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Insulin resistance is associated with carotid intima-media thickness in non-diabetic subjects. A cross-sectional analysis of the ELSA-Brasil cohort baseline

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ABSTRACT

Background and aims: Epidemiological studies have analyzed the association between carotid intima-media thickness (CIMT) and insulin resistance, glucose levels or glycated hemoglobin with mixed results. We aimed to evaluate the association between CIMT and homeostasis model assessment – insulin resistance (HOMA-IR), fasting and post-load plasma glucose and glycated hemoglobin in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) baseline.

Methods: We included 8028 participants (aged 35–74 years) without diabetes or overt cardiovascular disease who had complete CIMT data at baseline. We built crude and adjusted linear and binary logistic models to evaluate the association between CIMT and (a) HOMA-IR; (b) fasting plasma glucose; (c) post-load plasma glucose; and (d) glycated hemoglobin. We also built *post-hoc* models, stratified by sex.

Results: In the fully-adjusted linear models, only the association between CIMT (in mm) and HOMA-IR remained significant (β = 0.004; 95% confidence interval [95%CI]:0.001 to 0.006). Consistent with these results, only the association between the highest age- sex- and race-specific CIMT quartile and HOMA-IR was significant in the adjusted logistic model (odds ratio [OR]:1.10; 95% CI:1.04–1.17). The association between HOMA-IR and the highest CIMT quartile remained significant in sex-specific analyses (OR:1.10; 95% CI:1.02–1.20 for men and OR:1.10; 95% CI:1.02–1.20 for women). We did not find an independent association between CIMT and glucose or glycated hemoglobin.

Conclusions: We found a direct association between HOMA-IR and CIMT in a large sample of non-diabetic participants. Mechanisms unrelated to glucose homeostasis, as a direct effect of insulin on atherosclerosis, or medial hypertrophy, may be involved.

1. Introduction

Insulin resistance is the cornerstone of type 2 diabetes pathogenesis [1]. After an initial phase of compensatory hyperinsulinemia, post-prandial and fasting plasma glucose levels begin to rise, due to an imbalance between insulin demands and secretion, leading to the development of the disease [2]. It is well-known that high plasma glucose levels are a major risk factor for atherosclerotic cardiovascular disease [3], and additional risk may be present even in the non-diabetic range [4]. However, insulin resistance may be linked to atherosclerosis due to worse lipid profiles [5], a pro-inflammatory state [6], elevated blood pressure [7], and endothelial dysfunction as well [8].

Carotid intima-media thickness (CIMT) has been used as a surrogate measurement of the early phases of subclinical

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atherosclerosis, and has been shown to predict cardiovascular events [9–12]. Studies analyzing the association between insulin resistance and subclinical atherosclerosis assessed with CIMT have yielded positive [13,14] and negative [15,16] results. The relationship between CIMT and glucose or glycated hemoglobin levels is also controversial. A systematic review by Einarson et al. [17] found that individuals with impaired glucose tolerance had slightly (although significantly) higher CIMT values compared to individuals with normal glucose tolerance. Along similar lines, Neil Thomas et al. [18] found a positive association between fasting plasma glucose (in tertiles) and CIMT in 242 individuals without diabetes (aged 18–75 years) from the CATHAY study. Huang et al. [19] analyzed 1627 individuals with normal glucose tolerance and found a positive association between CIMT and glycated hemoglobin, but CIMT was not associated with fasting or 2-h post-load plasma glucose levels. Similar results were reported by Bobbert et al. [20].

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) is a multicenter cohort study of 15,105 individuals aged 35–74 years. Baseline assessment included the measurement of CIMT, HOMA-IR, fasting and post-load plasma glucose, and glycated hemoglobin levels. Compared to previous studies, ELSA-Brasil baseline assessment provides a very good scenario to evaluate a potential association between CIMT and insulin resistance or glucose measurements due to its large sample and comprehensive protocol. We hypothesized the associations between CIMT and insulin resistance or glucose measurements may be different in non-diabetic ELSA-Brasil participants without overt cardiovascular disease at baseline.

2. Materials and methods

2.1. Study design

The ELSA-Brasil study design [21] and cohort profile [22] have been described elsewhere. Briefly, ELSA-Brasil is a multicenter cohort study of 15,105 civil servants from six cities in Brazil (São Paulo, Belo Horizonte, Porto Alegre, Salvador, Rio de Janeiro, and Vitória) aimed to determine the incidence and risk factors for diabetes and cardiovascular diseases. All active or retired employees of the six institutions aged 35–74 years were eligible for the study. Exclusion criteria were current or recent (<4 months prior to the first interview) pregnancy, intention to leave employment at the institution in the near future, severe cognitive or communication impairment, and, if retired, residence outside of the study center's corresponding metropolitan area. Our sample includes volunteers (76%) and actively recruited participants (24%), the latter being recruited from listings of civil servants. Baseline assessment took place from August 2008 to December 2010 and included validated questionnaires and clinical and laboratory exams. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Approvals were granted from the institutional review boards of all the centers. All participants provided written informed consent.

2.2. Study sample

Of the 10,943 ELSA-Brasil participants with valid CIMT values for both common carotid arteries, we excluded 2101 (19.2%) participants who had a diagnosis of diabetes at the ELSA-Brasil baseline assessment or who were using hypoglycemic medications (WHO/ATC code A10) for any reason, as well as 12 (0.1%) individuals with missing data on diabetes classification or medication use. In addition, we excluded 259 (2.4%) participants with self-reported myocardial infarction, revascularization or stroke, 6 (0.1%) with missing data on overt cardiovascular disease, 296 (2.7%) participants who were Asian or Native (because of the low number of participants from these groups), 85 (0.8%) with missing race information, 141 (1.3%) with missing post-load plasma glucose tolerance test results, and 15 (0.1%) with missing insulin and/or glycated hemoglobin results. Therefore, our study sample comprises 8028 individuals (3396 men and 4632 women).

2.3. Study variables

The protocol for CIMT measurement has been detailed in previous publications [23,24]. In brief, a standardized protocol was applied in all centers using a clinical ultrasound scanner (Toshiba Aplio XG, Toshiba Corp., Tokyo, Japan) with a 7.5 MHz linear transducer. Common carotid artery intima-media thickness measurements were ECG gated (during three cardiac cycles) and automated using MIA software. All the participating centers obtained the carotid images and sent them to the centralized core reading center in São Paulo. CIMT was measured in the far wall of a pre-defined carotid segment, 1 cm in length, measured from 1 cm below the carotid bifurcation. For the analyses in this paper, we defined CIMT as the average of the mean left CIMT and the mean right CIMT values within an individual. We used CIMT as both a continuous variable or categorized, based on the CIMT distribution according to age, sex and race in the entire ELSA-Brasil sample [24]. This procedure has been used in previous analyses [25,26]. The cutoff at the 75th percentile of CIMT for a given age, sex, and race is considered to be a marker for increased cardiovascular risk [9]. Some analyses in this paper include this cutoff at the 75th percentile, considering individuals in the highest CIMT quartile as those with higher risk.

All participants in the sample had valid blood collections after a 12-h fast and 2 h after ingestion of a solution containing 75 g of glucose. Blood collection was performed on site at each ELSA-Brasil study center. All tubes were centrifuged under refrigeration, aliquoted, and cryopreserved. All laboratory measurements were performed at the central laboratory in São Paulo. Insulin concentrations were determined by immunoenzymatic assay [27]. Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated as (fasting plasma glucose (in mg/dl)*0.0555) * (fasting serum insulin (in mUI/L)/22.5) [28].

Race and smoking status were self-reported. We collected anthropometric measurements using standard protocols. Body mass index was calculated as weight (in kilograms) divided by height squared (in meters). Hypertension was defined as the use of medications to treat hypertension, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Dyslipidemia was defined as use of lipid-lowering treatment or a LDL cholesterol (LDL-c) level ≥ 130 mg/dl. Low HDL-cholesterol (HDL-c) was defined as HDL-c levels < 40 mg/dl for men and <50 mg/dl for women. Abdominal obesity was defined as waist circumference ≥102 cm for men and ≥88 cm for women. Excessive drinking was defined as an alcohol consumption >210 g/week for men and >140 g/week for women. Family history of premature cardiovascular disease (CVD) refers to a diagnosis of myocardial infarction, stroke, revascularization, or sudden death in a first-degree relative before age 60.

2.4. Statistical analysis

The categorical variables are presented as absolute counts and proportions and compared using chi-squared tests. Continuous variables are presented as mean ± standard deviations and compared using one-way ANOVA, or median [interquartile range] and compared using the Kruskal-Wallis test. We built four separate