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Impact of Impaired Fasting Glucose on Cardiovascular Disease

The Framingham Heart Study

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Objectives We sought to determine whether impaired fasting glucose (IFG) predicts cardiovascular disease (CVD) events.

Background It is unclear which glucose threshold should define prediabetes. We compared the 1997 and 2003 American Diabetes Association (ADA) definitions of IFG to predict CVD.

Methods Framingham offspring participants free of CVD, categorized by the 1997 ADA IFG definition (fasting plasma glucose 110 to 125 mg/dl; 6.1 to 6.9 mmol/l) or the 2003 definition (100 to 125 mg/dl; 5.6 to 6.9 mmol/l), were followed from 1983 to 2004. Pooled logistic regression was used to calculate multivariable-adjusted odds ratios (ORs) for incident coronary heart disease (CHD; 291 events) or CVD (423 events).

Results Four-year CHD event rates among women were 1.3% (100 to 109 mg/dl), 2.3% (110 to 125 mg/dl), and 2.9% (diabetes); whereas corresponding rates in men were 2.9%, 3.0%, and 8.7%. For the 2003 IFG definition, the OR for CHD among women was 1.7 (95% confidence interval [CI] 1.0 to 3.0, $p = 0.048$), whereas for the 1997 IFG definition, the OR for CHD in women was 2.2 (95% CI 1.1 to 4.4, $p = 0.02$), which was almost as high as for women with diabetes (OR 2.5, 95% CI 1.2 to 5.2, $p = 0.01$). For CVD, only the 1997 IFG definition yielded significantly greater odds of CVD in women (OR 2.1, 95% CI 1.2 to 3.6, $p = 0.01$). Men were not at increased odds of developing CVD or CHD by either definition.

Conclusions In women, both IFG definitions were associated with increased CHD risk, whereas neither IFG definition identified men at increased short-term risk for CHD or CVD. The finding that women with FPG 110 to 125 mg/dl had similar CHD risk compared with women with diabetes suggests that CHD risk in women may be elevated at a lower glucose level than for men. (J Am Coll Cardiol 2008;51:264–70) © 2008 by the American College of Cardiology Foundation

It has been recognized that prediabetic hyperglycemia confers an increased risk for cardiovascular disease (CVD) (1,2). In 1997, the American Diabetes Association (ADA) introduced the concept of impaired fasting glucose (IFG), a prediabetic state initially defined by fasting plasma glucose (FPG) of 110 to 125 mg/dl (6.1 to 6.9 mmol/l), in which those afflicted were significantly more likely to develop diabetes (3–5). The risk of developing CVD was not considered in establishing criteria for IFG.

Since the introduction of the concept of IFG, there has been considerable debate regarding where the lower limit should be set to achieve a reasonable balance between sensitivity and specificity for diabetes prediction. In 2003, the ADA lowered its threshold for diagnosis of IFG from 110 mg/dl (6.0 mmol/l) to 100 mg/dl (5.6 mmol/l) on the basis of evidence in selected samples that suggested diabetes prediction may be optimized at a lower threshold (6). The effect of this lowered cut point is that a much larger proportion of the population is now considered to have IFG. Using data from the Third National Health and Nutrition Examination Survey, Benjamin et al. (7) found that the prevalence of IFG among adults was estimated to increase from 8.3% to 30.2%.

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Since the publication of the 2003 IFG guidelines, relatively few studies have examined the impact of the 2003 IFG definition on CVD risk, and none have found a relation between FPG 100 to 125 mg/dl (5.6 to 6.9 mmol/l) and increased CVD risk or mortality (8–12). However, these studies have been limited by examination of samples with limited generalizability (9–11), relatively small samples with few CVD events during follow-up period (8), and potential inclusion of participants who develop diabetes in the IFG category (9,12).

Thus, on the basis of available data, it is uncertain whether the 2003 ADA definition of IFG offers improved risk prediction regarding cardiovascular disease as compared with the 1997 IFG definition. Therefore, the primary aims of this analysis were to characterize the new 2003 ADA definition of IFG in the Framingham Offspring study by examining incident CVD events as compared with the 1997 IFG definition. We also assessed the risk of developing diabetes based on the 2 IFG definitions.

Abbreviations and Acronyms

ADA = American Diabetes Association
BMI = body mass index
CHD = coronary heart disease
CI = confidence interval
CVD = cardiovascular disease
FPG = fasting plasma glucose
IFG = impaired fasting glucose
IGT = impaired glucose tolerance
OR = odds ratio
TIA = transient ischemic attack

Methods

Study sample. Participants for this study were drawn from the Framingham Offspring cohort. The design and inclusion criteria of the Framingham Heart Study have been described elsewhere (13). The current investigation included offspring participants who attended examinations (referred to as index examinations) in 1983 to 1987 (cycle 3), 1987 to 1991 (cycle 4), 1991 to 1995 (cycle 5), and 1995 to 1998 (cycle 6). Participants could contribute information to more than one examination cycle provided they reached the next examination cycle free of an outcome event of interest. All participants with CHD or CVD at the index examinations were excluded from further analyses. Participants were followed in approximately 4-year intervals, and events were accrued through December 31, 2004. Overall, 4,138 unique individuals contributed a total of 13,273 person-exams for analyses of incident CHD, and 4,058 unique individuals contributed 12,918 person-exams for analyses of incident CVD. For analyses involving incident diabetes, a total of 3,634 unique individuals free of diabetes and CHD at baseline were followed until diabetes or examination cycle 7 (1998 to 2001) contributing a total of 11,325 person-exams. The Institutional Review Board at Boston Medical Center approved the study protocol, and all participants gave written informed consent.

Baseline measurements and definitions. All Framingham clinic visits include a physician interview, physical examination, and laboratory tests. Participants who had a fasting plasma glucose ≥126 mg/dl (>7.0 mmol/dl) or were on insulin or oral hypoglycemic agents were considered to have diabetes. The 1997 ADA guidelines defined IFG as a FPG concentration of 110 to 125 mg/dl (6.1 to 6.9 mmol/l) (14), whereas the 2003 ADA guidelines define IFG as 100 to 125 mg/dl (5.6 to 6.9 mmol/l) (6).

Outcome ascertainment. The primary outcomes of interest were CHD, CVD, and diabetes. Coronary heart disease included cases of myocardial infarction, stable and unstable angina pectoris, and CHD death (15). Cardiovascular disease was defined as any CHD event, stroke, transient ischemic attack (TIA), intermittent claudication, congestive heart failure, or CVD death. Diabetes was defined as described previously in the previous section. A panel of 3 physicians reviewed each CHD and CVD event and adjudicated the end point according to pre-established criteria (16).

Covariates. Covariates were assessed and updated at all index examinations. Covariates included age, systolic blood pressure, hypertension treatment, total cholesterol to high-density lipoprotein cholesterol ratio, cigarette smoking within the past year, and body mass index (BMI). For incident diabetes, covariates were age, cigarette smoking within the past year, and BMI. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current treatment with antihypertensive medications. Current smoking was defined as at least 1 cigarette per day within 1 year of the index examination. Weight, measured to the nearest pound, was obtained with the participant wearing a gown without slippers or shoes. The BMI was calculated by dividing weight (kilograms) by square of height (meters^2).

Statistical analysis. A significant gender interaction was observed when age–gender-adjusted models were fit with an IFG-by-gender interaction. Therefore, all subsequent analyses were gender-specific.

All individuals with CHD or CVD at each index examination were excluded. Three separate models were used to examine incident CHD and CVD: 1) To examine the impact of the 1997 IFG definition on CHD and CVD risk, we compared FPG 110 to 125 mg/dl (6.1 to 6.9 mmol/l) to a referent group of FPG <110 mg/dl (<6.1 mmol/l). 2) To examine the impact of the 2003 IFG definition on CHD and CVD risk, we compared FPG 100 to 125 mg/dl (5.6 to 6.9 mmol/l) to a referent group of FPG <100 mg/dl (<5.6 mmol/l). 3) To directly compare the categorization and performance of the 1997 and 2003 IFG definitions, a multicategory model was created comparing both FPG 100 to 109 mg/dl (5.6 to 6.0 mmol/l) and 110 to 125 mg/dl (6.1 to 6.9 mmol/l) to a referent group of FPG <100 mg/dl (<5.6 mmol/l). This model ensured that the same referent group would be used to compare individuals in the 100 to 109 mg/dl category with those in the 110 to 125 mg/dl category.