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Revised Criteria for Diagnosing Diabetes - Rational or Not ?

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In 1985 World Health Organization (WHO) recommended fasting plasma glucose (FPG) ≥7.8 mmol/L or 2 hour post-challenge plasma glucose (2-h PG) ≥11.1 mg/dL as the criteria for diagnosing diabetes. In 1997, American Diabetes Association (ADA) proposed to use only FPG and lowered the threshold from 7.8 to 7 mmol/L. The objectives of this retrospective study were to compare the two criteria in the categorization of diabetes and to evaluate and compare different diagnostic cutpoints defined only by either FPG or 2-h PG. A total of 1421 oral glucose tolerance tests (OGTT) (457 men, 964 women; mean age 50.9 ± 12.8 years, rangeâ 18- 87 years) performed for subjects at different stages of hyperglycemia were rewieved. According to ADA and WHO criteria 9.5% and 16.9% of patients had diabetes mellitus, respectively. The overall ќ which measures the agreement between the two classification systems was poor (ќ=0.21). The optimal cut-off value for FPG to identify diabetic subjects as diagnosed with OGTT was between 6.5 mmol/L (50% sensitivity, 85% specificity) and 7.1 mmol/L (>95% sensitivity, 23% sensitivity). Our results show that, the subjects defined by FPG, does not cover the same subjects obtained from the 2-h PG and there are significant overlaps and discordances between ADA and WHO criteria.

Key words: OGTT, type 2 diabetes mellitus, WHO criteria, ADA criteria.

Introduction

In 1985 World Health Organization (WHO) recommended fasting plasma glucose (FPG) ≥7.8 or 2 hour post-challenge plasma glucose (2-h PG) ≥11.1 mmol/L as the criteria for diagnosing diabetes. Twelve years later, in 1997, American Diabetes Association (ADA) proposed to use only FPG and lowered the threshold from 7.8 to 7 mmol/L (1). The main rationale for this was to "avoid the discrepancy between the FPG and 2-h PG cutpoint levels, encourage the use of a simpler and equally accurate test and identify the appropriate cutpoint for risk of microvascular disease". However, the assumption that both FPG and 2-h PG cutpoints denote similar risks of micro- and macrovascular complications may be incorrect.

Ideally, one laboratory parameter should be used to define a disease state. If we use 2 parameters such as FPG and/or 2-h PG in the diagnosis of diabetes, then they both should denote similar stages of abnormal glucose homeostasis. If this is not the case, there will be a confusion with respect to the homogenity of covered patients. Since from a pathophysiological point of view fasting and postload glucose levels correspond to interrelated but different aspects of glucose homeostasis, it is important to know whether diagnosis with one parameter covers the same patient population.

In the light of these considerations, the objectives of this retrospective study were: 1) to compare the 1997 ADA and 1985 WHO criteria in the categorization of diabetes and to determine the impact of proposed changes on the diagnosis of diabetes, 2) to evaluate and compare different diagnostic cutpoints defined only by either FPG or 2-h PG.

Materials and Methods

We reviewed all the OGTTs except those performed for pregnant women between 1998 and 2000 at the laboratory of Akdeniz University which serves a population of nearly 500000. These

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OGTTs were requested by doctors in hospital or in primary health care, for subjects who had FPG < 6.1 mmol/L but had clinical suspicion of diabetes, and for subjects with FPG ≥6.1 mmol/L but < 7.8 mmol/ L. A total of 1421 OGTTs (457 men, 964 women; mean age 50.9 ± 12.8 years, range 18- 87 years) performed for subjects at different stages of hyperglycemia were evaluated.

The standardized procedure for OGTT was as follows: After an overnight fast, blood sample for FPG was taken at 9:00 a.m.; then the patient drinks a solution of 75 g glucose in 250 mL of water over 5 minutes. With the patient remaining seated, four blood samples were taken at 30, 60, 90 and 120 minutes for glucose and the results were recorded in the laboratory database. The subjects were divided into 6 groups, defined *only* by FPG and 2-h PG as seen in Table 1.

Table 1. Definition of different plasma glucose levels according to WHO and ADA criteria.

ADA criteria		WHO criteria	
FPG	(mmol/L)	2-h PG	(mmol/L)
Normal fasting glucose (NFG)	<6.1	Normal glucose tolerance (NGT)	<7.8
Impaired fasting glucose (IFG)	6.1-7	Impaired glucose tolerance (IGT)	7.8-11.1
Diabetes (DM-FPG)	≥7	Diabetes (DM-2-h PG)	≥11.1

In statistical analysis, ADA 1997 criteria were compared with the WHO 1985 criteria considered as the gold standard. Asymmetry between the two classifications was assessed by McNemar test. Comparison and concordance between ADA and WHO criteria was assessed by ќ statistics (2). The overall ќ which measures the agreement across all categories of glucose intolerance, was calculated. A value of 1 indicates perfect agreement; while 0 indicates that agreement is no better than chance. Values >0.75 may be taken to represent excellent , <0.40 poor, and 0.40- 0.75 fair to good agreement. Sensitivity was calculated as the number of true-positive subjects (in whom diabetes was correctly diagnosed in the diabetes group by some FPG cutpoint) divided by the total number of diabetic subjects; specificity was calculated as the number of true-negative subjects (in whom diabetes was correctly exluded in the NGT group or the IGT group by some FPG cutpoint) divided by the total number of subjects in the NGT group or the IGT group, and accuracy was calculated as the sum of true-positive and true-negative diabetic patients divided by the total number of subjects in the two groups (3).

For determining the cut-off value for FPG equivalent to a 2-h PG of 11.1 mmol/L, by using a receiver-operating characteristic (ROC) curve, the optimal value for identifying WHO 1985-diagnosed DM was determined. Statistical analysis was carried out with SPSS 10.0. Results were given as mean ± SD. Differences were considered statistically significant for $p<0.05$.

Results

Diabetes rate was higher and glucose intolerance rates were similar compared to ADA criteria when the WHO criteria was applied. Relationship between FPG and 2-h PG values are shown in table 2. As it is seen rate of diabetes diagnosed by OGTT increases as FPG levels increase. Table 3 shows the concordance between ADA and OGTT results. Sensitivity and specificity of ADA criteria was 28% and 94%, respectively. The overall ќ which measures the agreement between the two classification systems was poor (ќ=0.21). Figure 1 shows all patients distribution for different FPG and 2-h PG levels. The graph is seperated into 4 areas to show more clearly how the ADA and WHO defined criteria enclose different patient groups.

Table 2. Distribution of different FPG ranges in different glucose tolerance status groups. Last column shows in percentage the distribution of each FPG group according to 2-h PG in itself. All glucose values in mmol/L.

FPG	2-h PG	n	%
<6.1	<7.8 (NGT)	544	64
	≥7.8-<11.1 (IGT)	252	30
	≥11.1 (DM)	56	6
6.1-<7	<7.8	157	36.2
	≥7.8-<11.1	161	37.1
	≥11.1	116	26.7
7-<7.8	<7.8	30	22.2
	≥7.8-<11.1	37	27.4
	≥11.1	68	50.4
6.1-<7.8	<7.8	187	33
	≥7.8-<11.1	198	35
	≥11.1	184	32
TOTAL		1421*	

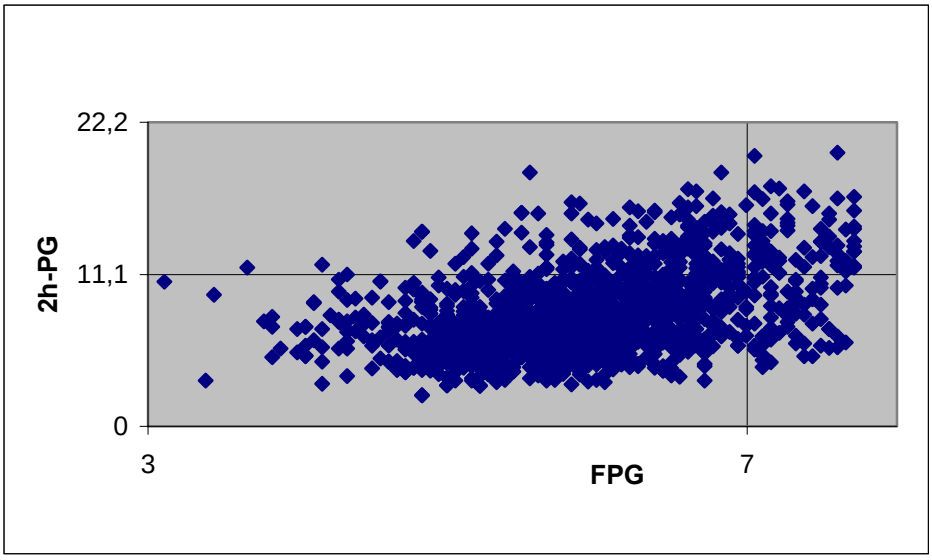

Figure 1. Distribution of FPG and 2-h PG in the whole group. Area 1, Non-diabetic FPG (<7 mmol/L) but 2-h PG consistent with diabetes according to WHO criteria; Area 2, both non-diabetic FPG (<7 mmol/L) and non-diabetic 2-h PG (<11.1 mmol/L); Area 3, diabetic FPG(≥7 mmol/L) but non-diabetic 2-h PG (<11.1 mg/dL); Area 4, both diabetic FPG (≥7mmol/L) and diabetic 2-h PG (≥11.1 mmol/L).

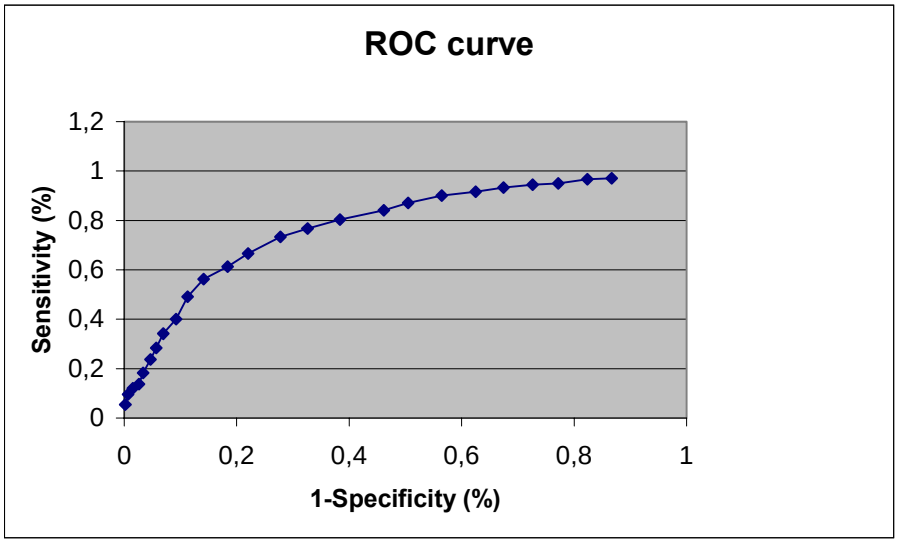

Figure 2. Receiver-operating characteristic (ROC) curve of fasting plasma glucose for identifying diabetes according to WHO 1985 criteria. Arrows indicates FPG thresholds (mmol/L).

Table 3- Overlap between OGTT results and ADA criteria.

	DM-ADA (n=135)	IFG-ADA (n=434)	NFG-ADA (n=852)
DM-OGTT	68 (28.3%)*	116 (48.3%)	56(23.3%)
IGT-OGTT	37 (8.2%)	161 (35.8%)	252(56%)
NGT-OGTT	30 (4.1%)	157 (21.5%)	544(74.4%)

*Percentage within that row.

In order to identify a FPG cut-off level for detecting OGTT diagnosed diabetes, a ROC curve was used. From the ROC curve, the optimal cut-off value for FPG to identify diabetic subjects as diagnosed with OGTT was between 6.5 mmol/L (50% sensitivity, 85% specificity) and 7.1 mmol/L (>95% sensitivity, 23% sensitivity) (Figure 2).

Discussion

Since the introduction of revised criteria in 1997, many studies have been performed comparing the ADA and WHO classification systems; the majority indicating lower prevalence of diabetes with ADA criteria (4- 8). Only two studies (9,10) report an increased diabetes prevalence with ADA criteria; in those studies the subjects were classified as, ADA-non diabetic FPG < 7 mmol/L, or ADA diabetic FPG ≥ 7 mmol/L, and on the basis of the 2-h PG only as WHO-nondiabetic, 2-h PG <11.1 mmol/L or WHO-diabetic, 2-h PG ≥ 11.1 mmol/L (9,10). The reason for this classification was noted as the 1985 WHO report, which recommended only the 2-h PG for epidemiological and diagnostic screening. Different characteristics of study populations were also alleged as a reason in critics of these studies.

In this study, we evaluated and compared FPG and 2-h PG values of a group of subjects retrospectively, who had either FPG < 6.1 mmol/L plus risk factors for diabetes or FPG between 6.1-7.8 mmol/L. The subjects were divided into groups defined only by FPG (similar to the ADA criteria) and 2- h PG and then compared.

It is clearly seen in Table 3 that definition of diabetes by both parameters does not cover the same set of subjects. If 2-h PG during OGTT is taken as the gold standard for diagnosis of diabetes, in the population studied, ADA fasting criteria missed the diagnosis of diabetes in 71.6 % of the cases. On the contrary, 22 % of ADA diagnosed DM cases were classified as normal and 27% were diagnosed as having IGT according to WHO criteria. Among IGT patients, ADA reported 56 % as normal. This last result is in concordance with previous studies which are reporting even higher percentages such as 64.7 % and 82 % (11, 12).

Although it is not clear whether IFG and IGT identify the same individuals in a given population, previous studies generally indicate the lack of agreement between them (11,12). Our results clearly show that only 37 % of IFG subjects had IGT; 36 % had NGT and 27 % had diabetes. These data strongly support the concept that, even with the use of this low threshold, the ability for fasting glucose levels to identify IGT does not improve substantially.

Although both criteria define a higher prevalance of cardiovascular disease, in Funagata Diabetes Study, IGT was found to be a risk factor for cardiovascular disease, while IFG was not (13).

From a pathophysiological point of view, fasting and 2-h PG represent different but interrelated aspects of glucose homeostasis. Our results show that, subjects covered by one parameter are not comparable with the other, and emphasize that they are not analogous**.** Twenty-three percent of diabetic patients had isolated postchallenge hyperglycemia and the rest is classified as IGT by WHO (Table 3).

Some authors suggest that use of OGTT (which relies largely on postprandial glucose value to define glucose tolerance) may bias toward selection of insulin resistance rather than beta-cell dysfunction (14). However, it is clear that, oral glucose tolerance test provides additional prognostic information and enables detection of individuals with IGT.

Our results clearly show that, the subjects defined by FPG, does not cover the same subjects obtained from the 2-h PG. In subjects having different stages of hyperglycemia, there are significant overlaps and discordances between ADA and WHO criteria which leads to confusion and errors in clinical and epidemiological studies. In order to eliminate these problems, we suggest to imply the parameter used and to add it as a prefix to the definition.

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