Evaluation of WHO and NDDG Criteria for Impaired Glucose Tolerance

Results From Two National Samples

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The considerable disagreement in the definition of impaired glucose tolerance (IGT) by National Diabetes Data Group (NDDG) and World Health Organization (WHO) criteria was explored in two independent representative adult population samples in Israel (n = 1119) and the United States (n = 1783). Five categories of nondiabetic glucose tolerance were defined according to fasting plasma glucose (FPG) values (mM) and 1- and 2-h plasma glucose values (PG1 and PG2, respectively) after oral glucose load: *1*) normal by WHO and NDDG (FPG <6.4 mM, PG1 <11.1 mM, PG2 <7.8 mM), *2*) Normal by WHO, nondiagnostic by NDDG (FPG 6.4–7.7 mM, PG1 <11.1 mM, PG2 <7.8 mM), *3*) normal by WHO, nondiagnostic by NDDG (FPG <7.8 mM, PG1 ≥11.1 mM, PG2 <7.8 mM), *4*) IGT by WHO, nondiagnostic by NDDG (FPG <7.8 mM, PG1 <11.1 mM, PG2 7.8–11.0 mM), and *5*) IGT by WHO and NDDG (FPG <7.8 mM, PG1 ≥11.1 mM, PG2 7.8–11.0 mM). Established markers of abnormal glucose tolerance were also measured, including glycosylated hemoglobin A_1, insulin response, plasma triglycerides, serum uric acid, and rate of hypertension in Israel as well as rates of hypertension, peripheral vascular involvement, family history of diabetes, and history of cholelithiasis in the U.S. Accounting for potential confounders, levels of these markers in both national samples were similar in categories 1 and 2 and in categories 3–5. Levels were significantly higher in the latter three categories than in the former two. It is therefore recommended that categories 3–5 be considered as constituting IGT. Group 3, with normal PG2 but abnormal PG1, cannot be identified by the WHO oral glucose tolerance test (OGTT), which omits PG1. Therefore, OGTT in studies relating to the nature and associated risks of IGT should include a midtest glucose sample. *Diabetes* 38:1630–35, 1989

Glucose	1 mM = 18 mg/dl	Uric acid	1 mM = 16.81 mg/dl
Triglyceride	1 mM = 88.57 mg/dl		

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Received for publication 27 March 1989 and accepted in revised form 9 August 1989.

Current definitions of glucose tolerance rest on two widely accepted sets of criteria for interpretation of the oral glucose tolerance test (OGTT). One set of criteria is that suggested by the National Diabetes Data Group (NDDG) of the National Institutes of Health (Bethesda, MD), and the other is that suggested by the Expert Committee of the World Health Organization (WHO) (1,2). The two definitions for diabetes, based mainly on evidence characterizing blood glucose levels conveying increased risk for microvascular complications (1–3), show ~95% agreement (4–6). With regard to lesser degrees of glucose tolerance, there is considerable discrepancy (4–6). Nondiabetic subjects are divided by WHO criteria into two categories—impaired (IGT) and normal glucose tolerance—whereas by NDDG criteria they are classified into three categories—IGT, normal glucose tolerance, and an intermediate nondiagnostic group (Table 1). The groups defined as normal or IGT by NDDG are also defined as such by WHO. In the NDDG nondiagnostic group, however, some subjects are defined by WHO criteria as normal and some as IGT, both parts constituting a significant portion of the total group of subjects with nondiabetic glucose tolerance (Table 2).

IGT is associated with increased risk for decompensation to diabetes and macrovascular complications (1,2,7–10). Disagreement between NDDG and WHO on definition of this category and the formulation of a nondiagnostic group by NDDG reflect the lack of sufficient evidence for unequivocal determination of cutoff points for differential risk strata. In this article, we evaluate the WHO and NDDG systems for classifying nondiabetic glucose tolerance according to selected established markers of abnormal glucose tolerance

TABLE 1
World Health Organization (WHO) and National Diabetes Data Group (NDDG) criteria for nondiabetic glucose tolerance

	Classification		Plasma glucose levels (mM)		
Category	WHO	NDDG	Fasting	Midtest	2 h
N-N	Normal	Normal	<6.4	<11.1	<7.8
N-ND1	Normal	Nondiagnostic level 1	6.4–7.7	<11.1	<7.8
N-ND2	Normal	Nondiagnostic level 2	<7.8	≥11.1	<7.8
I-ND3	Impaired	Nondiagnostic level 3	<7.8	<11.1	7.8–11.0
I-I	Impaired	Impaired	<7.8	≥11.1	7.8–11.0

Refs. 1 and 2.

in two independent samples of adult populations in Israel and the U.S.

RESEARCH DESIGN AND METHODS

Participants and procedures. This study is based on people aged 40–70 yr in two national population samples, the Israel Study of Glucose Intolerance, Obesity and Hypertension (GOH) and the 2nd National Health and Nutrition Examination Survey (NHANES II) in the U.S. The Israel GOH study is an ongoing longitudinal study of a sample (n = 5711) of the Jewish population born from 1912 to 1941, stratified by age and sex, drawn from the Israel Central Population Registry. This sample was first examined between 1969 and 1972. Between 1977 and 1982, a subgroup of 2333 individuals aged 40–70 yr who were not known as diabetic underwent an OGTT (OGTT group); weight and height were recorded, blood pressure was measured, and information regarding use of antihypertensive medications was obtained. Additional variables determined in the last 1211 participants within the OGTT group (insulin group) included the following established markers of IGT: glycosylated hemoglobin (HbA_1), serum uric acid, total fasting plasma triglycerides, and plasma insulin in post–glucose-load samples. Both the OGTT and insulin groups were representative of the original sample as evidenced by the similar recruitment rates in all age and sex strata and in categories by obesity and hypertension status in their first examination (11,12).

NHANES II studied a stratified probability cluster sample of U.S. residents from 1976 to 1980. A sample of 1922 Whites aged 40–70 yr with no medical history of diabetes underwent an OGTT and completed a household interview, which collected information on demographic and/or medical history including use of antihypertensive medications and the following markers of IGT: family history of diabetes (parent or sibling), history of gallstones, and measurement of blood pressure, weight and height, and peripheral vascular involvement (as reflected by diminished and/or absent pulsations of the dorsalis pedis artery) (13).

The OGTT was performed in both studies after a 10- to 16-h overnight fast. Venous blood samples were obtained in the fasting state (FPG) and at 1 (PG1) and 2 (PG2) h after a glucose load. In the U.S., a 75-g load was administered, whereas in Israel, a 100-g load was selected for its greater stimulation of insulin secretion (14). The difference between these two loads has little influence on blood glucose levels (15). Plasma glucose (mM) and insulin (mU/L) in all samples, and plasma triglycerides (mM), serum uric acid (mM), and HbA_1 (percent of total hemoglobin) in the fasting sample in the Israel study and plasma glucose in the U.S. study were determined by routine methods as previously described (4,5,11–13). This study addresses only subjects aged 40–70 yr whose OGTT results were in the nondiabetic range (2148 and 1119 subjects from the OGTT and insulin groups, respectively, from the GOH study and 1783 subjects from NHANES II).

Informed consent was obtained from all subjects in both studies.

Data analysis. WHO and NDDG criteria with OGTT results agree on two cutoff points relating to PG2: the upper limit defining diabetes (≥11.1 mM) and the lower limit defining normality (<7.8 mM). They also agree on the definition of fasting hyperglycemia (≥7.8 mM) (1,2). They differ because NDDG requires, in addition, a midtest glucose determination

TABLE 2
Distribution of nondiabetic subjects in glucose tolerance categories by World Health Organization (WHO) and National Diabetes Data Group (NDDG) criteria

	Distribution				Mean plasma glucose values (mM)					
	Israel		United States		Fasting		Midtest		2 h	
Category	%	n	%	n	Israel	United States	Israel	United States	Israel	United States
N-N	71.6	1538	74.6	1275	5.30	5.10	7.10	7.52	5.74	5.41
N-ND1	2.6	55	0.9	15	6.68	6.58	8.54	8.83	6.28	6.46
N-ND2	5.3	115	7.5	135	5.79	5.67	12.10	12.52	6.24	6.06
I-ND3	12.8	275	8.9	181	5.66	5.36	9.11	9.69	8.74	8.73
I-I	7.7	165	8.1	177	5.92	5.80	12.53	12.83	9.15	9.33
Total	100.0	2148	100.0	1783						

See Table 1 for definitions of glucose tolerance categories.

and defines levels ≥11.1 mM as abnormal values and uses as its criterion for normal fasting glucose levels <6.4 mM, whereas WHO uses levels <7.8 mM. WHO and NDDG criteria for nondiabetic OGTT can be classified into five categories by combinations of these cutoff points (Table 1). The categories at the two extremes, N-N (normal by WHO and normal by NDDG) and I-I (IGT by WHO and IGT by NDDG), are similarly defined (as normal and IGT, respectively) by both sets of criteria. The three intermediate categories are defined as nondiagnostic by NDDG, but of these three, WHO classifies N-ND1 (normal by WHO and nondiagnostic level 1 by NDDG) and N-ND2 (normal by WHO and nondiagnostic level 2 by NDDG) as normal although defining I-ND3 (IGT by WHO and nondiagnostic level 3 by NDDG) as impaired.

We evaluated these five glucose tolerance categories by comparing the levels of the markers of IGT mentioned above in the two populations. Because this is a post hoc analysis of two independent studies, the original aims of which did not include the current evaluation, these markers were different in the two samples with the exception of blood pressure and use of antihypertensive medications.

Statistical comparison of the markers between these five IGT categories was done separately in each of the two samples with different methods. This was necessary because of the different sampling schemes, different markers, and the fact that the markers in the Israel sample were continuous in nature, those in the U.S. sample being categorical. The main objective of the analyses was to obtain an overall com-

TABLE 3
Markers of impaired glucose tolerance in glucose tolerance categories by World Health Organization (WHO) and National Diabetes Data Group (NDDG) criteria

	N-N	N-ND1	N-ND2	I-ND3	I-I
Israel sample (insulin group)					
Cases (*n*)	845	23	53	135	63
HbA_1 (% total hemoglobin)					
A	6.8	6.7	7.2	7.2	7.2
B	6.8	6.7	7.2	7.2	7.2
C	6.8	6.5	7.1	7.1	7.3
Insulin response (mU/L)*					
A	133	156	177	176	200
B	135	149	175	169	198
C	132	139	169	166	196
Plasma triglycerides (mM)					
A	1.29	1.33	1.38	1.38	1.54
B	1.30	1.30	1.34	1.36	1.50
C	1.28	1.27	1.32	1.33	1.50
Serum uric acid (mM)					
A	0.30	0.32	0.35	0.34	0.35
B	0.31	0.31	0.34	0.33	0.34
C	0.30	0.30	0.33	0.33	0.34
Hypertensive (%)†					
A	32.1	38.4	43.5	49.2	45.3
B	33.6	34.1	42.6	47.2	47.0
United States sample					
Cases (*n*)	1275	15	135	181	177
Hypertensive (%)					
A	19.4	22.9	37.4	42.2	43.7
B	21.0	27.6	36.6	38.7	33.8
Diabetic family history (%)					
A	24.4	19.5	37.6	36.3	38.2
B	25.1	30.8	39.3	39.4	34.8
C	25.0	41.7	42.0	36.5	39.4
Peripheral vascular involvement (%)					
A	10.5	9.3	9.3	14.3	15.5
B	10.6	12.5	8.9	16.3	16.6
C	10.8	7.6	7.4	14.1	15.3
Gallstones (%)					
A	7.0	2.9	5.9	11.9	13.3
B	7.1	7.4	8.2	9.1	14.0
C	7.1	7.4	9.5	9.5	14.4
		NS		NS	
		$P < .01$			

See Table 1 for definitions of glucose tolerance categories.
*Sum of insulin values at 60 and 120 min after a glucose load.
†Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg and/or taking antihypertensive medications.

parison of the IGT categories, entering all measured variables simultaneously into the model. In the Israel sample, the most appropriate test was Hottelling T^2 (Biomedical Computer Programs, University of California Program 3D). In the U.S. sample, the required method was logistic regression analysis for application to stratified cluster design samples by use of SESUDANN and RTI LOGIT procedures of the Statistical Analysis System (SAS), which was developed for complex survey designs by Research Triangle Institute (Cary, NC). Standard errors in the U.S. sample were based on a Taylor series linearization method, and internal comparisons were done by Z test. In both samples, age and body mass index (BMI) were also entered into the model. Because these types of analysis enable comparison of only two groups at a time, it was first done comparing N-N to N-ND1 and N-ND2, I-ND3, and I-I to each other. Because no significant differences were found in these comparisons, the first two and latter three were combined, and these two combined groups were compared to each other.

The statistics for each variable (means for continuous variables and percentages for categorical ones) are presented in three ways: *1*) crude statistics, *2*) adjusted for age and BMI separately for each variable, and *3*) same analyses as 2, but excluding individuals taking antihypertensive medications to preclude a potentially greater effect of antihypertensive medications on the markers in categories N-ND2, I-ND3, and I-I where hypertension was more prevalent. The adjustment for age and BMI in the Israel study (for all variables except hypertension) was done by analysis of covariance (BMDP program 2V) with the glucose tolerance categories as a grouping factor and age and BMI as covariates. Hypertension in the Israel study and all variables in the U.S. study were adjusted for age and BMI by the direct method, with the total Israel sample as the standard population.

The distributions of the glucose tolerance categories in the two population samples were adjusted to account for the sampling schemes. Comparison of distributions of the N-ND2, I-ND3, and I-I categories by age and sex was done by χ^2-test.

RESULTS

The relative proportions of nondiabetic subjects in the two study populations falling in each of the five IGT categories were remarkably similar; so were the means of fasting, mid-test, and 2-h glucose levels despite the different glucose loads used (Table 2).

Although the specific markers of IGT (with the exception of hypertension) were different in the Israel and U.S. samples, the comparative trends between the five categories were the same (Table 3). In both populations, categories N-N and N-ND1 resembled each other in all variables, and the same was true for categories N-ND2, I-ND3, and I-I. Groups N-ND2, I-ND3, and I-I combined had significantly higher values ($P < .01$) than groups N-ND1 and N-N in both Israel and the U.S. These findings could not be explained by differences in age, sex, BMI distributions, or use of antihypertensive medications, because the pattern remained the same after adjusting for these factors. The same pattern was observed in both populations when the rates of subjects with at least one marker of IGT (by use of categorical definitions of the continuous variables in the Israel sample) were compared relative to category N-N (Fig. 1).

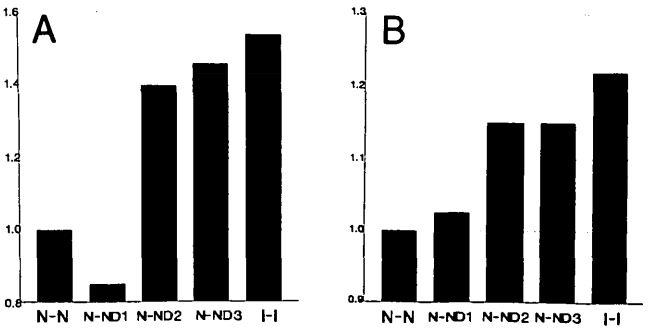

FIG. 1. Percentage of subjects with at least 1 marker of impaired glucose tolerance from Table 3 in each glucose tolerance category relative to percentage in N-N glucose tolerance category in each sample. For this calculation, markers in Israel population (*B*) were categorically defined according to 75th percentile of their distributions in group free of obesity, hypertension, and glucose intolerance (see refs. 11 and 12): HbA_1 ≥7.5% of total hemoglobin, insulin response ≥134 mU/L, plasma triglycerides ≥1.41 mM, and serum uric acid ≥0.30 mM. Subjects who were hypertensive and/or had at least 1 value above these cutoff points in Israel population were defined as having at least 1 marker, with analogous definition in United States population (*A*). Percentage of such subjects in N-N category was 79.8% in Israel and 49.1% in U.S. (difference in these values in 2 populations stems from difference in markers used; Table 3). For definitions of glucose tolerance categories see Table 1.

The similarity of categories N-ND2, I-ND3, and I-I suggests that they represent IGT to the same extent. Within this combined group, category N-ND2, which is defined as normal glucose tolerance by WHO criteria, constituted 20.7% in the Israel sample and 27.4% in the U.S. sample. In both populations, this rate was significantly higher in men and subjects with younger ages ($P < .01$; Table 4).

DISCUSSION

The years 1979–1980 were an important turning point in the definition of diabetes and IGT. At that time, expert groups

TABLE 4
Distribution of subjects within combined group of the 3 glucose tolerance categories that apparently represent impaired glucose tolerance by sex and age

	n	N-ND2 (%)	I-ND3 (%)	I-I (%)
Total Israel sample	555	20.7	49.6	29.7
Sex				
Male	309	27.8	41.4	30.7
Female	246	11.8	59.8	28.4
Age (yr)				
40–49	144	26.4	48.6	25.0
50–59	198	19.7	53.1	27.2
60–70	213	17.8	46.9	35.3
Total United States sample	493	27.4	36.7	35.9
Sex				
Male	264	36.3	30.3	33.3
Female	229	17.0	44.1	38.8
Age (yr)				
40–49	80	35.0	37.5	27.5
50–59	102	33.3	35.3	31.4
60–70	311	23.4	37.0	39.5

See Table 1 for definitions of glucose tolerance categories.

from NDDG and WHO (some of whom belonged to both groups) promulgated consensus criteria for these diagnoses (1,2). At least 17 sets of criteria for interpretation of the glucose tolerance test had been suggested previously, of which 5 rather divergent sets were in extensive use (1,16). In the absence of independent measures of their validity, all of these criteria were based, in effect, on arbitrarily chosen cutoff points along the continuous spectrum of glucose response to an oral glucose load. In contrast, both NDDG and WHO criteria were determined after thorough assessment of clinical and epidemiological studies. Their cutoff points were based on evidence concerning risk for subsequent micro- and macrovascular complications and decompensation to overt diabetes. Another new concept was designating as diabetic subjects in whom PG2 values were ≥11.1 mM in the absence of fasting hyperglycemia (1–3,7–10).

The NDDG and WHO classification systems have gained wide acceptance. However, they are similar in some aspects and divergent in others. Both methods recommend an oral glucose load of 75 g and require FPG and PG2 values. The NDDG criteria require at least one additional midtest glucose value at 30–90 min postload. For non-insulin-dependent diabetes, the definitions are formally not the same because of this additional requirement, but in reality there is virtually a complete (>95%) overlap (4–6).

With regard to nondiabetic glucose tolerance, however, considerable discrepancy occurs. WHO criteria classify nondiabetic subjects into two categories: those with IGT and those with normal glucose tolerance. NDDG definitions of both normal glucose tolerance and IGT are stricter than those of WHO, leaving a nondiagnostic group that NDDG was reluctant to label as IGT or to absolve as normal. This group is comprised of subjects who are distributed in both the normal and IGT categories of WHO. As our data show, this discrepant group has a significant prevalence in both populations. Correct definition of people in this group is thus of potential interest. Individuals with IGT are at increased risk for decompensation to diabetes and development of coronary heart disease (1–3,7–10). Precise identification of the group at risk for these conditions is important for epidemiological studies to quantitate risk factors for development of the above diseases, for clinical trials aimed at preventing their development, and for individual clinical follow-up. Since the NDDG and WHO criteria were published, no study providing evidence to enable more substantiated classification of abnormal glucose tolerance has been reported.

Our attempt to address this question was based on evaluation of established pathophysiological markers of IGT, which, in nondiabetic subjects, is characterized by hyperinsulinemia and insulin resistance (17,18). An inherent manifestation of insulin resistance and/or hyperinsulinemia is elevation of plasma triglycerides (19,20). Hypertension and elevated serum uric acid are correlates of IGT and have been shown to be independently characterized by hyperinsulinemia and/or insulin resistance (11,12,21–23). HbA_1 (4,24), family history of diabetes (10,13,25), and frequency of cholelithiasis and peripheral vascular involvement (13,26,27) are elevated in people with IGT. Thus, levels of these markers are direct or indirect manifestations of impairment of glucose homeostasis. Our data indicate that in two categories defined as nondiagnostic by NDDG, namely I-ND3 and N-ND2 (of which the former is defined as IGT and the latter as normal by WHO), levels of these markers are similar to levels in category I-I (defined as IGT by both sets of criteria; Table 3). By the same token, markers of IGT in category N-ND1 (defined as nondiagnostic by NDDG and normal by WHO) resemble group N-N (designated as normal by both sets of criteria).

That similar trends were observed with respect to different IGT markers in two totally independent studies, neither of which included the current analysis within its original aims, seems to underscore their validity. Particularly striking is that this finding holds for family history of diabetes in the U.S. sample (not elicited in the Israel study), even though subjects were unaware of their glucose tolerance status.

A limitation of our data is that they are cross-sectional and are not based on determination of actual risk for development of diabetes or macrovascular disease. However, our data have a bearing for future research relating to these issues because assessment of risks in longitudinal studies requires appropriate baseline data. Because group N-ND2 can be distinguished from group N-ND1 only by a midtest glucose level ≥11.1 mM, assessment of glucose tolerance including a midtest blood sample could provide valuable information.

The WHO recommendation to base diagnosis only on FPG and PG2 values, omitting a midtest glucose determination, was probably dictated by a desire to simplify the OGTT. It is our impression from discussions with colleagues internationally that there is a tendency to plan studies with use of WHO criteria to facilitate procedures. If a survey is based on PG2 levels, participants are available for a midtest blood drawing, and in our mutual experience, the refusal rate for such a drawing is insignificant. The increase in cost associated with an additional glucose determination is estimated to be <5% (4). Therefore, there seems to be no substantial reason to refrain from a three-sample OGTT, especially when characterization of the nature and associated risks of IGT is among the goals of the study.

In conclusion, a sizable group exists in the nondiabetic range of glucose tolerance whose PG1 level is abnormal, although the PG2 level is normal (N-ND2). This group resembles groups with abnormal PG2 levels (N-ND3 and I-I) in the profile of established pathophysiological markers of IGT. It is thus recommended that categories N-ND2, N-ND3, and I-I be considered as IGT. Group N-ND1 differs from N-N only by its higher (>6.4 mM) FPG levels and, based on the resemblance of the markers in the two groups, can apparently be considered as having normal glucose tolerance. Hence, the cutoff point for normal FPG values of NDDG might be raised to <7.8 mM. The fact that FPG is a poor predictor of glucose tolerance level in general (4–6) supports this contention. However, the small number of subjects in the N-ND1 category, particularly in the U.S. sample, calls for reserved judgment regarding its glucose tolerance status. From a practical standpoint, groups N-ND2 and N-ND1 cannot be identified by the WHO OGTT method, which omits midtest levels. Therefore, studies relating to the nature and associated risks of IGT should include at least three (FPG, midtest, and PG2) plasma glucose samples. Data from such studies should be reported in more detail, classifying IGT

into subgroups by glucose levels of all three samples, to enable future characterization of differential risks associated with various combinations of glucose levels.

ACKNOWLEDGMENTS

The two studies were independently supported by the National Institutes of Health.

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