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Comparison of the 1997 and 2003 American Diabetes Association Classification of Impaired Fasting Glucose

Impact on Prevalence of Impaired Fasting Glucose, Coronary Heart Disease Risk Factors, and Coronary Heart Disease in a Community-Based Medical Practice

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OBJECTIVES The goals of this study were to assess the effect of the 2003 American Diabetes Association definition of impaired fasting glucose (IFG) on prevalence of IFG, coronary heart disease (CHD) risk factors, and CHD compared with the 1997 IFG definition.

BACKGROUND Although IFG is viewed as increasing CHD risk, this association is unclear and has not been well studied after changing the IFG criterion, especially in a clinical practice setting.

METHODS This was a cross-sectional evaluation of 8,295 members (3,763 men and 4,532 women) of a community medical center who were between the ages of 30 and 69 years, without a history of diabetes mellitus, and who had available measurements of fasting plasma glucose and lipid concentrations within the past 2 years. The prevalence of IFG, CHD risk factors, and CHD with the 1997 and 2003 IFG definition was compared.

RESULTS The prevalence of IFG increased from 8% to 35% with the 2003 criterion. Individuals with glucose of 100 to 109 mg/dl had lower prevalence of most CHD risk factors (hypertension, triglyceride ≥150 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, meeting 2 components of the metabolic syndrome criteria, CHD risk ≥10% by Framingham score) compared with individuals with glucose 110 to 125 mg/dl. Individuals identified with the 2003 IFG definition did not have an increase in known CHD when adjusted for covariates (odds ratio 1.4 [95% confidence interval (CI) 0.7 to 2.3] vs. 3.2 [95% CI 1.8 to 5.9]).

CONCLUSIONS One-third of the population has IFG with the 2003 definition, yet many of these individuals do not have increased prevalence of CHD risk factors or CHD. (J Am Coll Cardiol 2006; 48:293–7) © 2006 by the American College of Cardiology Foundation

In 2003, the American Diabetes Association (ADA) lowered the fasting plasma glucose concentration range for diagnosing impaired fasting glucose (IFG) from 110 to 125 mg/dl to 100 to 125 mg/dl in an effort to better identify individuals at future diabetes risk (1). This change was also intended to improve selection of individuals at risk for coronary heart disease (CHD) (2). Impaired fasting glucose, however, might not be an independent predictor of CHD. Previous studies that have reported an independent role (3,4) might have lacked adjustment for established CHD risk factors in the analysis compared with those that did not (5,6). Even so, two major organizations recently incorporated the wider definition of IFG into the diagnostic criteria of the metabolic syndrome to better identify individuals at increased CHD risk (7,8).

Critics, however, have been concerned about the public health implications of this change (9–12), which might greatly increase the number of individuals labeled with IFG without a clear understanding of the benefits associated with this diagnosis. The present cross-sectional study was initiated to compare the prevalence of IFG, CHD risk factors, and CHD with the 1997 and 2003 IFG definition in a large community-based medical practice.

METHODS

The study population consisted of 8,295 members (3,763 men and 4,532 women) of the Palo Alto Medical Foundation, a community medical center located in Palo Alto, California. Individuals were selected from the Medical Foundation database if they were between 30 and 69 years of age, without a history of diabetes mellitus (13), and had available measurements of fasting plasma glucose and lipid concentrations within the past 2 years. Individual ethnicities could not be obtained, but the Palo Alto community comprises 75.8% whites, 17.2% Asians, 4.6% Hispanics, and 2% blacks on the basis of the 2000 census (14). The Institutional Review Board of Palo Alto Medical Foundation approved this study.

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Abbreviations and Acronyms

ADA = American Diabetes Association
BMI = body mass index
CHD = coronary heart disease
CI = confidence interval
HDL-C = high-density lipoprotein-cholesterol
IFG = impaired fasting glucose
LDL-C = low-density lipoprotein-cholesterol
OR = odds ratio

Laboratory and clinical information was retrieved from the Medical Foundation database and included demographics (age, gender), anthropometric measurements (height, weight, and blood pressure), medication profile, current smoking status, and diagnoses of hypertension and CHD. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). A person was considered to have hypertension if they had been previously diagnosed with hypertension, took blood pressure medications, or had systolic blood pressure ≥130 mm Hg and diastolic blood pressure ≥85 mm Hg. An individual was regarded as having CHD if this diagnosis was listed in their medical profile.

The CHD risk factors evaluated included overweight/obesity status (BMI ≥25 kg/m^2), presence of hypertension, total cholesterol ≥200 mg/dl, low-density lipoprotein-cholesterol (LDL-C) ≥100 mg/dl, high-density lipoprotein-cholesterol (HDL-C) <40 mg/dl, and 10-year CHD risk of ≥10% by Framingham point scores (15). Because insulin resistance is appreciated as an emerging risk factor for CHD (16), we thought it useful to assess the impact of the two definitions of IFG on surrogate estimates of insulin resistance. For this purpose we evaluated the effect of the 1997 and 2003 classification of IFG on plasma triglyceride and HDL-C concentrations (17), the plasma triglyceride/HDL-C concentration ratio (18), and the presence of the metabolic syndrome criteria as proposed by the National Cholesterol Education Program (7,15). The components of the metabolic syndrome are as follows: fasting plasma glucose ≥100 mg/dl, triglycerides ≥150 mg/dl (1.7 mmol/l), HDL-C <40 mg/dl (1.036 mmol/l) in men and <50 mg/dl (1.295 mmol/l) in women, blood pressure ≥130/85 mm Hg, and waist circumference >102 cm in men and >88 cm in women. Because waist circumference was not available, BMI ≥29 kg/m^2 for men and ≥25 kg/m^2 for women were substituted. These BMI values were chosen because they provide similar prevalence of the metabolic syndrome in the third National Health and Nutrition Examination Survey as using the waist circumference cut points (19).

All laboratory measurements were conducted by the Mills-Peninsula Health Services Laboratory in San Mateo, California. The LDL-C concentration was determined according to Friedewald Formula (20). Approximately 1% of the study population had a triglyceride level >399 mg/dl, where LDL-C could not be determined.

We excluded 947 of the 9,242 individuals who met initial entry criteria for missing BMI (n = 942) and hypertension (n = 56) information. Individuals were classified according to their fasting plasma glucose concentration as <100, 100 to 109, and 110 to 125 mg/dl. A general linear model was used to estimate the trend of variables across glucose categories with Cochran-Armitage test for trend used for proportions. Pairwise comparisons between glucose categories were adjusted for multiple comparisons with Scheffé's method; the adjusted p values are reported. Logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence intervals (CIs) for having specified cardiovascular risk factors by glucose category. Fasting plasma glucose concentration <100 mg/dl was set as the reference group. We adjusted for age, gender, BMI, and current smoking status in the model when testing for association between glucose categories and CHD. We also examined potential interactions of the glucose categories with age, gender, and BMI by using product terms. The p values <0.05 were considered significant. All analyses were conducted with SAS version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

Of 8,295 total individuals, 659 (8%) had a fasting glucose level of 110 to 125 mg/dl, 2,214 (27%) had a fasting glucose level of 100 to 109 mg/dl, and 5,422 (65%) had a fasting glucose level <100 mg/dl. Employing the 2003 ADA definition of IFG, which includes glucose from 100 to 125mg/dl, more than one-third of the study population (35%) qualified for this diagnosis.

Table 1 describes the clinical and laboratory characteristics of the individuals classified according to their fasting glucose status. Individuals with plasma glucose concentration at or above 100 mg/dl were more likely to be male and more likely to smoke when compared with those with glucose <100 mg/dl. With progressive increase in glucose concentration, individuals also tended to be older, heavier, and had higher blood pressure and heart rate. In addition, lipid components showed increased triglycerides and decreased HDL-C, resulting in a rise in the triglyceride/HDL-C ratio from a mean of 2.2 in individuals with glucose <100 mg/dl to 3.5 in those with glucose of 110 to 125 mg/dl. Although total cholesterol and LDL-C showed a linear association with glucose, levels in individuals with glucose 100 to 109 mg/dl were not significantly different from individuals with glucose 110 to 125 mg/dl.

To provide additional insight into the effect of fasting plasma glucose concentration on CHD risk, Table 2 shows the frequency and OR for the occurrence of several relevant variables by glucose category. The prevalence of most variables was increased in the two groups with the higher fasting plasma glucose values. Because this was qualitatively similar in both women and men, we pooled the data for OR calculations, with fasting plasma glucose concentration

Table 1. Clinical and Laboratory Characteristics According To Glucose Category

	Fasting Plasma Glucose			p Value for Trend	p Value for Pairwise Comparison*
	<100 mg/dl (n = 5,422)	100–109 mg/dl (n = 2,214)	110–125 mg/dl (n = 659)		
Fasting plasma glucose (mg/dl)	89 ± 6	103 ± 3	115 ± 4	—	—
Age (yrs)	45 ± 10	49 ± 10	51 ± 10	<0.0001	a, b, c
Male (%)	39%	58%	58%	<0.0001	a, b, c (NS)
Current smoker (%)	6%	8%	9%	<0.0001	a, b, c (NS)
BMI (kg/m^2)	26 ± 5	28 ± 5	30 ± 6	<0.0001	a, b, c
Blood pressure (mm Hg)					
Systolic	118 ± 14	123 ± 14	127 ± 15	<0.0001	a, b, c
Diastolic	75 ± 10	78 ± 9	79 ± 9	<0.0001	a, b, c
Heart rate (beats/min)	73 ± 10	74 ± 11	75 ± 11	<0.0001	a, b, c
Total cholesterol (mg/dl)	192 ± 35	198 ± 35	197 ± 37	<0.0001	a, b (p = 0.003), c (NS)
LDL-C (mg/dl)	109 ± 31	115 ± 30	114 ± 32	<0.0001	a, b, c (NS)
HDL-C (mg/dl)	61 ± 18	56 ± 16	53 ± 16	<0.0001	a, b, c (p = 0.003)
Triglycerides (mg/dl)	115 ± 76	138 ± 88	159 ± 133	<0.0001	a, b, c
Triglycerides/HDL-C ratio	2.2 ± 2	2.9 ± 2	3.5 ± 3	<0.0001	a, b, c

Data are presented as mean ± SD unless otherwise noted. *Pairwise comparison with p ≤ 0.001 unless otherwise noted, a: glucose <100 mg/dl versus 100–109 mg/dl, b: <100 mg/dl versus 110–125 mg/dl, c: 100–109 mg/dl versus 110–125 mg/dl.

BMI = body mass index; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

<100 mg/dl set as 1. The OR for every variable but total cholesterol and LDL-C was highest in the group with a fasting plasma glucose concentration between 110 and 125 mg/dl, and the confidence limits did not overlap with the values in subjects whose fasting plasma glucose is between 100 and 109 mg/dl.

Lastly, Table 3 reports the prevalence of established CHD according to fasting plasma glucose category. Men had a greater frequency of CHD than women, but gender did not significantly modify the effect between glucose category and CHD; therefore, the OR calculations were combined. The odds of having had a CHD event were about three-fold higher in individuals with fasting plasma glucose of 100 to 109 mg/dl (OR 2.8, 95% CI 1.6 to 4.8) and more than eight-fold higher in individuals with fasting plasma glucose of 110 to 125 mg/dl (OR 8.5, 95% CI 4.8 to 14.9) when compared with persons with fasting plasma glucose <100 mg/dl. Risk for CHD was attenuated when adjusted for age, gender, BMI, and smoking status, with the risk being no longer significant in persons with glucose of 100 to 109 mg/dl (OR 1.4, 95% CI 0.8 to 2.4) but remaining significant in those with the older definition of IFG (OR 3.2, 95% CI 1.7 to 6.0). There was no significant interaction with age or BMI.

DISCUSSION

Changing the IFG criterion to include individuals with glucose of 100 to 109 mg/dl increased the prevalence of IFG from 8% to 35% of the nondiabetic population seen in a large community-based health care facility. This magnitude of increase in the occurrence of IFG is in keeping with recently published estimates from the National Health and Nutrition Examination Survey 1999 to 2000 dataset, where the prevalence of IFG nearly tripled in the population with the revised criterion (9). In individuals 50 to 64 years of age, this translated into an increase in the diagnosis of IFG from 9.9% to 30.9%. The degree of change with the 2003 IFG criterion is not confined to the U.S., with a prevalence of 32% and 38%, respectively, in Singapore (10) and Denmark (11). On the basis of these findings, it seems reasonable to conclude that approximately one-third of the adult population of developed nations would qualify for the diagnosis of IFG with the 2003 ADA criterion.

In addition to the large number of additional individuals identified, individuals with fasting plasma glucose of 100 to 109 mg/dl had a substantially lower prevalence of CHD risk factors and established CHD when compared with those with glucose of 110 to 125 mg/dl. They were much less likely to have hypertension and had lower triglyceride and higher HDL-C concentrations. They also met fewer of the criteria for the metabolic syndrome and were less likely to have at least a 10-year 10% risk of CHD by Framingham scoring. Indeed, the only CHD risk factor that did not decrease in magnitude in individuals with glucose of 100 to 109 mg/dl was the concentration of LDL-C.

In support of this lower risk, individuals with glucose levels of 100 to 109 mg/dl had lower odds of having established CHD compared with individuals with glucose of 110 to 125 mg/dl, with unadjusted ORs of 2.8 (95% CI 1.6 to 4.8) and 8.5 (95% CI 4.8 to 14.9), respectively. Adjusting for covariates attenuated the ORs to 1.4 (95% CI 0.8 to 2.4) and 3.2 (95% CI 1.7 to 6.0), respectively, indicating that only the individuals with the 1997 definition of IFG had a significantly greater prevalence of CHD. Therefore, although increased plasma glucose concentration was associated with having more CHD risk factors, it was not an independent risk factor for having established CHD in the additional individuals identified by the 2003 IFG criterion. Conversely, our data show that fasting plasma glucose level of 110 to 125 mg/dl was significantly associated with having known CHD. Whether this is a true

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Table 2. Prevalence of Coronary Heart Disease Risk Factors According to Glucose Category

	Prevalence Within Glucose Category (%)			OR (95% CI)
	Women	Men	Combined	Combined
BMI ≥25 kg/m^2				
<100	44	67	53	1
100–109	66	78	73	2.4 (2.1–2.6)
110–125	81	82	82	3.9 (3.2–4.8)
Hypertension				
<100	15	26	19	1
100–109	28	39	34	2.2 (2.0–2.5)
110–125	48	51	50	4.2 (3.6–5.0)
Total cholesterol ≥200 mg/dl				
<100	39	40	40	1
100–109	50	43	46	1.3 (1.2–1.4)
110–125	52	39	44	1.2 (1.0–1.4)
LDL-C ≥100 mg/dl				
<100	54	69	60	1
100–109	68	69	69	1.5 (1.3–1.6)
110–125	69	63	65	1.3 (1.0–1.5)
HDL-C <40 mg/dl				
<100	3	17	8	1
100–109	5	18	12	1.5 (1.3–1.8)
110–125	9	23	17	2.3 (1.8–2.9)
Triglycerides ≥150 mg/dl				
<100	14	31	21	1
100–109	25	36	31	1.7 (1.5–1.9)
110–125	36	45	41	2.6 (2.2–3.1)
Triglycerides/HDL-C ≥3				
<100	12	38	22	1
100–109	22	42	33	1.7 (1.6–1.9)
110–125	36	49	44	2.7 (2.3–3.2)
Metabolic syndrome criteria ≥2 (aside from glucose)				
<100	24	28	26	1
100–109	44	39	41	2.0 (1.8–2.2)
110–125	65	53	58	3.9 (3.3–4.6)
Framingham 10-yr risk ≥10%				
<100	0.2	13	5	1
100–109	0.3	23	14	2.8 (2.4–3.4)
110–125	2.9	33	20	4.6 (3.7–5.8)

Fasting glucose ranges are mg/dl.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

association also has been debated even before the institution of the 2003 IFG criterion (5,6). Recently, examination of the data from the Heart and Estrogen/progestin Replacement Study supports our findings, showing a lack of association between the 2003 IFG definition and new CHD events in 2,763 postmenopausal women with established CHD, whereas there was increased risk in those fulfilling the 1997 IFG criterion (21). Although the independent association of fasting plasma glucose concentration with CHD will continue to be debated, we have provided substantial evidence that the prevalence of CHD and its risk factors is less in individuals with fasting plasma glucose concentration of 100 to 109 mg/dl as compared with levels of 110 to 125 mg/dl.

In conclusion, there are two important effects of widening the fasting plasma glucose criterion for making a diagnosis of

Table 3. Prevalence of Coronary Heart Disease According to Glucose Category

	Fasting Plasma Glucose		
	<100 mg/dl	100–109 mg/dl	110–125 mg/dl
No. of cases of coronary heart disease (%)			
Women	5 (0.2)	1 (0.1)	4 (1.4)
Men	20 (1.0)	27 (2.0)	21 (5.5)
Combined	25 (0.5)	28 (1.3)	25 (3.8)
Combined unadjusted OR (95% CI)	1	2.8 (1.6–4.8)	8.5 (4.8–14.9)
Combined adjusted OR (95% CI), age, gender, BMI, smoking status	1	1.4 (0.8–2.4)	3.2 (1.7–6.0)

Abbreviations as in Tables 1 and 2.

IFG in our community-based medical practice: 1) approximately one-third of the patient population served by a large community-based health care facility has IFG; and 2) the prevalence of CHD and its risk factors are attenuated with the 2003 IFG definition compared with the 1997 definition. On the basis of the data presented, it is difficult to suggest that the 2,214 individuals identified with the 2003 criterion deserve the same medical attention and possible therapeutic intervention as the 658 patients with IFG by the 1997 definition. Indeed, irrespective of the criterion for IFG used, the effectiveness of initiating an intervention strategy to decrease the development of CHD has not been established. In the absence of such information, it seems reasonable to question the utility of the clinical information gained by identifying the four-times-as-many individuals that meet the 2003 definition of IFG, who are clearly at less risk of CHD than persons identified with the 1997 criterion. If the diagnosis of IFG is to have clinical utility in identifying apparently healthy individuals at increased CHD risk, the first step might more usefully be the initiation of an experimental protocol to evaluate the clinical utility of intervention efforts in individuals meeting the original criterion of IFG (e.g., persons at the greatest risk of CHD).

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