Abnormal Glucose Tolerance and Increased Risk for Cardiovascular Disease in Japanese-Americans With Normal Fasting Glucose

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OBJECTIVE — To compare the American Diabetes Association (ADA) fasting glucose and the World Health Organization (WHO) oral glucose tolerance test (OGTT) criteria for diagnosing diabetes and detecting people at increased risk for cardiovascular disease (CVD).

RESEARCH DESIGN AND METHODS — Study subjects were 596 Japanese-Americans. Fasting insulin, lipids, and C-peptide levels; systolic and diastolic blood pressures (BPs); BMI (kg/m^2); and total and intra-abdominal body fat distribution by computed tomography (CT) were measured. Study subjects were categorized by ADA criteria as having normal fasting glucose (NFG), impaired fasting glucose (IFG), and diabetic fasting glucose and by WHO criteria for a 75-g OGTT as having normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and diabetic glucose tolerance (DGT).

RESULTS — Of 503 patients with NFG, 176 had IGT and 20 had DGT. These patients had worse CVD risk factors than those with NGT . The mean values for NGT, IGT, and DGT, respectively, and analysis of covariance *P* values, adjusted for age and sex, are as follows: intra-abdominal fat area by CT 69.7, 95.0, and 101.1 cm^2 ($P < 0.0001$); total CT fat area 437.7, 523.3, and 489.8 cm^2 ($P < 0.0001$); fasting triglycerides 1.40, 1.77, and 1.74 mmol/l ($P = 0.002$); fasting HDL cholesterol 1.56, 1.50, and 1.49 mmol/l ($P = 0.02$); C-peptide 0.80, 0.90, 0.95 nmol/l ($P = 0.002$); systolic BP 124.9, 132.4, and 136.9 mmHg ($P = 0.0035$); diastolic BP 74.8, 77.7, and 78.2 mmHg ($P = 0.01$).

CONCLUSIONS — NFG patients who had IGT or DGT had more intra-abdominal fat and total adiposity; higher insulin, C-peptide, and triglyceride levels; lower HDL cholesterol levels; and higher BPs than those with NGT. Classification by fasting glucose misses many Japanese-Americans with abnormal glucose tolerance and less favorable cardiovascular risk profiles.

Diabetes Care 24:39–44, 2001

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Received for publication 25 April 2000 and accepted in revised form 12 September 2000.

Abbreviations: ADA, American Diabetes Association; ANCOVA, analysis of covariance; ANOVA, analysis of variance; CAD, coronary artery disease; CT, computed tomography; DFG, diabetic fasting glucose; DGT, diabetic glucose tolerance; IAF, intra-abdominal fat; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; JACDS, Japanese-American Community Diabetes Study; NFG, normal fasting glucose; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

In 1997, the American Diabetes Association (ADA) Expert Committee on the Diagnosis and Classification of Diabetes Mellitus recommended two changes in the diagnostic criteria for diabetes (1). First, the committee suggested using only fasting glucose without an oral glucose tolerance test (OGTT) to diagnose diabetes for clinical and epidemiologic applications. In addition, the committee created three new categories based on the fasting plasma glucose level: normal fasting glucose (NFG), glucose <6.1 mmol/l; impaired fasting glucose (IFG), glucose 6.1–7.0 mmol/l; and diabetic fasting glucose (DFG), glucose ≥7.0 mmol/l. The new diagnostic criteria were proposed to remedy criticisms of the original 1985 World Health Organization (WHO) (2) and National Diabetes Data Group diagnostic criteria (3), which relied on both a fasting glucose level and additional glucose measurements during a 2-h 75-g OGTT. It was thought that using the fasting glucose alone would simplify the screening process to a single more reproducible laboratory test without the need to perform a cumbersome OGTT. In addition, the previous DFG threshold of ≥7.8 mmol/l was judged to be too high. The DFG level therefore was lowered to ≥7.0 mmol/l, a level determined to correspond more closely to individuals with a 2-h plasma glucose level of ≥11.1 mmol/l after a 75-g oral glucose load. After the publication of the ADA Expert Committee's fasting glucose criteria, a provisional report by a WHO consultation endorsed the new diabetic fasting plasma glucose threshold of ≥7.0 mmol/l (4). However, the provisional report from the WHO continues to recommend using the OGTT with measurement of a 2-h glucose value in screening for diabetes.

Many recent studies have examined and questioned the exclusive use of the fasting glucose criterion for diabetes. Three concerns have been raised: *1*) although the ADA fasting glucose criterion for diabetes is specific, sensitivity is variable (5); *2*) NFG is a heterogeneous group that includes many patients with impaired glucose tolerance (IGT) and diabetic glucose

Table 1—*Distribution of 596 study subjects by fasting glucose and glucose tolerance categories*

Glucose tolerance category (WHO criteria)	Fasting glucose category (ADA criteria)		
	Normal (*n* = 503)	Impaired (*n* = 59)	Diabetic (*n* = 34)
Normal (*n* = 307)	307	0	0
Impaired (*n* = 212)	176	36	0
Diabetic (*n* = 77)	20	23	34

Data are *n*.

tolerance (DGT) who, therefore, may be at increased risk for diabetes-related complications, including CVD (6–8); and *3*) IFG has correlated poorly with IGT, a known risk factor for future development of diabetes and CVD (9).

The Japanese-American population living in King County, Washington, has been shown to have an increased risk for developing type 2 diabetes and CVD (10–16). We undertook this study to compare the ADA fasting glucose criteria with the provisional WHO criteria for determining the different categories of glucose tolerance as well as for examining the variables related to adiposity, dyslipidemia, and insulin metabolism that have been associated with the insulin resistance syndrome. We did so to determine if additional information provided by the OGTT was helpful in detecting individuals at increased risk for developing CVD. Our results suggest that although use of only the fasting glucose criterion may still be preferable in the clinical setting because of simplicity and specificity, diagnostic categories that include the OGTT should be retained for epidemiologic studies.

RESEARCH DESIGN AND METHODS

— Participants for this study were selected from 658 individuals participating in the baseline examination of the Japanese-American Community Diabetes Study (JACDS), all of whom resided in King County, Washington, and were either second-generation (Nisei) or third-generation (Sansei) Americans of 100% Japanese ancestry. A total of 62 study subjects on oral medications for diabetes or insulin were not included in this study. The final study cohort for the current analysis therefore included 596 participants (310 men and 286 women) 35–75 years of age.

Fasting blood samples and OGTT

Following a 10-h overnight fast, blood samples were withdrawn for measurement of glucose, insulin, and C-peptide levels and percentage of HbA_{1c}, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. For the OGTT, 75 g glucose was administered orally over 5 min. A blood sample was drawn at 120 min after administering the oral glucose load. Using the fasting and 120-min plasma glucose values, study subjects were designated as having NFG (<6.1 mmol/l), IFG (6.1–7.0 mmol/l), and DFG (≥7.0 mmol/l) and as having normal glucose tolerance (NGT) (fasting glucose <6.1 mmol/l and 2-h glucose <7.8 mmol/l), IGT (fasting glucose <7.0 mmol/l and 2-h glucose 7.8–11.0 mmol/l), and DGT (fasting glucose ≥7.0 mmol/l and/or 2-h glucose ≥11.1 mmol/l).

Adiposity

BMI was determined as weight corrected for height: weight (kg)/height $(m)^2$. Subcutaneous and intra-abdominal fat (IAF) as cross-sectional areas were measured by computed tomography (CT) as described in a previous study (17). To measure fat areas (cm^2) per CT scan, a single scan was performed at the following three levels: the chest at the nipples, the abdomen at the umbilicus, and the thigh at the midpoint between the greater trochanter of the femur and the upper margin of the patella. An estimate of total CT fat was calculated as the sum of the following fat areas: IAF, chest subcutaneous, abdominal subcutaneous, and twice the left thigh subcutaneous.

Assays and measurements

Weight was measured to the nearest 0.01 kg and height to the nearest 0.1 cm. Blood pressure (BP) was measured three times (with patients supine) by auscultation over the brachial artery with a mercury sphygmomanometer, and systolic and diastolic (Korotkoff fifth phase) BPs were recorded as the mean of the second and third measurements. Plasma glucose was measured by an automated glucose oxidase method, and HbA_{1c} was measured by column chromatography (University of Washington Medical Center, Department of Laboratory Medicine). Insulin and C-peptide levels were measured by radioimmunoassays performed by the Immunoassay Core of the Diabetes Endocrinology Research Center. Lipid and lipoprotein measurements were done at the Northwest Lipid Research Laboratory according to modified procedures of the Lipid Research Clinics.

Statistical analyses

Statistical analyses were performed using MathSoft SPSS for Windows (version 7.5; SPSS, Chicago) and S-PLUS 4.0 for Windows (MathSoft). A χ^2 test was used to determine significance in comparison of percentages among groups. Analysis of variance (ANOVA) was used to determine significance in differences among means. Kruskal-Wallis tests were also used (but not presented) as a confirmation of the parametric tests for comparison of mean values. Analysis of covariance (ANCOVA) was used to test differences in means adjusting for age and sex. In addition, because values for fasting insulin and triglycerides were not normally distributed, log transformation was performed before statistical testing. For significant ANOVA results, polynomial contrasts were applied to test for linear and quadratic trends. Helmert contrasts were also used to determine which groups were different from each other. These contrasts were set up to compare the two most similar groups and to compare the combined mean of these two groups to the third group (18). All results are expressed as means ± SEM. All *P* values shown are two-tailed.

RESULTS

— Table 1 shows the distribution of the 596 subjects based on the two sets of diagnostic criteria. All subjects who had NGT (*n* = 307) also had NFG. However, not all 503 subjects with NFG had NGT; 176 had IGT and 20 had DGT. Moreover, whereas 212 subjects were classified as having IGT, only 59 subjects were identified as having IFG. Of the subjects having IFG, 36 had IGT and 23 DGT. Thus, the IFG category was poorly related to the IGT category. The ADA Expert Committee designated IFG and IGT as "impaired glucose homeostasis." Using the WHO criteria as a basis of comparison, the sensitivity of detecting impaired glucose homeostasis was only 17% (36 of 212) with the ADA criteria. We also compared how many study subjects were classified as having diabetes.

Table 2—*Study subjects with normal fasting glucose subdivided by glucose tolerance: demographic, metabolic, adiposity, lipid, and BP mean values*

	Glucose tolerance category by OGTT				
	Normal	Impaired	Diabetic	*P* (ANOVA)	*P** (ANCOVA)
Age	49.4 ± 0.7	55.1 ± 0.8	60.3 ± 1.9	<0.0001*	—
% Female	48.5	56.3	55.0	0.3	—
Metabolic					
Fasting insulin (pmol/l)	76.0 ± 2.2	87.1 ± 3.6	80.1 ± 10.4	0.02	0.003
Fasting C-peptide (nmol/l)	0.80 ± 0.01	0.90 ± 0.02	0.95 ± 0.06	0.0001	0.002
Fasting glucose (mmol/l)	5.04 ± 0.03	5.29 ± 0.04	5.39 ± 0.11	<0.0001†	<0.0001
HbA_{1c} (%)	5.93 ± 0.04	6.29 ± 0.06	6.67 ± 0.17	<0.0001†	<0.0001
Adiposity					
BMI (kg/m^2)	23.6 ± 0.2	24.5 ± 0.3	24.3 ± 0.9	0.01	0.0004
Intra-abdominal fat area (cm^2)	69.7 ± 2.5	95.0 ± 4.0	101.1 ± 15.0	<0.0001	<0.0001
Total fat area (cm^2)	437.7 ± 10.8	523.3 ± 15.9	489.8 ± 36.1	<0.0001	<0.0001
Lipids					
Total cholesterol (mmol/l)	5.78 ± 0.06	6.00 ± 0.09	6.09 ± 0.19	0.06	0.8
LDL cholesterol (mmol/l)	3.60 ± 0.05	3.72 ± 0.08	3.83 ± 0.19	0.3	1.0
HDL cholesterol (mmol/l)	1.56 ± 0.03	1.50 ± 0.03	1.49 ± 0.100	0.3	0.02
Total triglycerides (mmol/l)	1.40 ± 0.06	1.77 ± 0.13	1.74 ± 0.28	0.009	0.002
BP					
Systolic (mmHg)	124.9 ± 1.0	132.4 ± 1.4	136.9 ± 3.5	<0.0001*	0.004
Diastolic (mmHg)	74.8 ± 0.6	77.7 ± 0.7	78.2 ± 1.7	0.004	0.01

Data are means ± SEM unless otherwise indicated. *Adjusted for age and sex; †significant linear trend across groups ($P < 0.01$).

According to the WHO criteria, all subjects with DFG were classified as having DGT. However, of the 77 subjects with DGT, over one-half had NFG or IFG, with only 34 individuals having DFG (Table 1). Using the WHO criteria as a basis of comparison, the ADA criteria had a sensitivity of detecting diabetes of 44% (34 of 77).

To determine the association between OGTT status and risk factors for coronary artery disease (CAD), we compared lipid, lipoprotein, glucose, insulin, and C-peptide levels; BP; and adiposity for participants with NFG but differing OGTT categories. Table 2 shows that levels of fasting insulin, C-peptide, HDL cholesterol, triglycerides, HbA_{1c}, BMI, IAF, total fat, and systolic and diastolic BP were all significantly different across the three glucose tolerance groups. Furthermore, contrasts showed significant differences between the NGT group and the combined IGT and DGT groups for all of the metabolic measures; IAF and total fat ($P < 0.001$); BMI and systolic BP ($P < 0.01$); and HDL cholesterol, triglycerides and diastolic BP ($P < 0.05$). There were no significant differences, however, between the IGT and DGT groups. There was a trend toward higher fasting insulin and C-peptide levels in those with IGT and DGT, suggesting greater insulin resistance. Additionally, BMI, IAF, and total fat were also significantly higher in the IGT and DGT groups. Triglycerides were higher and HDL cholesterol lower in the abnormal glucose tolerance groups. Although LDL cholesterol did not significantly change among the groups, these findings are consistent with greater dyslipidemia in the IGT and DGT groups. Lastly, systolic and diastolic BPs were also higher in the IGT and DGT study subjects.

HbA_{1c}, insulin, C-peptide, adiposity, lipids, and BP values were also compared for study subjects with IFG/IGT, IFG/DGT, and DFG/DGT (Table 3). By ANCOVA, HbA_{1c} was significantly different across the three groups, with the DFG/DGT group having a much higher mean HbA_{1c} than the combined IFG/IGT and IFG/DGT groups (Helmert contrast, $P < 0.0001$), these latter two groups not being significantly different from each other. This observation suggests that the combination of DFG and DGT results in the greatest degree of hyperglycemia, whereas the IFG/IGT and IFG/DGT groups have very similar degrees of hyperglycemia despite differences in glucose tolerance. Fasting insulin and C-peptide levels were significantly different across the three groups, with the combined DGT categories having a higher mean than the IFG/IGT category (Helmert contrast, $P < 0.05$), a result that is indicative of greater insulin resistance in the two DGT groups. For adiposity, BMI remained similar across the categories, but the combined DGT groups had higher mean IAF than the IFG/IGT category (Helmert contrast, $P = 0.042$), with the IFG/DGT group the most obese in terms of both IAF and total fat. The combined diabetic groups also had higher mean triglycerides (Helmert contrast, $P = 0.011$) than the IFG/IGT group. The other lipid measures and BPs were not significantly different across these groups.

CONCLUSIONS — In our Japanese-American population, the ADA criteria are markedly less sensitive than the revised WHO standards for diagnosing diabetes and for detecting impaired glucose homeostasis. We found that the provisional WHO criteria detected more than twice the number of diabetic individuals as the ADA fasting criteria; we would therefore predict that using only the fasting glucose criteria will markedly decrease the number of Japanese-Americans diagnosed with diabetes. Gimeno et al. (19) conducted a similar analysis in Japanese-Brazilians and found a similar lack of sensitivity using the fasting glucose criteria.

The ADA Expert Committee had predicted the new fasting glucose criteria would be slightly less sensitive than the WHO cri-

Table 3—*Subjects classified as having impaired fasting glucose, subdivided by glucose tolerance category (by OGTT), and diabetic fasting glucose: demographic, metabolic, adiposity, lipid, and BP mean values*

	IFG/IGT	IFG/DGT	DFG/DGT	*P* (ANOVA)	*P** (ANCOVA)
Age	62.0 ± 1.4	63.3 ± 1.3	60.0 ± 1.4	0.3	—
% Female	16.7	52.2	26.5	0.013	—
Metabolic					
Fasting insulin (pmol/l)	79.2 ± 6.1	123.9 ± 11.7	129.0 ± 14.0	0.002†	0.006
Fasting C-peptide (nmol/l)	1.03 ± 0.05	1.20 ± 0.08	1.25 ± 0.08	0.05	0.05
HbA_{1c} (%)	7.26 ± 0.29	7.12 ± 0.21	9.55 ± 0.42	<0.0001	<0.0001
Adiposity					
BMI (kg/m^2)	25.6 ± 0.5	26.1 ± 0.5	26.0 ± 0.6	0.8	0.3
Intra-abdominal fat area (cm^2)	115.8 ± 8.0	153.1 ± 12.0	133.7 ± 9.5	0.04	0.02
Total fat area (cm^2)	482.9 ± 30.3	613.7 ± 43.9	488.5 ± 26.7	0.02	0.09
Lipids					
Total cholesterol (mmol/l)	6.01 ± 0.16	6.50 ± 0.24	5.96 ± 0.15	0.1	0.2
LDL cholesterol (mmol/l)	3.90 ± 0.16	3.62 ± 0.24	3.52 ± 0.15	0.3	0.4
HDL cholesterol (mmol/l)	1.34 ± 0.06	1.35 ± 0.09	1.24 ± 0.06	0.5	0.6
Total triglycerides (mmol/l)	1.74 ± 0.14	3.12 ± 0.62	2.43 ± 0.30	0.03	0.02
BP					
Systolic (mmHg)	139.3 ± 2.8	141.9 ± 2.8	140.6 ± 3.7	0.9	0.8
Diastolic (mmHg)	81.1 ± 1.2	82.8 ± 1.8	79.6 ± 1.6	0.4	0.3

Data are means ± SEM unless otherwise indicated. *Adjusted for age and sex; †significant linear trend across groups ($P < 0.01$).

teria in detecting diabetes (1). However, it was believed that the ease of performing a single blood test without having to perform the OGTT would increase the use of screening and subsequently increase detection of diabetes. Although some studies have shown relative agreement between the ADA and WHO criteria, many investigations have shown otherwise. The DECODE Study and the Hoorn Study both found a marked lack of sensitivity in using the ADA fasting glucose criteria in their European populations (20,21). In the Hong Kong and Taiwan Chinese populations, fasting glucose was similarly less sensitive than the OGTT in detecting subjects with diabetes (22,23). In the American populations, both African-Americans and Mexican-Americans have been shown to be underdiagnosed using fasting glucose alone (8,24).

IGT is an important intermediate stage of glucose tolerance and has been shown to be associated with an increased risk of progression to diabetes in several populations (9). Participants in a major clinical trial in the prevention of type 2 diabetes, the Diabetes Prevention Program, have been selected from among people who have IGT because of the high risk that this condition confers for subsequent diabetes (9). In our previous studies, we have shown that Japanese-Americans with IGT have metabolic abnormalities (plasma insulin, C-peptide, triglycerides, and HDL cholesterol) that are intermediate between individuals with NGT and those with DGT (9,25). Unfortunately, the IFG category misses the majority of individuals who have IGT. In fact, 39% of the present study subjects with IFG already had diabetes according to the WHO criteria. Moreover, 83% of IGT subjects had normal fasting glucose levels and would therefore be overlooked when using only the fasting glucose criteria.

There is also reason to be concerned that the fasting glucose criteria may overlook individuals who are at risk for developing CVD. As shown above, the NFG group is heterogeneous in regard to glucose tolerance and includes study subjects with NGT, IGT, and DGT. According to the ADA, all individuals with NFG are at equal risk for CVD. To test this assertion, we measured cardiovascular risk factors that are related to insulin resistance. Among subjects with NFG only, we compared lipid profiles, insulin and C-peptide levels, adiposity, and BPs with subjects further classified as having NGT, IGT, and DGT. HDL cholesterol significantly decreased and triglycerides significantly increased as glucose tolerance worsened among NFG subjects. Lower HDL cholesterol and higher triglycerides have been associated with greater CVD risk. Fasting insulin, C-peptide, and HbA_{1c} levels significantly differed among the NGT, IGT, and DGT groups. Using insulin, C-peptide, and HbA_{1c} levels as surrogate measurements of insulin resistance, these data suggest relatively more insulin resistance in study subjects with worsening glucose tolerance. Furthermore, there were significant differences in BMI, total fat, and most notably in IAF, suggesting greater central adiposity as glucose tolerance worsens. These trends in lipids, lipoprotein levels, central adiposity, and insulin resistance parallel characteristics associated with the insulin resistance syndrome. Thus, although the mean values of these measurements remain in the normal range, there appears to be an increased risk for CVD within the NFG population as glucose tolerance deteriorates. The Funagata Diabetes Study in Japan also predicted an increased risk of CAD in Japanese subjects with IGT but not IFG (7). While our data focused on cardiovascular risk factors, other investigations have measured hard end points of CVD in the NFG and the NGT groups. The Cardiovascular Health Study showed the incidence of CVD was significantly higher in individuals with NFG compared with those with NGT and that IGT was more sensitive than IFG in identifying people who later developed CVD (6).

The discrepancies between the ADA criteria and the revised WHO criteria can be explained by examination of the multiple metabolic dysfunctions that lead to hyperglycemia and diabetes. In type 2 diabetes, hyperglycemia results from a combi-

nation of islet β-cell dysfunction, insulin resistance, and increased hepatic glucose production (26,27). It is therefore not surprising that the combination of the fasting and the 2-h plasma glucose is superior to the fasting glucose alone in detecting individuals who have these abnormalities. Fasting hyperglycemia results from increased hepatic glucose production that occurs in the setting of insulin deficiency and hepatic insulin resistance (26). Postprandial hyperglycemia, however, is largely a consequence of both β-cell dysfunction and insulin resistance in peripheral tissues such as fat and muscle (27). Thus, the physiology of glucose metabolism is consistent with diabetic glucose tolerance in the setting of normal fasting glucose levels. Moreover, based upon our observations, such individuals display characteristics associated with an increased risk for CVD.

It should be pointed out, however, that although the mean glucose responses to two OGTTs performed 48 h apart have been shown to be essentially the same, there can be considerable intraindividual variation (28). The reproducibility of the OGTT was not examined in our study population because doing more than one OGTT would not have been practical; it is likely that this will be the case in other epidemiologic studies. Nonetheless, it is clear that despite this caveat, the important differences found among study subjects within the NFG and the IFG categories once they were reclassified according to their OGTT diagnostic category suggest that even a single OGTT may be very useful in epidemiologic studies.

In conclusion, the fasting glucose criterion may have a place in the diagnosis of diabetes in the clinical setting, in which simplicity and specificity are very important. However, for epidemiologic studies (especially those investigating the development of disease over time), the diagnostic categories that include the OGTT are superior in capturing the pathophysiology of type 2 diabetes. Furthermore, the OGTT can identify individuals who provide valuable information on the etiology and pathogenesis of both type 2 diabetes and its complications.

Acknowledgments — This research was supported by National Institutes of Health Grants DK-31170, HL-07028-25, HL-49293, and DK-02654 and by facilities and services provided by the Diabetes and Endocrinology Research Center (DK-17047), Clinical Nutrition Research Unit (DK-35816), General Clinical Research Center (RR-00037), and Northwest Lipid Research Laboratory at the University of Washington.

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