Original Article

Relationship between simple markers of insulin resistance and coronary artery calcification

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BACKGROUND: Insulin resistance in apparently healthy persons is associated with a cluster of metabolic abnormalities that promote coronary atherosclerosis. Identifying these individuals before manifest disease would provide useful clinical information.

OBJECTIVE: We hypothesized that combining 2 simple markers of insulin resistance, prediabetes (PreDM) and triglyceride (TG) concentration ≥150 mg/dL, would identify apparently healthy persons with adverse cardiometabolic risk profiles and increased coronary artery calcium (CAC) compared with those with neither or only 1 abnormality.

METHODS: A cross-sectional analysis was performed using data from 25,886 apparently healthy individuals (18,453 men and 7433 women) evaluated at the Cooper Clinic from 1998 to 2015. Participants were divided into those with a normal fasting glucose concentrations (<100 mg/dL = normal fasting glucose) or PreDM (fasting plasma glucose ≥100 and <126 mg/dL) and further subdivided into those with a plasma TG concentration <150 or ≥150 mg/dL. These 4 groups were compared on the basis of multiple coronary artery disease risk factors and the presence of CAC determined during their evaluation.

RESULTS: Participants with PreDM and a TG concentration ≥150 mg/dL had a significantly more adverse coronary artery disease risk profile than individuals with either abnormality or only 1 abnormality (PreDM or TG concentration ≥150 mg/dL). Furthermore, the odds of detectable CAC were higher in participants with PreDM and a TG ≥ 150 mg/dL than in participants with neither or only 1 abnormality.

CONCLUSION: The presence of 2 markers of insulin resistance, PreDM and TG concentration ≥150 mg/dL, is associated with increased cardiometabolic risk and detectable CAC within a population of apparently healthy individuals.

Introduction

Prospective studies[1,2] have indicated that between one-quarter and one-third of an apparently healthy population is sufficiently insulin resistant to be at increased risk to develop coronary artery disease (CAD). Given this

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information, it would seem clinically useful to identify those apparently healthy individuals whose degree of insulin resistance (IR) puts them at enhanced CAD risk to initiate clinically appropriate preventive interventions. However, specific quantification of IR, as assessed by measuring insulin-mediated glucose disposal, is not practical at a clinical level.[3,4] Plasma insulin concentrations in nondiabetic persons are significantly correlated with direct measures of IR, and several surrogate estimates of IR have been proposed based on measurements of plasma insulin and glucose concentrations.[5–7] However, in the absence of a standardized insulin assay,[8] it is not possible to generate a universally accepted index of IR based on measurement of plasma insulin concentration.

An alternative way to identify apparently healthy individuals that are sufficiently insulin resistant to be at increased risk of CAD is to use commonly measured metabolic abnormalities associated with IR. The metabolic syndrome diagnostic criteria are an example of this approach.[9] To see if there was an even simpler way to accomplish the same goal, we performed this analysis, which takes advantage of the significant relationship between IR, glucose intolerance, and hypertriglyceridemia.[10,11] The prevalence of IR is increased in individuals whose fasting plasma glucose concentrations meet the definition of prediabetes (PreDM), but not all such individuals are insulin resistant.[12,13] Prevalence of IR is also increased in persons with elevated plasma triglyceride (TG) concentrations,[11,14] and apparently healthy individuals who have both PreDM and a plasma TG concentration ≥150 mg/dL are significantly more insulin resistant than individuals with only 1 of these abnormalities.[14] This finding has the potential to serve as the basis of a simple clinical approach to identify a subgroup of apparently healthy individuals whose degree of IR places them at high risk of developing CAD.[1,2] The current analysis was an attempt to test the hypothesis that apparently healthy individuals with PreDM and a plasma TG ≥ 150 mg/dL have a cardiometabolic risk profile that places them at enhanced risk for CAD, with a significantly greater likelihood of having detectable coronary artery calcium (CAC), a marker of coronary atherosclerosis.

Methods

Design and participants

An observational study was conducted to examine the cross-sectional association between fasting plasma glucose and TG concentrations, multiple cardiometabolic risk factors, and CAC in men and women who presented to the Cooper Clinic (Dallas, TX) from 1998 to 2015 for a preventive medical visit. Informed consent was obtained from all study participants. Participants were excluded from these analyses if they (1) reported a personal history of

cardiovascular disease or type II diabetes mellitus (n = 769), (2) were missing covariate data (n = 10,230), or (3) used fibrates, niacin, or antidiabetic medication (n = 211). As a result, a total of 18,453 men and 7433 women aged 35 to 75 years were included in the analytic sample, 95% of whom were of European ancestry. The Institutional Review Board of The Cooper Institute reviewed and approved the study annually.

Measures

The clinical examination has been described previously.[15] Body mass index (kilogram per square meter) was computed from height (meter) and weight (kilogram). Tobacco use was dichotomized as current cigarette smoker or current nonsmoker. History of hypertension, dyslipidemia, and use of lipid-lowering drugs were determined from a medical history questionnaire.

Serum samples were collected after a 12-hour fast and analyzed to quantify plasma glucose, insulin, and lipid/lipoprotein concentrations by automated bioassays in accordance with standard procedures. Participants were classified by American Diabetes Association criteria[16] as having either normal fasting glucose (NFG; glucose <100 mg/dL) or PreDM (glucose ≥100 and <126 mg/dL). These 2 groups were further subdivided in those with TG concentrations <150 or ≥150 mg/dL. Thus, the following 4 experimental groups were created: NFG&TG < 150; NFG&TG ≥ 150; PreDM&TG < 150; and PreDM&TG ≥ 150.

CAC was assessed by computed tomography scan using Imatron C-150XP, C-300 (Siemens, Malvern, PA), or LightSpeed VCT model (GE Healthcare, Princeton, NJ) and dichotomized into 2 CAC categories: (1) 0 vs >0 and (2) < 100 vs ≥100.

Statistical analyses

The collected data for each participant was based on 1 visit; for example, any repeat measures were not included in this analysis. Demographic and metabolic characteristics were summarized within each of the 4 experimental groups, and pairwise differences between the PreDM&TG ≥ 150 group and the other 3 groups tested using chi-square tests for nominal characteristics and rank-sum tests for continuous characteristics. Multiple logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals of CAC = 0 vs CAC > 0 and CAC <100 vs CAC ≥100, for the PreDM&TG ≥ 150 group compared with each of the other 3 groups. All models included the experimental group and were adjusted for CAD risk factors not known to be significantly associated with IR, for example, age, current smoking, and low-density lipoprotein cholesterol (LDL-C), but not for risk factors associated with IR, for example, high-density lipoprotein cholesterol, blood