ORIGINAL ARTICLE

Meaning of upper limit of normal range of post-load 1-h plasma glucose level defined by oral glucose tolerance test in Japanese subjects

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ABSTRACT

Aims/Introduction: To identify upper limit post-load 1-h plasma glucose (1-h PG) after 75-g oral glucose test in a Japanese population.

Materials and Methods: A total of 918 subjects were enrolled. We divided the subjects into two groups: normal 2-h post-load plasma glucose (2-h PG; <140 mg/dL) and impaired 2-h PG group (≥140 mg/dL).

Results: A total of 417 subjects had normal 2-h PG and 501 had impaired 2-h PG. The receiver operating characteristic (ROC) curve showed that the optimal cut-off value of 1-h PG was 179 mg/dL (area under ROC curve = 0.89), providing that the sensitivity, specificity, and positive and negative predictive value were 85, 79, 82 and 83%, respectively. The subjects with 1-h PG < 179 mg/dL consisted of 0.5% diabetes and 99.5% non-diabetes, whereas those with 1-h PG ≥ 179 mg/dL consisted of 26.9% diabetes and 73.1% non-diabetes ($P < 0.01$). Furthermore, there was a significant correlation between 1-h PG and 2-h PG ($r^2 = 0.57$, $P < 0.01$).

Conclusions: These data suggested that 179 mg/dL is the upper limit of the normal range of post-load of 1-h PG in a Japanese population. Thus, the subjects with 1-h PG ≥ 179 mg/dL might be at risk of developing future diabetes. Therefore, appropriate prospective study should be carried out to test this hypothesis. (J Diabetes Invest, doi: 10.1111/jdi.12060, 2013)

INTRODUCTION

The 75-g oral glucose test (OGTT) has become the standard method for diagnosis of different stages of glucose tolerance. According to American Diabetes Association (ADA) criteria[1], post-load 2-h plasma glucose (2-h PG) ranging from 140 to 199 mg/dL is defined as impaired glucose tolerance (IGT) and a value ≥200 mg/dL is defined as diabetes. Although IGT patients have an increased risk of type 2 diabetes, only less than 50% develop type 2 diabetes within 10 years of follow up[2], suggesting that the future risk of diabetes is varied among patients with IGT.

Several models have been proposed to improve the prediction of future diabetes[3–6]. However, these models are based on established risk factors for type 2 diabetes. In contrast, recent studies carried out in USA have showed that post-load 1-h plasma glucose (1-h PG) level is a better prediction for future type 2 diabetes than fasting plasma glucose (FPG) level[7,8]. In this situation, 155 mg/dL of 1-h PG is the best cut-off value.

In Japan, no published information is available regarding the upper limit of 1-h PG. Thus, the aim of the present study was to define the upper limit of 1-h PG level. For this purpose, we compared subjects with normal 2-h PG and those with impaired 2-h PG in a large number of Japanese subjects who received 75-g OGTT.

METHODS

Construction of Database

From September 1998, we started to construct a hospital-based database concerning 75-g OGTT. The database consisted of date of investigation, age, sex, height, weight, biochemical data, glycated hemoglobin (HbA$_{1c}$), and fasting and post-load plasma glucose and immunoreactive insulin. 75-g OGTT was carried out if the presence of diabetes was suggested (e.g., FPG ranging from 100 to 125 mg/dL, the presence of family history of diabetes, secondary examination for suspicion of diabetes by a medical check-up and/or obesity). Up to July 2012, we carried out 75-g GTT in a total of 962 participants.

Participants and Assignment

According to the criteria of the ADA[1], we divided the participants into two groups: post-load normal glycemic group and post-load hyperglycemic group. The former group had 2-h PG < 140 mg/dL and the later group had 2-h PG ≥ 140 mg/dL.

Inclusion criteria were: (i) no antidiabetic drug or insulin administration; (ii) Japanese. A total of 962 participants satisfied these criteria. From September 1998 to July 2012, participants

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underwent 75 g-OGTT. However, 44 participants with FPG > 150 mg/dL were excluded, because they all showed diabetic pattern; that is, 2-h PG ≥ 200 mg/dL.

Thus, a total of 918 participants (96.0%) were finally enrolled. In the present study, the diagnosis of diabetes was based on both the data of 75-g OGTT (i.e., either FPG ≥ 126 mg/dL or 2-h PG ≥ 200 mg/dL) and the value of HbA_{1c} ≥ 6.5%[1]. Before the 75-g OGTT was carried out, informed consent was obtained from each individual. The present study was carried out in accordance with local institutional review board approval and carried out in accordance with the Declaration of Helsinki.

Measurements and Calculations

A 75-g OGTT was carried out after a 12-h overnight fast. Participants ingested carbohydrate equivalent to 75 g of glucose (Torelan-G, Ajinomoto Pharmaceuticals., Tokyo, Japan), and blood samples were taken at 0, 30, 60 and 120 min. Plasma glucose was measured with an automatic analyzer by the glucose oxidase method.

HbA_{1c} was measured, using high-performance liquid chromatography according to an assay certified by the Japan Diabetes Society. In the present study, we converted HbA_{1c} to the National Glycohemoglobin Standardization Program equivalent value (%) calculated by the formula HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society; %) + 0.4%[9]. The intra-assay coefficient of variation was 0.4% for plasma glucose and 0.5% for HbA_{1c} in 20 samples, respectively.

Body mass index (BMI) was calculated as weight (kg) divided by the square of height in meters (m^2).

Statistical Analysis

The data were expressed as mean ± standard deviation. For univariate analyses, we used t-test for continuous variables, and χ^2-test and Fisher's exact test for the proportion of discrete variables between the two groups. The receiver operating characteristic (ROC) curve was used to assess the optimal cut-off value for 1-h PG. Additionally, the sensitivity, specificity, and positive and negative predictive value were calculated. Simple Pearson's correlation was used to assess the relationship between 1-h PG and 2-h PG. All P-values were two-tailed, and P-values <0.05 were considered statistically significant. Statistical analyses were carried out using Excel 2010 statistical software package (version 1.13, Tokyo, Japan).

RESULTS

Characteristic of the Participants

A total of 918 participants consisted of 360 participants with normal glucose tolerance (NGT), 317 participants with IGT and 241 participants with a diabetic pattern based on 75-g OGTT. There were 434 participants with post-load normal glycemia and 484 participants in the post-load hyperglycemic group. The mean fasting plasma glucose was 98 ± 16 mg/dL. The mean HbA_{1c} was 6.0 ± 0.7%.

When the data of 75-g OGTT and value of HbA_{1c} was considered together, there were 781 non-diabetic participants and 137 diabetic participants.

ROC Curve Analysis

Table 1 shows the sensitivity, specificity, and positive and negative predictive value at a 10-mg/dL interval of 1-h plasma glucose ranging from 160 to 200 mg/dL. The level of 179 mg/dL was the highest sum of sensitivity and specificity. When the level of this cut-off value was used, the sensitivity, specificity,

Table 1 | Sensitivity, specificity, and positive and negative predictive values at a 10-mg/dL interval of 1-h plasma glucose ranging from 160 to 200 mg/dL

1-h Plasma glucose	Predictive value			
Cut-off value (mg/dL)	Sensitivity (%)	Specificity (%)	Positive (%)	Negative (%)
160	92.1	63.6	73.8	87.9
170	88.4	69.8	76.6	84.4
179	**84.9**	**79.3**	**82.0**	**82.5**
180	84.1	79.7	82.2	81.8
190	76.9	84.3	84.6	76.6
200	71.1	88.7	87.5	73.3

179 mg/dL was specially noted, because this cut-off point was the highest sum of sensitivity and specificity.
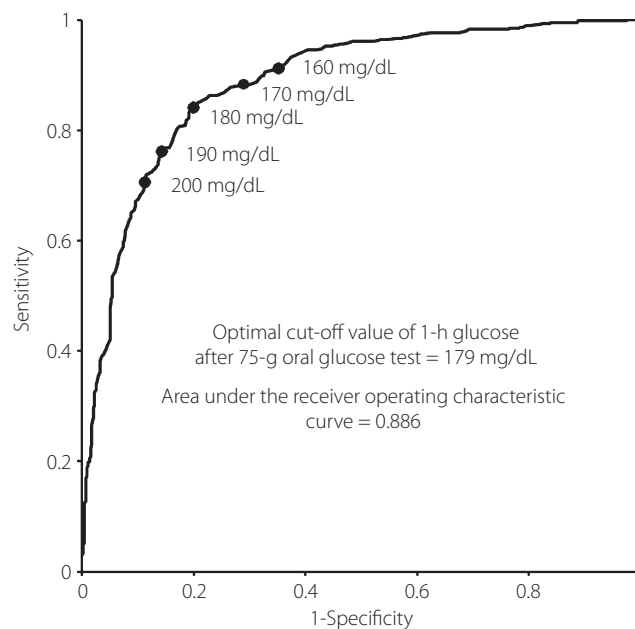

Figure 1 | The receiver operating characteristic curve of post-load 1-h plasma glucose is graphically shown. Markers at a 10-mg/dL interval of 1-h plasma glucose ranging from 160 to 200 mg/dL are also shown. The optimal cut-off value of post-load 1-h plasma glucose was 179 mg/dL (see Table 1). In this situation, the area under the receiver operating characteristic curve was 0.89.

and positive and negative predictive were 85, 79, 82 and 83%, respectively.

Figure 1 shows the ROC curve representing the sensitivity and specificity at a 10-mg/dL interval of 1-hplasma glucose ranging from 160 to 200 mg/dL. The optimal cut-off value of 1-h PG was 179 mg/dL, providing that area under the ROC curve was 0.89.

Clinical Characteristics Between Participants with 1-h PG < 179 mg/dL and Those With 1-h PG ≥ 179 mg/dL

Although no significant difference was observed in sex, participants with 1-h PG ≥ 179 mg/dL were older than those with 1-h PG < 179 mg/dL. The BMI was similar in the two groups. The mean HbA_{1c} was significantly higher in participants with 1-h PG ≥ 179 mg/dL than in those with 1-h PG < 179 mg/dL (Table 2).

On the basis of 75 g-OGTT, deterioration of glucose tolerance was significantly different in the participants with 1-h PG < 179 mg/dL to those with 1-h PG ≥ 179 mg/dL. For example, diabetic pattern was only seen in 1% in the participants with 1-h PG < 179 mg/day, whereas it was observed in 47% of those with 1-h PG ≥ 179 mg/dL. When the data of 75-g OGTT and value of HbA_{1c} were considered together, the incidence of diabetes was significantly higher in participants with 1-h PG ≥ 179 mg/dL than in those with 1-h PG < 179 mg/dL (27% vs 1%, $P < 0.01$; Table 2).

Correlation Between 1-h PG and 2-h PG

As shown in Figure 2, a significant correlation was noted between 1-h PG and 2-h PG ($r^2 = 0.57$, $P < 0.01$).

Table 2 | Clinical characteristics of participants with post-load 1-h plasma glucose <179 mg/dL (n = 417) and participants with post-load 1-h plasma glucose ≥179 mg/dL (n = 501)

	Post-load 1-h glucose <179 mg/dL	Post-load 1-h glucose ≥179 mg/dL	P-value
Age (years)	57.3 ± 18.0	60.7 ± 12.8	<0.01
Male (%)	55.6	60.7	0.12
Body mass index	22.9 ± 4.2	23.7 ± 3.9	<0.01
75-g Oral glucose tolerance test			
Normal glucose tolerance (%)	307 (73.6)	53 (10.6)	<0.01
Impaired glucose tolerance (%)	106 (25.4)	211 (42.1)	
Diabetic pattern (%)	4 (1.0)	237 (47.3)	
HbA_{1c} (%)	5.6 ± 0.5	6.3 ± 0.8	<0.01
Diabetes*			
Yes (%)	2 (0.5)	135 (26.9)	<0.01
No (%)	415 (99.5)	366 (73.1)	

*Diagnosis of diabetes was based on both the 75-g oral glucose tolerance test and the value of glycated hemoglobin (HbA_{1c}).
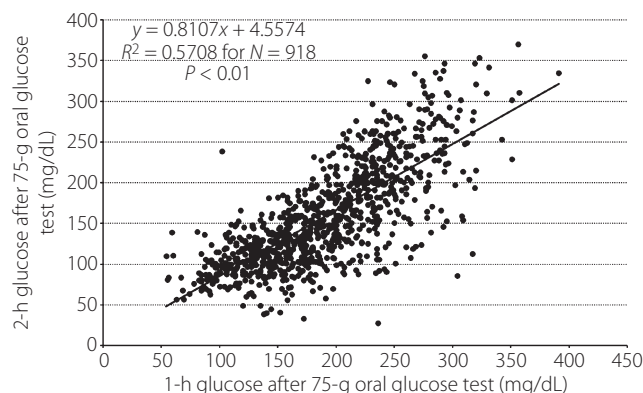

Figure 2 | The correlation between post-load 1-h plasma glucose and 2-h plasma glucose after 75-g oral glucose tolerance test is graphically shown. There was a significant correlation between the two variables ($r^2 = 0.57$, $P < 0.01$). A straight approximation line and linear function are also shown.

DISCUSSION

In the current study, there were 44 participants with FPG > 150 mg/dL. It should be noted that they all showed a diabetic pattern. Thus, we excluded them. It seems likely that the level of FPG > 150 mg/dL is an absolute value to diagnose diabetes. Further study is required to test this hypothesis.

There is substantial evidence that major cardiovascular dysfunction and/or events or mortality are related to prevailing postprandial hyperglycemia[10–12]. Thus, to define the upper limit of 1-h PG after 75-g OGTT seems to be an important issue. It has recently been reported that 1-h PG is a better prediction for future type 2 diabetes than FPG level[7,8]. In that study[8], 155 mg/dL of 1-h PG was the best cut-off value.

The definition of normal ranges for a clinical parameter is to use the ROC curve in the cohort. This technique has been used to define the upper limit for serum alanine aminotransferase levels[13]. Using this method, we found that the optimal cut-off value of 1-h PG was 179 mg/dL. When this cut-off value was used, ROC analysis showed that sensitivity, specificity, and positive and negative predictive value was 85, 79, 82 and 83%, respectively, in the diagnosis of normal or abnormal 75-g OGTT. Regarding the diagnosis of diabetes based on both 75-g OGTT and HbA_{1c} value, 27% of participants with 1-h PG ≥ 179 mg/dL had diabetes, whereas only 1% of participants with 1-h PG < 179 mg/dL had diabetes. These data suggest that the participants with 1-h PG ≥ 179 mg/dL might be at risk for future diabetes.

In the same way, we further examined the optimal cut-off value of 1-h PG for 2-h PG = 200 mg/dL. ROC analysis showed that 214 mg/dL was the best cut-off value (area under the ROC curve 0.92), providing that sensitivity, specificity, and positive and negative predictive values were 89, 83, 63 and 96%, respectively, in the diagnosis of non-diabetic or diabetic 75-g OGTT. In this situation, 38% of participants with 1-h PG ≥ 214 mg/dL had 'true' diabetes, whereas just 2% of

participants with 1-h PG < 214 mg/dL had non-diabetes (data are not shown). Thus, the participants with 1-h PG ≥ 214 mg/dL might be more at risk of developing future diabetes.

As suggested in previous reports[7,8], when we used a cut-off value 155 mg/dL of 1-h PG in the current model, the sensitivity was 95%, but specificity was just 57%. The lower specificity might be a result of the difference of study design, and the different ethnic groups and varying states of glucose tolerance, family history of diabetes, and obesity[14-17].

In conclusion, the present data suggested that the upper limit of the normal range of 1-h PG is 179 mg/dL in a Japanese population. Thus, the subjects with 1-h PG ≥ 179 mg/dL might be at risk of developing future diabetes. Therefore, appropriate prospective study should be carried out to test this hypothesis.

ACKNOWLEDGEMENT

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