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Relationships between adipokines, biomarkers of endothelial function and inflammation and risk of type 2 diabetes

C. Julia [a,b,*], S. Czernichow [c,d,e], N. Charnaux [f], N. Ahluwalia [a], V. Andreeva [a], M. Touvier [a], P. Galan [a], L. Fezeu [a]

[a] Equipe de Recherche en Epidémiologie Nutritionnelle (EREN), Centre de Recherche en Epidémiologies et Biostatistiques Sorbonne Paris Cité (CRESS) U1153 Inserm; U1125, Inra; Cnam; Université Paris 13, Université Paris 7, Uniersité Paris 5, Bobigny, France

[b] Département de Santé Publique, Hôpital Avicenne (AP-HP); Université Paris 13, Bobigny, France

[c] INSERM, U1018, Centre for Research in Epidemiology and Population Health, Villejuif, France

[d] Université Versailles St-Quentin, Boulogne-Billancourt, France

[e] APHP, Hôpital Ambroise Paré, Service de Nutrition, Boulogne-Billancourt, France

[f] Department of Biochemistry, Jean-Verdier Hospital (AP-HP), Bondy, France

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ABSTRACT

Aims: Identification of novel biomarkers of diabetes risk help to understand mechanisms of pathogenesis and improve risk prediction. Our objectives were to examine the relationships between adipokines, biomarkers of inflammation and endothelial function and development of type 2 diabetes; and to assess the relevance of including these biomarkers in type 2 diabetes prediction risk models.

Methods: 1345 subjects from the SU.VI.MAX study, who were free of diabetes at baseline and who completed 13 years of follow-up were included in the present analyses. Odds ratios (OR) with 95% confidence intervals (95% CI) of incident type 2 diabetes associated with a 1-SD increase in adiponectin, leptin, C-reactive protein (CRP), soluble intracellular adhesion modecule-1 (sICAM-1), soluble vascular cell adhesion molecule 1 (sVCAM-1), E-selectin and monocyte chemoattractant protein-1 (MCP-1) were estimated. Predicitive performances of models including biomarkers were assessed with area under the receiver operating curves (AUC) and integrated discrimination improvement (IDI) statistics.

Results: 82 subjects developed type 2 diabetes during follow-up. The risk of developing type 2 diabetes increased with increasing concentrations of leptin (2.04 (1.28;3.26)), sICAM-1 (1.39 (1.08;1.78)) and sVCAM-1 (1.29 (1.01;1.64)). Type 2 diabetes associations with leptin remained significant after adjusting for a combination of biomarkers. Models adjusted for novel biomarkers had improved performance compared to models adjusted for classical risk factors as assessed by IDI, but not by AUC.

* *Corresponding author at*: Equipe de Recherche en Epidémiologie Nutritionnelle (EREN), Centre de Recherche en Epidémiologies et Biostatistiques Sorbonne Paris Cité (CRESS) U1153 Inserm; U1125, Inra; Cnam; Université Paris 13, Bâtiment SMBH, 74 rue Marcel Cachin, F-93017 Bobigny, France. Tel.: +33 148388953; fax: +33 148388931.
E-mail address: c.julia@uren.smbh.univ-paris13.fr (C. Julia).

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Conclusions: Adipokines, biomarkers of inflammation and endothelial function were significantly associated to onset of type 2 diabetes. However their inclusion in predictive scores is not supported by the present study.

1. Introduction

Epidemiological research has recently focused on the identification of novel biomarkers implicated in the development of insulin resistance and type 2 diabetes [1], with an emphasis on antioxidants [2,3], adipokines [4–6], inflammatory cytokines [7–9] and endothelial function biomarkers [10]. Adipokines most consistently studied are adiponectin and leptin, which are solely secreted by adipose tissue and act as hormones with antagonistic effects. While adiponectin is suggested to have anti-inflammatory and insulin-sensitizing properties, leptin is thought to have pro-inflammatory effects and its increase in obese subjects has been related to insulin resistance [11]. The pattern of secretion of these adipokines reflects adipose tissue dysfunction, associated with endocrinopathy. Inflammation is also involved in the development of insulin resistance: obesity is characterized by a chronic low-grade inflammatory response which inhibits downstream signaling of insulin receptors [12,13]. More recently, endothelial dysfunction [14] has also been linked to the development of insulin resistance, as increased expression of adhesion molecules (soluble intracellular adhesion modecule-1 (sICAM-1), soluble vascular cell adhesion molecule 1 (sVCAM-1), E-selectin) has been associated with risk of incident type 2 diabetes [15]. Biological pathways are complex and predominant ones have not been clearly identified. Moreover, if these biomarkers provide new insights on pathogenesis, it is not certain that their inclusion in diabetes prediction algorithms would provide information beyond that obtained with well-known risk factors such as anthropometry and classical biological risk factors (glycemia, lipid concentrations) [1,16]. The objectives of this study were (1) to examine the associations between incident type 2 diabetes and adipokines, biomarkers of inflammation and endothelial function; (2) to evaluate the additonal contribution of new biomarkers to well-known risk factors in the prediction of type 2 diabetes.

1.1. *Subjects*

This study is an ancillary protocol of a nested case-control study. Subjects were selected from the SU.VI.MAX (SUpplémentation en VItamines et Minéraux AntioXydants) study, a double-blind placebo-controlled randomized primary prevention trial designed to assess the effect of a daily antioxidant supplementation on the incidence of cardiovascular disease and cancer [17]. Inclusion of 35–60 years-old women and 45–60 years-old men began in 1994–1995 for a planned follow-up of 8 years. In 2006, participants who had completed the SU.VI.MAX study in 2002 were invited to enroll in a new prospective study, the SU.VI.MAX 2 study, on the impact of nutrition on aging, thus prolonging follow-up duration [18]. Subjects provided written informed consent to participate in the study and both the SU.VI.MAX and the SU.VI.MAX2 studies were approved by the Ethics Committee for Studies with Human Subjects of Paris-Cochin Hospital (no. 706 and no. 2364, respectively) and the Comité National Informatique et Liberté (no. 334641 and no. 907094, respectively). The initial nested case-control study included all cases of cancer and cardiovascular disease diagnosed during follow-up and controls free these diseases during follow-up (two controls for each case). Cases and controls were matched on sex, age, BMI and initial supplementation group in the trial phase of the SU.VI.MAX study. Subjects with available data on adipokines, biomarkers of endothelial disfunction and inflammation, who were free of diabetes at baseline and with known diabetes status up to 13 years later were eligible for analyses. Further exclusions were made for subjects with missing data on any of the following covariates: sex, age, supplementation allocation in the initial SU.VI.MAX study, family history of diabetes, anthropometric measurements, glycemia and lipid concentrations.

2. Materials

At inclusion, socio-demographic, health status, medical and family history and anthropometric measurements (weight and height) data were collected. Blood samples were drawn, a part of which were immediately frozen at −80 °C and used to determine the following plasma biomarkers' levels for a subsample of the initial SU.VI.MAX cohort: adiponectin, leptin, CRP, sICAM-1, sVCAM-1, E-selectin and MCP-1. Biomarkers' levels were determined with ELISA sandwich technique (R & D laboratory Systems). Intra-assay (IACV) and inter-assay (IRCV) coefficients of variation were all <10%. CRP had the lowest (1.6%) and MCP-1 had the highest (6.2%) IACV, and CRP had the lowest (3.6) and E-selectin had the higest (9.1%) ICRV.

Follow-up included information on current diabetes medication at years 8 and 13. Fasting plasma glucose (FPG), total cholesterol and triglycerides concentrations were obtained at years 3, 5, 6 and 13. Subjects were considered to have incident type 2 diabetes if they had a FPG ≥7.0 mmol/l at any follow-up biological test or if they were under antidiabetic medication at any follow-up investigation.

3. Methods

Body mass index (BMI) was computed as weight (in kg) divided by the square of height (in m). Descriptive statistics were summarized as mean (±SD) for continuous variables or median (25th–75th percentiles) for continuous variables with skewed distributions. The latter variables were log-transformed before