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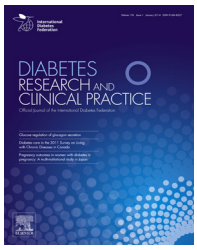

Novel biomarkers of cardiometabolic risk are associated with plasma glucose within non-diabetic range. The Brazilian Longitudinal Study of Adult Health – ELSA-Brasil

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ABSTRACT

Abnormal glucose metabolism preceding overt diabetes is associated with increased cardiovascular risk. Whether novel biomarkers are useful to identify this condition is unclear. The objective was to investigate associations of biomarkers of atherogenesis with plasma glucose within non-diabetic range. 998 participants (35–54 years) of the Brazilian Longitudinal Study of Adult Health without diabetes or cardiovascular disease were classified as normal glucose tolerance (NGT), impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT). Traditional risk factors and markers of atherogenesis were evaluated among groups and across plasma glucose concentrations. IFG and IGT had worse profile considering traditional cardiovascular risk factors than the NGT group, although these values were within the reference range. NGT, IFG and IGT groups differed (medians and interquartile intervals) regarding transforming growth factor-β1 [12.2 (6.4–22.3), 16.8 (8.4–26.5), and 15.5 (8.0–26.1) pg/mL, $p < 0.05$], C-reactive protein [1.1 (0.6–2.9), 1.2 (0.6–2.7), and 1.4 (0.8–3.7) ng/mL, $p < 0.001$] and monocyte chemoattractant protein-1 [35.9 (21.2–57.8), 32.2 (18.7–55.8), and 34.1 (18.6–52.4) pg/mL, $p < 0.05$]. TGF-β1 and E-selectin concentrations increased while MCP-1 decreased across quartiles of fasting plasma glucose. C-reactive protein increased with increments in 2-h plasma glucose. In linear regression, TGF-β1 was independently associated with fasting plasma glucose, and C-reactive protein with 2-h plasma glucose after adjustments. In conclusion, association of TGF-β1, E-selectin, C-reactive protein and MCP-1 with slight elevations in glycemia may be anticipating alterations in traditional cardiovascular risk factors. Independent association of TGF-β1 with plasma glucose suggests that this may be useful to identifying atherogenic process, deserving further investigation on the prediction of cardiovascular outcomes.

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Abbreviations: T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; CRP, C-reactive protein; BMI, body mass index; BP, blood pressure; Apo B, apolipoprotein B; TGF-β1, transforming growth factor β1; IL-6, interleukin-6; IL-10, interleukin-10; TNF-α, tumor necrosis factor α; MCP-1, monocyte chemoattractant protein-1.

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1. Introduction

Enhancing knowledge about the natural history and risk factors for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) is desirable to reduce major causes of morbidity and mortality [1]. The relevance of elevated plasma glucose as a cardiovascular risk factor has been recognized since the Framingham Heart Study [2]. Despite the recognized parallelism of deterioration of glucose metabolism and risk of CVD [3], the plasma glucose cut-off value remains a matter of discussion. Attempt to identifying more accurately individuals at higher cardiovascular risk has a direct impact in the number of people receiving the diagnosis of disturbed glucose metabolism, as well as in the amount of antidiabetic agents prescribed [4]. The categories of impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT) [5] should be seen not as clinical entities but risk factors for T2DM and health-adverse cardiovascular outcomes.

An important epidemiological study conducted in several European countries called attention to the importance of post-challenge glucose for cardiovascular mortality [6,7]. Two-hour plasma glucose after of 75-g glucose ingestion showed to be significantly associated with cardiovascular events in a stronger manner than the fasting glucose level. The impact of postprandial glycemia on morbidity and mortality, independent of T2DM diagnosis, has been reinforced [8–10]. Several studies have compared the effects of IGT and IFG on cardiometabolic outcomes [11] and a systematic review estimated the magnitude of risk for CVD associated with these categories based on prospective studies [12]. Both were shown to be associated with cardiovascular outcomes with modest increases in cardiovascular risk.

Changes in the reference cut-off for plasma glucose have been motivated by associations with risk of diabetic complications [13,14]. In 2003, the American Diabetes Association proposed values <100 mg/dL for normal fasting glycemia [15], although the World Health Organization and others have not adopt this change [16,17]. Based on the observations that cardiovascular outcomes occurred in a continuum [18], the term dysglycemia – referring to near-normal fasting plasma glucose levels – has been used [19]. In this early phase of natural history of T2DM pathophysiological mechanisms, such as low-grade inflammation and insulin resistance, contribute to atherogenesis [20,21].

Inflammatory adipose tissue-derived cytokines detected in circulation have been proposed as novel biomarkers of cardiometabolic risk [22]. The addition of high-sensitivity C-reactive protein (CRP) concentration to the traditional risk factors included in the Framingham cardiovascular risk score [23] was shown to improve prediction of outcomes in women and men [24,25]. CRP is involved in the immunologic process that triggers endothelial dysfunction and plaque formation [26], but definitive evidence for its role as a causative factor in atherothrombosis is lacking. Even greater is the debate concerning other circulating biomarkers of inflammation, insulin resistance, endothelium adhesion and fibrinolysis [27]. These biomarkers are increased in obesity and may have roles in atherogenesis [28–30].

In Brazil, a large multicenter cohort study, the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), has been conducted in 15,105 civil servants from six cities [31]. This will permit innovative investigation of multiple exposures and outcomes in longitudinal analysis, particularly T2DM and CVD. The availability of traditional cardiovascular risk factors, as well as a broad spectrum of novel biomarkers, represents an opportunity to describe their profile according to glucose tolerance status in a large sample of middle-aged adults.

This study investigated which novel biomarkers of inflammation and atherogenesis could be associated with plasma glucose within non-diabetic range in middle-aged Brazilians in a sample of participants of the ELSA-Brasil.

2. Material and methods

The ELSA-Brasil aims at investigating incidence of T2DM and CVD and their biological, behavioral, environmental, occupational, psychological and social risk factors. Details on objective and methodological aspects were previously reported [31]. Briefly, all active or retired employees of six Brazilian universities, aged 35–74 years, were eligible for the cohort study. First examinations of 15,105 individuals (54% women) were carried out from August 2008 through December 2010. The present analysis is a cross-sectional study using a subsample of participants from ELSA-Brasil research center from the University of São Paulo. A random sample of 1000 individuals without diabetes and CVD and age between 35–54 years was drawn from all the 5061 participants of ELSA-Brasil in São Paulo. Two individuals were excluded from the final sample due to insufficient aliquots frozen for the analysis of novel biomarkers. The institutional ethics committee approved the study and written consent was obtained from all individuals.

Participants had an initial interview at the job site and then they were scheduled for clinical examination and laboratory tests in the research center. Body weight and height were measured using calibrated electronic scales and a fixed rigid stadiometer, while individuals wore light clothing without shoes. Body mass index (BMI) was calculated as weight (kilograms) divided by squared height (meters). Waist circumference was measured with an inextensible tape according to the WHO technique. Blood pressure (BP) was taken three times after a 5-min rest in the sitting position. The mean of the second and third measurements was used [32].

After overnight fasting, blood samples were taken for several determinations. They underwent a 2-h 75-g oral glucose tolerance test. American Diabetes Association diagnostic criteria were used for diagnosing IFG (fasting plasma glucose ≥100 mg/dL and <126 mg/dL and 2-h plasma glucose <140 mg/dL) and IGT (2-h plasma glucose ≥140 mg/dL and <200 mg/dL and fasting plasma glucose <126 mg/dL) [5].

Plasma glucose was measured by the hexokinase method (ADVIA Chemistry; Siemens, Deerfield, IL, USA) and lipid profile was determined by enzymatic colorimetric assay (ADVIA Chemistry; Siemens, Deerfield, IL, USA) and low-density lipoprotein cholesterol was calculated by means of the Friedewald equation. When triglyceride concentration was greater than 400 mg/dL, the high-density lipoprotein