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Comparison of two surrogate estimates of insulin resistance to predict cardiovascular disease in apparently healthy individuals

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Abstract *Background and aims:* Insulin resistance is associated with a cluster of abnormalities that increase cardiovascular disease (CVD). Several indices have been proposed to identify individuals who are insulin resistant, and thereby at increased CVD risk. The aim of this study was to compare the abilities of 3 indices to accomplish that goal: 1) plasma triglyceride × glucose index (TG × G); 2) plasma triglyceride/high-density lipoprotein cholesterol ratio (TG/HDL-C); and 3) Metabolic Syndrome (MetS).
Methods and results: In a population sample of 723 individuals (486 women and 237 men, 50 ± 16 and 51 ± 16 years old, respectively), baseline demographic and metabolic variables known to increase CVD risk and incident CVD were compared among individuals defined as high vs. low risk by: TG × G; TG/HDL-C; or MetS. CVD risk profiles appeared comparable in high risk subjects, irrespective of criteria. Crude incidence of CVD events was increased in high risk subjects: 12.2 vs. 5.3% subjects/10 years, $p = 0.005$ defined by TG/HDL-C; 13.4 vs. 5.3% subjects/10 years, $p = 0.002$ defined by TG × G; and 13.4% vs. 4.5% of subjects/10 years, $p < 0.001$ in subjects with the MetS. The area under the ROC curves to predict CVD were similar, 0.66 vs. 0.67 for TG/HDL-C and TG × G, respectively. However, when adjusted by age, sex and multiple covariates, hazard ratios for incident CVD were significantly increased in high risk patients classified by either TG/HDL-C ratio (2.18, $p = 0.021$) or MetS (1.93, $p = 0.037$), but not by TG × G index (1.72, $p = 0.087$).
Conclusion: Although the 3 indices identify CVD risk comparably, the TG × G index seems somewhat less effective at predicting CVD.

Introduction

Insulin-mediated glucose disposal varies more than six-fold in volunteers with a normal medical history, physical examination, routine clinical laboratory tests, as well as a normal oral glucose tolerance test [1]. Approximately one-quarter to one-third of the most insulin resistant segment of such a population is at significantly greater risk [2–5] of a number of metabolic abnormalities known to increase risk of cardiovascular disease (CVD). Although it seems clinically beneficial to identify these high risk individuals in order to attempt interventions that might prevent manifest disease, how best to accomplish this goal is not self-evident.

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The plasma insulin concentration in response to a 75 g oral glucose challenge in apparently normal individuals is the surrogate estimate of insulin resistance most closely correlated to direct measures of insulin resistance [1,6]. However, the absence of a standardized clinical insulin assay prevents establishment of a specific numerical cut-point that can be of general use to identify insulin resistant individuals [7]. Another approach is to use standardized measurements of changes closely associated with insulin resistance, and the characteristic dyslipidemia of insulin resistant individuals, high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) concentration, provided an attractive alternative [8]. The plasma concentration ratio of TG/HDL-C is significantly correlated with a direct measure of insulin-mediated glucose disposal [6], and sex-specific cut-points have been shown to identify apparently healthy individuals (without diabetes or CVD event) with cardio-metabolic risk profiles comparable to what was seen when these individuals met the diagnostic criteria for the metabolic syndrome (MetS) [9–11].

Guerrero Romero et al. [12] have taken a somewhat similar approach, using the fasting plasma TG and glucose concentration to create a mathematical formula (TG × G index) to serve as a surrogate estimate of insulin resistance, and shown that this value is significantly correlated with euglycemic clamp measurements of insulin action. More recently, data have been published showing that the TG/HDL-C ratio and the TG × G index are significantly correlated to a similar degree with insulin-mediated glucose disposal using the insulin suppression test [13].

Both of these approaches were initially evaluated because of their relationship to insulin resistance, but their ultimate clinical utility will depend upon their ability to serve as simple clinical measures with which to identify individuals at increased risk of diabetes, hypertension, and/or incident CVD associated with insulin resistance [2–5]. In that context, the TG/HDL-C ratio has previously been shown to predict incident CVD in apparently healthy persons [11]. More recently, Sánchez-Iñigo et al., have shown that the TG × G index can predict incident ischemic heart and peripheral artery disease [14]. Both approaches seem comparable in terms of their simplicity to identify a subset of individuals at significantly enhanced risk of developing CVD. However, the fact that they are similarly associated with a direct measure of insulin resistance [13] does not mean that they would be equally effective in predicting incident CVD. Thus, the current analysis was initiated to address this issue by comparing the ability of the TG × G index, the TG/HDL-C ratio and MetS criteria [15] to predict CVD outcome in individuals without diabetes or previous CVD event.

Methods

Study population

In 2003, as part of a community intervention program focused on cardio-metabolic risk factors, an epidemiological study was conducted in Rauch city, Buenos Aires, Argentina (RAUCH project, phase 2). According to the last national census available at the time of the survey, there were 8246 individuals ≥15 years old in the urban area of Rauch. The city lies in a rural area in the Centre-Southeast region of the province of Buenos Aires and the population is primarily of European origin. Blocks of the urban area of Rauch city were randomly selected; because there were no differences in socioeconomic factors or the number of inhabitants within the city, a proportional probability was not taken into consideration. Previously trained, nurses from Hospital Municipal of Rauch conducted the survey in the subject's place of residence. They went to the selected homes (on up to 3 occasions when necessary to measure BP, weight, and height and construct an epidemiological chart. To minimize the chance of rejection, before the study a diffusion campaign was performed that delivered written information about the study to each selected residence. Because the design was a prospective cohort study, the sample size was determined taking into account the possibility of losing track of subjects during the study. Twenty percent of the inhabitants were regarded as a suitable and affordable sample according to the economic resources available. The survey was performed from subjects between 15 and 80 years old who lived in chosen blocks (n = 1308, 855 women 51 ± 17 years old and 453 men 52 ± 16 years old, P between sexes = 0.63). Fifty-four subjects who had previously suffered CVD events were excluded. All measurements necessary for the present study were available in 926 individuals (622 women and 304 men).

In 2012, 796 individuals (86% of the baseline sample), 527 women and 269 men (or their relatives in case of death), could be surveyed again to obtain information concerning incident CVD events; the remaining inhabitants (n = 130) could not be found because they had moved from Rauch city. As previously published [11], there was no significant difference in the baseline characteristics between subjects with and without follow-up period. In order to avoid the effects of outliers, individuals with TG concentration >500 mg/dL or a HDL-C concentration >100 mg/dL were excluded [9–11]. Participants with a history of diabetes or a fasting glucose concentration ≥126 mg/dL were also excluded. The remaining 723 individuals (486 women, and 237 men) were included in the present analysis (Fig. 1).

Measurements

Clinical and biological variables were quantified as previously described [16]. In brief, weight was determined with individuals wearing light clothes and no shoes. Height also was measured without shoes, using a metallic metric tape; waist circumference was measured with a relaxed abdomen using a metallic metric tape on a horizontal plane above the iliac crest; body mass index (BMI) was calculated using the formula weight (kg)/height $(m)^2$. Concentrations of plasma glucose, TG, HDL-C, and fasting plasma insulin were determined after an overnight (12-h) fast. Low-density lipoprotein cholesterol (LDL-C) concentrations were estimated by the Friedewald formula [17].