Fasting Glucose, Obesity, and Coronary Artery Calcification in Community-Based People Without Diabetes

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OBJECTIVE—Our objective was to assess whether impaired fasting glucose (IFG) and obesity are independently related to coronary artery calcification (CAC) in a community-based population.

RESEARCH DESIGN AND METHODS—We assessed CAC using multidetector computed tomography in 3,054 Framingham Heart Study participants (mean [SD] age was 50 [10] years, 49% were women, 29% had IFG, and 25% were obese) free from known vascular disease or diabetes. We tested the hypothesis that IFG (5.6–6.9 mmol/L) and obesity (BMI ≥ 30 kg/m2) were independently associated with high CAC (> 90th percentile for age and sex) after adjusting for hypertension, lipids, smoking, and medication.

RESULTS—High CAC was significantly related to IFG in an age- and sex-adjusted model (odds ratio 1.4 [95% CI 1.1–1.7], P = 0.002; referent: normal fasting glucose) and after further adjustment for obesity (1.3 [1.0–1.6], P = 0.045). However, IFG was not associated with high CAC in multivariable-adjusted models before (1.2 [0.9–1.4], P = 0.20) or after adjustment for obesity. Obesity was associated with high CAC in age- and sex-adjusted models (1.6 [1.3–2.0], P < 0.001) and in multivariable models that included IFG (1.4 [1.1–1.7], P = 0.005). Multivariable-adjusted spline regression models suggested nonlinear relationships linking high CAC with BMI (J-shaped), waist circumference (J-shaped), and fasting glucose.

CONCLUSIONS—In this community-based cohort, CAC was associated with obesity, but not IFG, after adjusting for important confounders. With the increasing worldwide prevalence of obesity and nondiabetic hyperglycemia, these data underscore the importance of obesity in the pathogenesis of CAC.
and all participants weighed <350 lb because of the scanner specifications.

From Framingham offspring participants and third-generation participants that underwent scanning, 3,505 underwent a physical exam for measurement of risk factors. Of these, 3,399 had evaluable calcification scans. We excluded those with prevalent diabetes (n = 203) or cardiovascular disease (n = 120) and those who were underweight (BMI < 18.5 kg/m²; n = 20), which left 3,054 participants for analysis. The institutional review board of Boston University approved the study protocol, and all participants gave informed consent at each examination. All participants provided written consent.

**Clinical definitions and laboratory methods**

Participants were classified as underweight (BMI < 18.5 kg/m²), nonobese (18.5–29.9 kg/m²), or obese (≥ 30.0 kg/m²) (24). We used 2003 American Diabetes Association thresholds to classify fasting glucose levels as normal (< 5.6 mmol/L [<100 mg/dL]) or impaired (5.6–6.9 mmol/L [100–125 mg/dL]) (25). Diabetes was defined as the use of any hypoglycemia medication or fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) at the index examination. Current smoking was defined as at least one cigarette per day during the year before the examination. Blood pressure was estimated from the mean of two measurements taken after the participants had been seated for at least 5 min. High waist circumference was defined as male > 102 cm and female > 88 cm (26).

Plasma glucose was measured in fresh specimens with a hexokinase reagent kit (A-gent glucose test, Abbott, South Pasadena, CA). Glucose assays were run in duplicate; the intra-assay coefficient of variation was < 3%. Total cholesterol was measured enzymatically, and the HDL cholesterol fraction was measured after precipitation of LDLs and VLDLs with dextran sulfate magnesium.

Participants underwent an eight-slice multiple detector computed tomography scan (LightSpeed Ultra; General Electric, Milwaukee, WI) according to our published protocol (27). In brief, images were taken using electrocardiographic triggering during breath holding in midinspiration. Forty-eight contiguous 2.5-mm-thick slices were acquired (120 kVp, 320 mA for < 220 pound body wt [400 mA for heavier individuals]) on two occasions. All images were read independently by an experienced reader using a dedicated offline workstation (Aquarius; Terarecon, San Mateo, CA).

A calcified lesion was defined as an area of three or more connected pixels with an attenuation > 130 Hounsfield units. A modified Agatston score was calculated for each subject as \( \sum \text{lesion area} \times \text{lesion maximum attenuation score} \) (28).

Participants were classified as having high CAC if their Agatston score exceeded the 90th percentile value for their age- and sex-specific strata derived from Framingham offspring and third-generation participants without known cardiovascular disease or its risk factors (27).

**Statistical methods**

We used mean (SD) and median (range) to describe continuous variables and frequencies for categorical variables. We performed unadjusted between-group comparisons (e.g., IFG vs. normal fasting glucose) on risk factors using the two-sample \( t \) test and the Wilcoxon rank sum test or the \( \chi^2 \) test for continuous and categorical data, respectively. We used logistic regression to assess the relationship between high CAC (outcome) and IFG and/or obesity (exposures) using participants with normal fasting glucose or participants without obesity as referent. We presented the results as odds ratios with two-sided 95% CIs. Models included IFG or obesity individually or both exposures together in the same model. All models were age- and sex-adjusted followed by multivariable adjustment, which included age, sex, systolic blood pressure, total-to-HDL cholesterol ratio, smoking status, and use of lipid-lowering and antihypertension therapy. All models initially included a sex interaction term that was not significant, and therefore male and female groups were combined and the interaction term was not included in the final models. In separate secondary analyses, we used high waist circumference in place of obesity. In a separate analysis of male and female participants, CAC was considered as a continuous variable (natural log [coronary artery calcium score + 1]), and we assessed multivariable-adjusted relationships with BMI and fasting glucose (considered as discrete or continuous variables) using linear regression. We performed similar analyses using waist circumference in place of BMI. Finally, we explored the potential nonlinear relationships linking CAC with BMI, fasting glucose, and waist circumference using multivariable-adjusted spline regression models. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC); two-sided \( P < 0.05 \) was considered statistically significant.

**RESULTS**—There were 3,054 participants who satisfied the study inclusion criteria and were available for analysis. The mean age of the participants was 50 years; nearly one-half of the participants were women. IFG was present in 29% of participants, and 25% were obese (Table 1). IFG and obesity were positively associated with age, waist circumference, total cholesterol, triglycerides, systolic blood pressure, and use of antihypertension and lipid-lowering therapy and were negatively associated with HDL cholesterol.

Figure 1 shows the age- and sex-adjusted proportion of participants who had elevated CAC in each of four groups defined by the presence or absence of IFG and obesity. In participants with normal fasting glucose, those who were obese were more likely than nonobese individuals to have high CAC (the proportion with high CAC was 21% in obese participants vs. 15% in nonobese participants; \( P = 0.001 \)). Likewise, in the subgroup of participants with IFG, the presence of obesity also was associated with high CAC (high CAC was found in 26% of obese participants vs. 17% of nonobese participants; \( P = 0.002 \)). Conversely, in individuals who were obese, the presence of IFG was not associated with high CAC (the proportion with high CAC was 17% in those with IFG vs. 15% in those with normal fasting glucose; \( P = 0.16 \)), and a similar relationship was observed in nonobese participants (high CAC was seen in 26% of those with IFG vs. 21% with normal fasting glucose; \( P = 0.14 \)). In this analysis, the associations of IFG and obesity to high CAC were somewhat weakened by considering relationships between subgroups with reduced sample size, when compared with the strategy of including all participants as shown in Table 2.

Table 2 shows the adjusted odds ratio of having high CAC in relation to the presence of IFG and/or obesity. We present the results of models that included IFG or obesity individually, followed by the results of models including both variables together. Here we present the results of age- and sex-adjusted models, and the result of models adjusted for additional potential confounders. In age- and sex-adjusted models, IFG and obesity were associated with the presence of high CAC when considered individually (odds ratio 1.4 [95% CI 1.1–1.7], \( P = 0.001 \), for IFG and 1.7 [1.4–2.1], \( P < 0.001 \), for obesity) and when included together in the same model (1.3 [1.04–1.6], \( P = 0.045 \), for IFG and 1.6 [1.3–2.0], \( P < 0.001 \), for obesity). When we adjusted for
additional potential confounders, obesity was associated with high CAC regardless of whether IFG was included in the model (1.4 [1.1–1.7], \( P = 0.003 \), without IFG in the multivariable-adjusted model and 1.4 [1.1–1.7], \( P = 0.005 \), with IFG in the model). There was no attenuation in the odds ratio for the association of obesity with high CAC when IFG was included in the multivariable-adjusted model. Conversely, IFG was not associated with high CAC in multivariable-adjusted models regardless of whether obesity was included (1.2 [0.9–1.4], \( P = 0.20 \), without obesity in the multivariable-adjusted model and 1.1 [0.9–1.4], \( P = 0.46 \), with obesity in the model).

In a secondary analysis, we included high waist circumference in place of obesity. High waist circumference was present in 47% (38% men and 57% women) of our cohort. In age- and sex-adjusted models, both IFG and high waist circumference were associated with high CAC, even when both variables were included together in the same age- and sex-adjusted model (odds ratio 1.3 [95% CI 1.0–1.6], \( P = 0.022 \), for IFG and 1.3 [1.1–1.6], \( P = 0.005 \), for high waist circumference) (see Supplementary Table S2). However, in multivariable-adjusted models, neither IFG nor high waist circumference were associated with CAC individually (1.1 [0.9–1.4], \( P = 0.37 \), for high waist circumference) or when included in multivariable-adjusted models together (1.1 [0.9–1.3], \( P = 0.47 \), for high waist circumference and 1.1 [0.9–1.4], \( P = 0.28 \), for IFG).

In support of the above findings, when CAC was considered as a continuous variable (natural log [coronary artery calcium score + 1]), obesity (\( \beta [\text{SE}] = 0.25 [0.08], P = 0.001 \)) was significantly related to CAC independently of IFG, but IFG was not significantly related to CAC in multivariable-adjusted models that included or excluded obesity (Supplementary Table 3). In a similar analysis, when BMI and fasting plasma glucose were included as continuous variables, only BMI was significantly related to CAC (Supplementary Table 4). The same analysis strategy showed that waist circumference (considered as a discrete or a continuous variable) was not related to CAC in multivariable-adjusted models that included or excluded fasting plasma glucose (Supplementary Tables 5 and 6).

We used a spline regression model to explore the potential nonlinear relationships linking CAC with BMI, fasting glucose, and waist circumference. This suggested that there is a J-shaped multivariable-adjusted relationship between BMI and CAC with...
significant nonlinearity in the nonobese BMI range (Fig. 2). The relationship between CAC and waist circumference also was J-shaped (Supplementary Fig. S1). With regards to fasting plasma glucose, the risk for high CAC seemed to increase approximately linearly up to a fasting glucose value of ~5.3 mmol/L, and then the risk seemed to plateau at higher fasting glucose levels (Supplementary Figs. S2 and S3).

**CONCLUSIONS**

**Main findings**

We have shown that obesity defined by BMI was strongly associated with high CAC, and the magnitude of the association remained significant after adjusting for other cardiovascular risk factors, including IFG. Our data suggested that the multivariable-adjusted relationship between BMI and CAC is J-shaped and nonlinear in the nonobese BMI range, and we observed similar findings for the relationship between waist circumference and CAC. We showed that IFG was associated with high CAC in age- and sex-adjusted models with or without adjustment for obesity or high waist circumference. However, IFG was not associated with high CAC after adjusting for other cardiovascular risk factors. Our spline regression models suggested that multivariable-adjusted risk for high CAC seemed to increase approximately linearly up to a fasting glucose value of ~5.3 mmol/L and then seemed to plateau at higher fasting glucose levels.

**Cross-sectional studies, IFG, and CAC**

Several studies have assessed the cross-sectional relationship between IFG and CAC (3–10). Five of these studies adjusted for potential confounding risk factors, and, of these, three (6,8,9) showed a significant positive relationship between IFG and CAC, and the remaining two (3,5) showed nonsignificant results.

The largest of the positive studies was the Heinz Nixdorf Recall Study, which assessed 2,184 population-based nondiabetic participants (9). After adjusting for potential confounders including BMI, IFG was associated with prevalent CAC in men but not in women. In this study, IFG was classified as a fasting glucose value of 6.1–6.9 mmol/L, but our study adopted a different definition of IFG and included potentially lower-risk IFG participants with fasting glucose values as low as 5.6 mmol/L. Therefore, this may have contributed to our finding of a nonsignificant relationship between IFG and CAC.

In addition to our use of more contemporary and lower-risk IFG cut points, publication bias related to sample size may be a factor. Our present study (n = 3,054) and the second largest study (n = 3,043) have shown no significant relationship between IFG and CAC after adjusting for important confounders.

**Previous cross-sectional studies linking BMI or obesity with CAC**

The cross-sectional data that links BMI to prevalent CAC is mixed. In keeping with our data presented here, some previous studies have demonstrated a positive association...
(11–15), whereas the majority have shown neutral (5,16–22) or negative (23) associations.

These discrepant results may be explained by differences in analysis strategy, participant selection, and sample size. For example, the neutral results reported by some groups could be explained by small sample size (16,18–20) and imprecision in the of ascertainment of cardiovascular risk factors (22).

However, differences between studies in their analysis strategy, such as whether BMI was treated as a continuous or discrete variable, could be critically important in explaining the discrepant results. To illustrate this, it is useful to point out that our findings in the current analysis seem to contradict those of our recent report from the Framingham cohort showing that BMI was not associated with CAC in multivariable-adjusted models (21). Our earlier analysis modeled BMI as a continuous variable rather than a dichotomous variable (obesity: yes/no) as we have done in the current study. Cross-sectional data from our previous study (21), and from others (17,22,23), have indicated that the relationship between BMI and CAC is relatively flat and may be nonlinear in the nonobese range.

To explore this further, we performed a spline regression analysis, which suggested that the multivariable-adjusted relationship between BMI and CAC is J-shaped and nonlinear in the nonobese BMI range. This might explain why some previous studies relating CAC to BMI, modeled as a continuous variable, have yielded neutral results, particularly if a large proportion of the participants were nonobese. For example, the Coronary Artery Risk Development in Young Adults Study reported a nonsignificant association between BMI and prevalent CAC (5). Their analysis strategy, and the low prevalence of CAC among young women in this study, also may have contributed to the neutral result.

Our earlier analysis (21), which failed to show a relationship between CAC and BMI, modeled CAC only as a discrete variable (high CAC). In the current study, our additional modeling of CAC as a continuous variable (natural log [coronary artery calcium score + 1]) may have increased the statistical power to show a relationship between CAC and BMI.

In contrast to these studies with non-significant results, Allison et al. (12) showed a positive relationship between BMI and CAC in men. They studied a large cohort (n = 3,028) of self-referred individuals who may have been at higher risk than the background population because one in five reported hypercholesterolemia, hypertension, and a family history of premature CHD. The majority of women in this study had no detectable CAC, and this, along with relating CAC to BMI quintiles, may have contributed to the nonsignificant results in their female subgroup.

**Measured and unmeasured variables linking obesity and waist circumference to CAC**

In keeping with our earlier work (21), and that from others (29), the analysis presented here suggests that a sizable proportion of the obesity-associated risk for CAC may be mediated by standard cardiovascular risk factors. In the current study, the odds ratio for high CAC associated with obesity was not attenuated by IFG but was attenuated from 1.7 to 1.4 after adjusting for blood pressure, lipids, smoking, and medication (Table 2). This highlights the importance of obesity in the pathogenesis of cardiovascular disease (30). We cannot rule out that unmeasured variables may in part explain this association, including diet and physical activity, inflammation, oxidative stress, disorders of coagulation and fibrinolysis, and autonomic dysfunction.

It is unclear why BMI, but not waist circumference, was related to CAC in the current study. Our current report, and our previous cross-sectional study (21) as well as data from other studies (16–20), have indicated that waist circumference is not related to CAC in multivariable-adjusted models. One possible explanation is that when compared with BMI, waist circumference is more strongly associated with visceral adipose tissue (14,18) and could therefore confer more of its associated vascular risk through the standard risk factors that are commonly included multivariable-adjusted models.

**Strengths and limitations**

The study has several strengths that make it an important advance in the field: 1) It is the largest cross-sectional study assessing the associations of IFG and obesity to CAC. Having a large population-based cohort that excluded participants with known vascular disease or diabetes has restricted our assessment to early disease and has limited confounding by therapy for these conditions. 2) It used a single scanner working under a validated testing protocol. 3) It related individual CAC values to a population-based reference range. Finally, 4) it identified possible nonlinear relationships linking CAC with BMI, waist circumference, and fasting glucose.

Our study has some limitations. We are unable to determine causal relationships because of the observational and cross-sectional design. The study was performed in white men and women, and, therefore, it may have limited generalizability to other racial or ethnic groups. However, the Multi Ethnic Study of Atherosclerosis has suggested that relationships between standard risk factors and CAC are similar across ethnic groups (31). Finally, participant IFG status was based on the results of a single blood test and therefore there may have been some misclassification of participants that may have weakened the effect size associated with IFG.

**Implications**

We have shown the dominant role of obesity over IFG in the cross-sectional associations with subclinical atherosclerosis (CAC). Although this is cross-sectional observational data, our work may have public health implications because it has suggested the possible importance of targeting obesity over IFG for preventing subclinical atherosclerosis in the general population. Our study does not lead to any immediate change in clinical practice: CHD screening using CAC currently is not recommended to improve clinical outcomes, although the evidence is consistent for improved risk prediction by CAC in intermediate risk persons (32–34).

In this community-based cohort, we showed that obesity defined by BMI, but not IFG, was related to CAC after adjusting for important confounders. We also have identified possible nonlinear relationships linking CAC to BMI, waist circumference, and fasting glucose.

**Acknowledgments**—This work was supported by the National Heart, Lung, and Blood Institute’s Framingham Heart Study (Bethesda, Maryland; N01-HC-25195). M.K.R. was supported by the Higher Education Funding Council for England (Clinical Senior Lecturer Award). We also acknowledge support from the Manchester National Institute for Health Research Biomedical Research Centre and Manchester Academic Health Science Centre.

No potential conflicts of interest relevant to this article were reported.

M.K.R. conceived the study design, researched data, and wrote, reviewed, and edited the manuscript. J.M.M. contributed to the study design, performed the statistical analysis, and contributed to the editing of the manuscript. U.H. supervised the computed tomography scanning.
and contributed to data interpretation and editing of the manuscript. C.J.O. and C.S.F. contributed to the study design, data interpretation, and editing of the manuscript. C.S.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Parts of this study were presented in abstract form at the American Heart Association 50 Cardiovascular Disease Epidemiology and Prevention, San Francisco, California, 3–5 March 2010.

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