Impaired Glucose Tolerance, but not Impaired Fasting Glucose, Is Associated With Increased Levels of Coronary Heart Disease Risk Factors

Results From the Baltimore Longitudinal Study on Aging

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Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) identify individuals at high risk for progression to diabetes. Whether IFG and IGT have comparable coronary heart disease (CHD) risk factor profiles, independent of their progression to diabetes, is unclear. We determined CHD risk factor levels in 937 nondiabetic individuals at baseline and biannually over a mean follow-up period of 9.5 years. Subjects had no known CHD at baseline and had ≥2 (mean 4.2) oral glucose tolerance tests during follow-up. We classified glucose tolerance categories using American Diabetes Association diagnostic criteria or modified criteria that redefined IFG as 100–126 mg/dl, creating a similar baseline prevalence of IFG and IGT. Subjects who developed diabetes during follow-up were excluded from our analysis. Baseline CHD risk factors were similar in subjects with normal glucose tolerance (NGT) and IFG, but significantly more atherogenic in those with IGT or IFG + IGT. These findings were unchanged when the modified criteria were used, suggesting that IGT is phenotypically different from IFG and is associated with increased levels of CHD risk factors. Subjects with isolated IFG had similar levels of CHD risk factors as NGT subjects, even when IFG was redefined with a lower threshold. Although CHD risk factors were increased in the IGT group, the incidence of CHD events was not significantly different among groups, perhaps owing to the limited number of events. The differences in CHD risk factors among prediabetic groups may have clinical implications for screening strategies and CHD risk stratification of individuals with IFG and IGT.

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Diabetes Association (ADA) criteria and modified criteria that used a lower cut point for IFG of 5.55 mmol/l (100 mg/dl). The lower cut point for IFG was recently adopted by the ADA (14).

**RESEARCH DESIGN AND METHODS**

The BLSA is a prospective open cohort study of predominantly Caucasian, middle- to upper-middle-class individuals predominantly from the Baltimore, Maryland/Washington, DC area. The study was established in 1958 and has been previously described (15). Initially, only men were included; women were recruited into the study beginning in 1978. Study subjects provide written informed consent at each examination. The BLSA has continuing support from the Internal Review Board of the Johns Hopkins Bayview Medical Center.

Our longitudinal analysis of glucose tolerance and cardiovascular risk factors over time involved 937 subjects (547 men and 390 women) who, at their initial examination, had no history of diabetes (having received treatment with insulin or oral hypoglycemic agents or having a fasting glucose level ≥7.0 mmol/l and/or a 2-h postchallenge glucose level of ≥11.1 mmol/l) or cardiovascular disease (prior myocardial infarction, revascularization procedure, or episode of congestive heart failure).

Subjects who had undergone a baseline examination and at least one additional examination (with a maximum of 4 years allowed between any two examinations) were included in this study. The examinations included an oral glucose tolerance test (OGTT) and measurement of cardiovascular risk factors during a mean observation period of 9.5 years (range 0.9–30.9). The mean number of OGTT examinations was 4.2 years (range 2–13); the majority of examinations took place from 1977 to 1998.

For the purposes of this study, subjects were classified into categories of abnormal glucose homeostasis if they had a single abnormal fasting plasma glucose or OGTT result at baseline and/or at any point during follow-up. The categories of glucose homeostasis were defined based on 1997 ADA criteria (1) or modified criteria that have been recently adopted by the ADA (14). Using the 1997 ADA criteria, we defined normal glucose tolerance (NGT) as fasting plasma glucose (FPG) <5.55 mmol/l and 2-h plasma glucose (2hPG) concentration (2 h after an oral glucose challenge) ≤7.8 mmol/l, IFG as FPG 6.1–7.0 mmol/l and 2hPG <7.8 mmol/l, IGT as FPG <6.1 mmol/l and 2hPG 7.8–11.1 mmol/l, and IFG + IGT as FPG 6.1–7.0 mmol/l and 2hPG 7.8–11.1 mmol/l. Using the modified criteria, we defined NGT as FPG <5.55 mmol/l and 2hPG <7.8 mmol/l, IFG as FPG 5.55–7.0 mmol/l and 2hPG <7.8 mmol/l, IGT as FPG <6.1 mmol/l and 2hPG 7.8–11.1 mmol/l, and IFG + IGT as FPG 6.1–7.0 mmol/l and 2hPG 7.8–11.1 mmol/l. Subjects classified as having NGT by either set of criteria never had an abnormal OGTT or fasting result at baseline or during the entire follow-up period. Subjects classified as having isolated IFG never had an abnormal 2hPG value during an OGTT, and those classified as having isolated IGT never had an abnormal FPG. Those classified as having IFG + IGT had an abnormal FPG and 2hPG at baseline or at some point during follow-up. The modified criteria for plasma glucose levels were chosen a priori, before examining the CHD outcomes and CHD risk factors. The levels were chosen to incorporate the ADA definitions of diabetes and to provide exclusive IFG and IGT categories that had similar prevalence at baseline. In addition to subjects with diabetes at baseline, those who progressed to diabetes during follow-up were excluded.

**Clinical examinations and coronary heart disease risk factor assessment.** The majority of examinations were performed between 1977 and 1998. Subjects were admitted to the Gerontology Research Center, National Institute on Aging (Baltimore, MD), the night before each examination. No significant physical activity was permitted, and the subjects fasted for 9–12 h overnight. Blood was drawn the following morning for fasting glucose levels and fasting lipids, and an OGTT (see below) was performed. Anthropometric measurements, including height, weight, waist circumference, and blood pressure, were obtained using methods described previously (16). A smoking history was completed by each subject. Smokers were defined as subjects who currently smoked or who had quit smoking <2 years before the baseline examination.

**OGTT.** Most of the OGTTs in this analysis were performed between 1977 and 1998. Before June 1977, the dosage of oral glucose used for the OGTT was 1.75 g/kg body wt. This dosage was used for 5.2% of the OGTTs used in this analysis. Given that the average body weight of the male subjects during that period was 79 kg, the average oral glucose load was 138 g. In July 1977 the dosage was changed to 40 g/m² body surface area, which in this cohort was calculated to a mean dosage of 78 g glucose in men (mean surface area 1.96 m²) and in women (mean surface area 1.70 m²) (2). Of the 547 male subjects, 322 received both the 1.75 g/kg and the 40 g/m² tests. The following mathematical formula was used to convert 2hPG levels obtained using the older 1.75 g/kg OGTT (2hPGG) to values that would have been obtained from the newer 40 g/m² test (2hPGm). This formula was derived by regressing the glucose concentrations obtained using the 1.75 g/kg test on glucose concentrations obtained using the 40 g/m² test in the 322 men who underwent both tests.

\[ g_{\text{m}} = -17.5 + 1.02 \times g_{\text{G}} \]

was introduced to analyze variables with a binary response (ie, yes or no) at baseline. The glycosylated hemoglobin (HbA1c) was determined by the dextran sulfate–mediated precipitation procedure (16) and LDL cholesterol concentrations were estimated by the Friedewald formula (20).

**Statistical analysis.** Mean baseline CHD risk factors were calculated for each category of glucose homeostasis, adjusted for age and sex and compared across groups using ANCOVA (3 degrees of freedom). Generalized linear models were used to compare differences in incident CHD by glucose homeostasis category and also for the models that adjusted for age and sex. For categorical variables, univariate analyses were performed using χ² tests. Binomial proportions were computed to compare the prevalence of baseline glucose homeostasis categories. SAS software was used to perform the analyses (21), and statistical significance was defined as a P <0.05.

**RESULTS**

The mean age of the subjects at baseline was 53.2 years (range 17–91); 41.6% were female (Table 1), and 93.9% were Caucasian. Using the 1997 ADA criteria, 398 (42.5%) subjects had NGT throughout the analysis; 33 (3.5%) had isolated IFG, 376 (40.3%) had isolated IGT, and 128 (13.7%) had IFG + IGT at baseline or during follow-up. Using the modified criteria, 232 (24.8%) subjects remained NGT throughout. The modified criteria provided more similar frequency at baseline of IFG (17.9%) and IGT (12.7%); combining baseline and follow-up, there were 199 (21.2%) subjects with isolated IFG, 153 (16.3%) subjects with isolated IGT, and 353 (37.7%) subjects with IFG + IGT.

The subjects with NGT or isolated IFG were younger than those with IGT or IFG + IGT (Table 1), regardless of which criteria were used. The subjects with isolated IFG were similar to those with NGT in terms of baseline CHD risk factors, whereas the subjects with isolated IGT and IFG + IGT had a higher prevalence of CHD risk factors, adjusted for age and sex (Table 1). Specifically, those with isolated IGT or IFG + IGT had more atherogenic lipid profiles, with higher triglyceride and lower HDL cholesterol levels than those with NGT or isolated IFG. In addition, those with IFG + IGT tended to be more obese than subjects in any of the other categories of glucose homeostasis, with higher BMIs and waist circumferences. The mean Adult Treatment Panel III (ATP III) MetS scores and FRs were significantly higher in the IGT and IFG + IGT groups than in the NGT and IFG groups.
Table 1: Characteristics of subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>ADA Modality</th>
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<tr>
<td>Age (years)</td>
<td>39.8 (±4.2)</td>
<td>39.2 (±3.8)</td>
<td>41.8 (±4.3)</td>
<td>39.5 (±4.7)</td>
<td>38.9 (±4.5)</td>
<td>43.2 (±4.9)</td>
<td>39.0 (±4.6)</td>
<td>43.1 (±5.0)</td>
<td>37.2 (±3.8)</td>
<td>43.4 (±4.9)</td>
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<td>Men (%)</td>
<td>46.2</td>
<td>39.2</td>
<td>84.8</td>
<td>60.8</td>
<td>61.4</td>
<td>48.4</td>
<td>80.5</td>
<td>73.9</td>
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<td>LDL cholesterol (mg/dl)</td>
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<td></td>
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<td></td>
<td>113.5</td>
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<tr>
<td>HDL cholesterol (mg/dl)</td>
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<td></td>
<td>53.0</td>
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**Notes:**
- **NGT** refers to normal glucose tolerance.
- **IFG** refers to impaired fasting glucose.
- **IGT** refers to impaired glucose tolerance.
- **ADA Modality** refers to ADA criteria for IFG, with a cut point of 6.1 mmol/l.
- **NGT** refers to normal glucose tolerance using a lower cut point for IFG of 5.5 mmol/l.

**Statistical Tests:**
- $P < 0.0001$ indicates a statistically significant difference.
age of subjects who met the ATP III criteria for MetS (three of five traits abnormal) was significantly higher in those with isolated IGT (28.3%) and highest in those with IFG + IGT (46.9%) than in subjects with NGT or IFG (4.0 and 6.1%; \( P < 0.0001 \)) (Fig. 1A). There was no significant difference in prevalence of MetS between the NGT and IFG groups (\( P = 0.57 \)). The baseline prevalence of FRS >10 was also similar in subjects with NGT and IFG (47.6 and 51.5%; \( P = 0.78 \)), but was significantly higher in subjects with IGT and IFG + IGT (67.2 and 73.0%; \( P < 0.0001 \)) (Fig. 1B). All of the differences in CHD risk factors between the IGT and IFG categories remained significant and of the same magnitude when the analyses were adjusted for differences in obesity and BMI (data not shown) in addition to age and sex.

The relative profiles of CHD risk factors among the NGT, IFG, IGT, and IFG + IGT groups did not change when the modified criteria for the states of glucose tolerance were applied (Table 1). The IGT and IFG + IGT groups continued to have a more atherogenic profile than the IFG and NGT groups, with significantly greater BMI and triglyceride and blood pressure levels, lower HDL concentrations, and increased prevalence of MetS and FRS >10.

The total number of CHD events in the study population during the mean 9.5 years of observation was small (\( n = 117 \)). There was no significant difference in the age- and sex-adjusted incidence of CHD events between the IGT and IFG groups, using either the 1997 ADA or the modified criteria (Table 1). Even when the study population was increased to include those who developed diabetes during follow-up (\( n = 1,089 \)), the number of CHD events remained small (\( n = 146 \)) and the differences in CHD incidence among the groups, defined by the 1997 ADA or modified criteria, remained nonsignificant (data not shown).

**DISCUSSION**

Several previous studies have suggested that postchallenge hyperglycemia, measured as a continuous variable, is a better predictor of CHD than fasting hyperglycemia (8,11). The association between the IFG category and CHD risk is less clear (8). Moreover, the relative risks of IGT versus IFG for CHD may be a function of the current cut-off values (1), which have been shown to be associated with different rates of progression to diabetes (13). How much of the apparent additional risk for CHD associated with IGT compared with IFG is secondary to the higher rate of progression to diabetes is unknown.

In 1997, the ADA defined IFG as an FPG concentration of 6.1–7.0 mmol/l (110–126 mg/dl) (1). The admittedly arbitrary choice of the 6.1 mmol/l threshold was based partially on the risk of developing microvascular and macrovascular complications above this level (1). However, it has now been shown that the fasting glycemic threshold of 6.1 mmol/l does not create an equivalent category of glucose homeostasis as IFG for either the subsequent development of diabetes (13) or in terms of CHD risk factors, as shown in this study.

We followed 937 subjects longitudinally over a mean period of 9.5 years and showed that subjects with IGT, alone or in combination with IFG, had increased baseline CHD risk factors and a higher prevalence of MetS compared with subjects with NGT or isolated IFG. Of note, the individuals with IGT had an increased prevalence of MetS compared with individuals with IFG, despite the fact that IFG (\( >6.1 \text{ mmol/l} \)) and not impaired postchallenge glucose is one of the traits that comprise the definition of MetS according to NCEP criteria (17). Moreover, the baseline CHD risk factor profile associated with IFG was no different than that found with NGT.

It is important to note that we eliminated from our analysis those individuals who progressed to diabetes, thus avoiding the potential confounding effect of higher rates of progression to diabetes associated with IGT (13). We also analyzed the data using modified diagnostic criteria for IFG. The modified criteria we chose used a lower glucose threshold of 5.55 mmol/l to define IFG; this threshold was selected to create a similar baseline prevalence of individuals with isolated IFG and isolated IGT in our particular cohort. Even when such modified glucose
criteria were used, the finding that IGT, but not IFG, was associated with increased baseline CHD risk factors persisted. Thus, risk for CHD associated with IFG appears not to be a function of any particular FPG threshold, but rather a function of concomitant IGT. IGT alone is associated with elevated CHD risk factor levels, but IFG is associated with increased risk only in combination with IGT.

The differences in CHD risk factors suggest that IGT represents a different metabolic phenotype from IFG. We have previously shown that there are differences in the natural history of IGT and IFG in terms of progression to diabetes (13). These differences, however, were to a large extent a function of the diagnostic threshold used, as using a definition of 5.55–6.1 mmol/l to define IFG not only equalized the prevalence of isolated IFG and isolated IGT in the cohort, but also equalized the rates of progression from IFG and IGT to diabetes (13). The phenotypic differences between IGT and IFG in terms of CHD risk factor profiles persisted, however, even when the modified criteria were used. The subjects with isolated IGT had more atherogenic profiles at baseline than those subjects with isolated IFG.

Despite the differences in CHD risk profile between the glucose-intolerant groups, the incidence of CHD events was not significantly different. Our inability to demonstrate a significant difference in CHD events was probably attributable to the modest number of events during the follow-up period and the relatively young average age of the population. The differences in CHD risk factors will probably translate into differences in outcomes with further follow-up.

Some, but not all, cross-sectional studies have suggested differences in other atherogenic traits between IGT and IFG. Elevated C-reactive protein (CRP) levels have been demonstrated in individuals with newly diagnosed type 2 diabetes and IGT (22), but not with IFG (23). A direct comparison of CRP levels in association with postchallenge glycemia versus fasting glycemia has demonstrated a greater association between CRP and postchallenge glycemia (24). On the other hand, a recent study by Hanefeld et al. (25) did not demonstrate any differences in lipid (other than free fatty acid) or blood pressure levels between IFG and IGT, with both categories being defined using the 1997 ADA criteria (1).

The BLSA is a unique cohort in that subjects are being followed longitudinally with biannual examinations, including repeated OGTTs and assessment of CHD risk factors, some for as long as 30 years. This enables us to track changes in both glucose homeostasis and CHD risk over time; we could also eliminate subjects who developed diabetes and examine the course of IGT and IFG in the absence of diabetes. However, the BLSA is not without limitations. A variable dosage of glucose (graded according to body surface area) was used to assess glucose tolerance in these individuals. In addition, we defined the categories of glucose homeostasis based on the results of a single OGTT at baseline or during follow-up, which might overestimate the prevalence of abnormal glucose homeostasis in the cohort. Although the BLSA glucose testing results may not be strictly comparable with the results of other studies, neither of the factors noted above should affect the comparison of NGT, IFG, and IGT within the current study.

The differences between IGT and IFG with regard to CVD risk may have major clinical implications. The use of the current ADA recommended approach to screen for diabetes will miss those individuals with isolated IGT and will not discriminate those with isolated IFG from those with IFG + IGT, the latter of whom are at higher risk for CHD. The most recent change in ADA diagnostic criteria for IFG, in which the threshold for IFG was lowered to 5.55 mmol/l (100 mg/dl) (14), still misses the increased CHD risk associated with IGT, as IGT will be undetected if OGTTs continue to be discouraged.

Our findings are of relevance not only in terms of screening strategies for diabetes and pre-diabetes categories, such as IFG and IGT, but also in terms of primary prevention of CHD in these individuals. Currently, diabetes is considered a CHD risk equivalent (17), and individuals with diabetes and pre-diabetes are aggressively targeted with strategies to lower CHD risk. In this regard, because IFG per se does not appear to be associated with increased CHD risk factor levels, it may be that individuals with isolated IFG need no longer be considered at greater risk for CHD than those with NGT. Further long-term follow-up is needed to determine if this difference in baseline CHD risk factor levels will translate to a difference in CHD end points.

In summary, we have shown that IGT, compared with NGT or isolated IFG, is associated with elevated baseline CHD risk factors, even when IFG is redefined with a lower fasting glucose threshold to create a similar baseline prevalence as IGT and similar rates of progression to diabetes. The CHD risk profile associated with IFG is not statistically different from that associated with NGT. Thus individuals with IGT should be more aggressively targeted with strategies to lower CHD risk than those with IFG.

REFERENCES

8. Meigs JB, Nathan DM, D’Agostino RB Sr, Wilson PW: Fasting and post-


