follow-up evaluations, diabetes was defined as a follow-up FPG level >=7.~~0~~0 mmol/l, in accordance with the ADA, JDA criteria [6, 7] or as a diagnosis of diabetes by a physician during the follow-up period. We used the receiver operating characteristic (ROC) curve to define the 'epidemiologically' optimal~~um~~ cut-off level of FPG to predict the progression to diabetes the best balance between sensitivity and specificity.~~.~~ We calculated the positive and negative predictabilities between two cut-off values of baseline FPG levels (ADA, WHO and EDEG criteria) and diabetes at follow-up. Men and women were analyzed separately, since the prevalence of IFG was higher in men than in women in the previous study[4]. All analyses were performed using the SPSS15.0 and MEDCALC 10.0 for Windows. Informed consent for anonymous participation in epidemiological research was obtained at every checkup.

Results

The 10,475 subjects (5,372 men and 5,103 women; age, 52.9±11.6 years; BMI, 22.9±3.0) were followed up for an average of 5.4 years (range, 0.5- 8.0years). During follow-up, 279 men (5.2%) and 98 women (1.9 %) developed diabetes. When baseline FPG were classified into three categories using the IFG cut-off values employed by ADA and EDEG criteria(<5.6, 5.6-6.1, and 6.1-6.9 mmol/ ~~(<5.56, 5.56-6.06, and 6.11-6.94 mmol/~~l), 28/3,401 (0.8%), 91/1,456(6.3%) and 160/515 (31.1%) men and 13/4,218 (0.3%), 30/695(4.3%) and 55/177 (31.1%) women developed diabetes, respectively. Namely, there was 5 and 7 fold difference in relative risk of diabetes incidence between the original (6.1-6.9 mmol/l) IFG and the IFG newly added by the ADA (5.6-6.1 mmol/l) in men and women, rspectively.

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Figure 1 shows ROC curves for predicting diabetes which plot the sensitivity versus 1-specificity for the baseline FPG levels in men and women. The area under the ROC curve corresponding to the FPG and used to diagnose diabetes was 0.877 (95% confidence interval, 0.868–0.885) for men and 0.920 (0.912–0.927) for women. The optimal cut-off value of FPG used to predict diabetes was 5.72 mmol/l both for men (sensitivity 84.2% [95% confidence interval 79.4 - 88.3] and specificity 76.9% [75.7 - 78.1]), and for women (sensitivity 81.6% [72.5 - 88.7]; specificity 91.0% [90.2 - 91.8]).

Table 1 shows the performance of various cut-off points obtained using ROC curves analysis for predicting diabetes. Applying a FPG value of 5.~~5~~6 mmol/l to the study participants as the IFG cut-off value (according to ADA criteria), included 90% of male and female subjects who went on to develop diabetes. Compared with the conventional IFG parameters (FPG of 6.1~~1~~-6.9~~4~~ mmol/l), including subjects with FPG 5.~~5~~6-6.1~~06~~ mmol/l increased the prevalence of IFG by 3.8 times (36.7% versus 9.6 %) in men and 4.9 times (17.1% versus 3.5%) in women. The positive likelihood of progressing to diabetes in subjects with IFG values that meet this criteria (5.~~5~~6-6.9~~4~~ mmol/l) were lower than in those with FPG value of 5.7~~2~~(the optimum cut-off in this study) -6.9~~4~~ mmol/l and 6.1~~1~~-6.9~~4~~ mmol/l (conventional criteria).

Next, using a FPG value of 5.7~~2~~ mmol/l as the lower limit of IFG provided reasonable sensitivity and specificity as a screening test for progression to diabetes than the cut-off FPG value of 5.~~5~~6 or 6.11 mmol/l. Compared with the conventional IFG, however, this definition of IFG (5.7~~2~~-6.9~~4~~ mmol/l) increased the prevalence of IFG by 2.7 times (26.2% versus 9.6 %) in men and 3.0 times (10.4% versus 3.5%) in women.

Then, using a FPG value of 6.~~1~~1 mmol/l as the cut-off, IFG included less than 60% of male and female subjects who developed diabetes, whereas a FPG >6.~~1~~1 mmol/l highly excluded those with false positive results due to its superior specificity. The positive likelihood of progressing to diabetes in subjects with this criteria of IFG (6.~~1~~1-6.9~~4~~ mmol/l) were, higher than in those with the other two FPG cut-offs.

Discussion

Since FPG is a continuous variable, defining IFG with a certain cut-off is always a matter of trade-off between sensitivity and specificity. In this study, a FPG value of – 5.7~~2~~ mmol/l was the 'epidemiologically' optimal point to distinguish individuals who will develop diabetes after 5.4 years of mean follow-up. This cut-off value is identical to that obtained in a Dutch population, and the top one among those of the four population (5.2~~2~~-5.7~~2~~ mmol/l) reported by the ADA [1]. Thus, FPG >=5.~~5~~6 mmol/l suggested by ADA, may be acceptable as the 'epidemiological' cut-off for the prediction of diabetes.

On the other hand, this study also questioned the utility of the new range of FPG (5.~~5~~6-6.9~~4~~ mmol/l) for IFG suggested by the ADA, considering the undue burden it possibly imposes on the population from the public health viewpoint. First, including

FPG values of 5.~~5~~6-6.1~~06~~ mmol/l in the IFG category creates a remarkably higher prevalence of IFG (three to four fold-increase) as concerned by EDEG [2] and JDA [3]. Furthermore, it is important to reconsider the benefit and disadvantage of labeling more individuals with IFG since there is no current evidence of the primary prevention of diabetes or CVD among those with IFG [2]. Second, there was 5-7 fold difference in relative risk of diabetes incidence between the original ~~(6.11-6.94 mmol/l)~~ IFG and the IFG newly added by the ADA ~~(5.56-6.06 mmol/l) both in men and women~~. This finding agrees with that of Hunagata study Considering these differences, it may not be legitimate to lower the cut-off of IFG without careful consideration of its potential impact on populations. In our view, it is reasonable to preserve the original definition of IFG, and treat FPG of 5.~~5~~6-6.1~~06~~ mmol/l as non-diabetic hyperglycemia[2] or higher normoglycemia[3] just as EDEG and JDA suggested to avoid the pandemic of IFG causing a atrong burden on public health care resources and costs. When a next step is needed, a glucose tolerance test should be recommended to determine the presence of impaired fasting glucose.

The limitations of this study are as follows. First, since the study subjects participated on a voluntary basis, they may be healthier than the general population. Accordingly, a caution may be needed to apply this study result to the general population. Second, there were subjects who rapidly progressed to diabetes during the baseline period, who therefore were not eligible to participate during the follow-up period, which may cause an underestimation of the incidence of diabetes. Third, for follow-up evaluations, we used a single FPG level, even though the diagnosis of diabetes requires two sequential measurements of FPG or a 2-hour glucose tolerance test. Although it is considered acceptable to be based upon a single fasting glucose measurement for epidemiological estimates of diabetes prevalence and incidence[6], it is possible that some cases defined as diabetes had, by chance, FPG levels higher than the defined cut off.

About half of the study's participants who underwent at least one check-up during the baseline period (N=21,885) did not return for a check-up during the follow-up period (N=11,129). Thus, a sampling bias, potentially generated from this loss of follow-up, can evolve and need to be addressed. In the previous study[4], we compared the 10,475 subjects (exactly identical to this study subjects) with the remaining 9,949 persons who did not attend during the follow-up period, using the same exclusion criteria used by the previous study. Those who participated during the follow-up period were older (mean (SD): 52.9 (11.6) vs. 51.8 (13.5), P<0.001), not obese by BMI

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(22.9 (3.0) vs. 22.8 (3.1), P=0.10), had slightly lower fasting blood glucose levels (5.27 (0.50) vs. 5.28 (0.52) mmol/l, P<0.001) and had slightly higher HbA1c levels (4.97 (0.40) vs. 4.95 (0.41) percent, P<0.001) than non-study subjects[4].

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Further research should investigate unanswered questions for non-diabetic hyperglycemia including IFG. Risk evaluation according to continuous glucose levels in various populations should be performed for diabetes and cardiovascular disease. It is noteworthy that a recent study showed that only the original IFG definition yielded greater risks of CVD in women (OR 2.1, 95% CI 1.2 to 3.6)[8], but not in men. Of more importance is whether diabetes could be prevented or at least delayed with pharmacological and life-style interventions in individuals who have non-diabetic hyperglycemia, like impaired fasting glucose.

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Declaration of Competing Interests: Nothing to declare.

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Figure 1 The ROC curve for fasting plasma glucose predicting the progression to diabetes in 5,372 men and 5,103 women

Figure legend
The round mark indicates a point of the highest accuracy.

Table 1. Sensitivity, Specificity and Predictabilities of Diabetes at Each Cut-off Level of Baseline Fasting Plasma Glucose (FPG)

Men (N=5,372)						
Cut-off level of FPG(mmol/l)	Defined as impaired fasting glucose	Progressed to diabetes, %	Incidence densities, n/1000 person-years	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive likelihood ratio, % (95% CI)
5.6~~56~~	1971	251(12.7)	23.2	90.0(85.8 - 93.2)	66.2(64.9 - 67.5)	2.7(2.5 - 2.8)
5.7~~2~~(Optimum)*	1410	235(16.7)	30.3	84.2(79.4 - 88.3)	76.9(75.7 - 78.1)	3.7(3.5 - 3.8)
6.1~~1~~	515	160(31.1)	56.9	57.4(51.3 - 63.2)	93.0(92.3 - 93.7)	8.2(7.4 - 9.1)
Women (N=5,103)						
Cut-off level of FPG(mg/dl)	Defined as impaired fasting glucose	Progressed to diabetes, %	Incidence densities, n/1000 person-years	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive likelihood ratio, % (95% CI)
5.~~5~~6	872	85(9.7)	18.2	86.7(78.4 - 92.7)	84.3(83.2 - 85.3)	5.5(5.1 - 6.0)
5.7~~2~~(Optimum)	531	80(15.1)	28.9	81.6(72.5 - 88.7)	91.0(90.2 - 91.8)	9.0(8.2 - 10.0)
6.1~~1~~	177	55(31.1)	58.4	56.1(45.7 - 66.1)	97.6(97.1 - 98.0)	23.0(19.3 - 27.4)

During follow-up, 279 men and 98 women developed to diabetes.

*Optimal cut-off levels of FPG to predict diabetes, defined using ROC curves.