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Reduced serum beta-trace protein is associated with metabolic syndrome

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ABSTRACT

Objectives: β-trace protein (BTP), also known as lipocalin-type prostaglandin D2 synthase, has shown to regulate glucose and lipid metabolism *in vivo*. We sought to study the relationship of serum BTP with diabetes and metabolic syndrome (MetS).
Methods: Data on 3136 participants aged ≥20 years of the National Health and Nutrition Examination Survey III were examined. Logistic regression was used to assess the association of BTP with diabetes and MetS.
Results: Reduced levels of BTP were associated with diabetes and MetS in age, sex, and race/ethnicity adjusted models. After further multivariable adjustment, BTP levels in quartile 1 remained significantly associated with MetS (odds ratio 2.04 [95% CI 1.14–3.70], $P_{trend} = 0.003$) when compared with quartile 4. Among the five components of MetS, BTP was associated with hypertriglyceridemia ($P_{trend} < 0.001$) but not diabetes ($P_{trend} = 0.099$).
Conclusion: MetS is associated with a reduced serum level of BTP.

1. Introduction

β-trace protein (BTP) is a lipocalin-type prostaglandin D2 synthase (L-PGDS). It is expressed in adipose and other tissues, and is secreted into the circulation [1]. The main function of L-PGDS is to convert prostaglandin (PG)H_2 to PGD_2. PGD_2 has diverse physiological actions including inhibition of platelet aggregation [2], recruitment of inflammatory cells [3], and induction of vasodilatation and bronchoconstriction [4]. Moreover, PGD_2 can be further metabolized to PGJ_2, which is a potent ligand for peroxisome proliferator-activated receptor-γ [3]. It is a critical transcription factor for the differentiation of adipocytes and macrophages. Therefore, L-PGDS may have a role in adipocyte and macrophage development and function, and hence in the pathogenesis of diabetes and the metabolic syndrome.

In humans, BTP was first isolated from cerebrospinal fluid and can be used for detecting leakage of cerebrospinal fluid [5]. It has also been proposed as a marker of kidney function [6]. Another member of the lipocalin family, lipocalin-2, is associated with obesity and insulin resistance [7]. Therefore, we examined the relationship of serum BTP with diabetes and metabolic syndrome (MetS) in the participants of the National Health and Nutrition Examination Survey (NHANES).

2. Research design and methods

2.1. Participants recruitment

Data from NHANES III were used [8]. The NHANES survey included a stratified multistage probability sample which represented the civilian non-institutionalized U.S. population. Selection was based on counties, blocks, households, and individuals within households. It also included non-Hispanic blacks and Mexican-Americans to provide an adequate estimate of these ethic groups. Participants were required to sign a consent form before their

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participation, and approval was obtained from the Human Subjects Committee of the U.S. Department of Health and Human Services.

This study included participants aged 20 or above whose BTP and fasting glucose data were available ($N = 4251$). Pregnant participants or participants with missing data in the multivariable models were excluded. After exclusion, 3136 participants were included in the analysis.

2.2. BTP measurements

Serum BTP was measured using the N Latex β-trace protein assay (Siemens Diagnostics, IL). The assay range was 0.23–7.25 mg/dl. The inter-assay coefficient of variation for the BTP assay was 5.7% (mean 0.594 mg/l).

2.3. Definition of diabetes

Plasma glucose and insulin were measured from fasting blood samples (fasted for 8–24 h) using a hexokinase enzymatic method (COBAS MIRA; Roche Diagnostics, Indianapolis, IN) and RIA (Pharmacia Diagnostics, Uppsala, Sweden), respectively. Glycohemoglobin (A1C) was measured using an ion-exchange HPLC method with a Diamat Analyzer System. Diabetes was defined by the presence of one or more of the following conditions: 1) A1C $\geq$ 6.5%; 2) fasting glucose $\geq$ 126 mg/dl; 3) self-report of diabetes; or 4) use of diabetes medications (oral hypoglycemic agents and/or insulin). The coefficient of variation was 1.6–3.7%, 5.9–13.8%, and 1.1–3.1% for fasting glucose, insulin, and A1C, respectively.

2.4. Definition of MetS

MetS was defined using the Adult Treatment Panel definition [9]: three or more of the following factors: 1) Hypertension: Systolic $\geq$ 130 mmHg and/or diastolic $\geq$ 85 mmHg and/or participants who received anti-hypertension drug therapy. 2) Triglycerides: $\geq$150 mg/dl (1.69 mmol/l); 3) HDL cholesterol: <40 mg/dl (1.03 mmol/l) in men and <50 mg/dl (1.29 mmol/l) in women; 4) Plasma glucose: $\geq$100 mg/dl (5.6 mmol/l) and/or participants who received treatment for elevated glucose, and 5) Waist circumference: >102 cm in men and >88 cm in women. The methods of measurement of serum cholesterol, triglycerides, and HDL cholesterol are given in the supplemental appendix.

2.5. Statistical analyses

We categorized the level of serum BTP into quartiles. Using the lowest quartile as the reference, the odds ratio (OR) and 95% CI of diabetes and MetS for each quartile were calculated using univariable and multivariable logistic regression models. The definitions of co-variables are stated in the supplemental appendix. A P-value of $\leq$0.05 was considered statistically significant. Variables with skewed distributions were natural log-transformed before analysis. Sample weights that account for the unequal probabilities of selection, oversampling, and nonresponse were applied in all analysis using the complex sampling module in SPSS version 18.0 software (SPSS Inc, Chicago, IL). All values presented are weighted to represent the U.S. civilian population.

3. Results

3.1. Participant characteristics

Participants with higher serum BTP were older, more likely to be non-Hispanic white, and former smokers. Serum BTP levels were positively associated with age, waist circumference, systolic blood pressure, serum total cholesterol, CRP, A1C, AST, ALP, and MetS, and negatively associated with current smoker, active drinker, serum albumin, ALT, and eGFR (Table 1).

3.2. Association of serum BTP with diabetes

In the unadjusted model, no significant association was observed (Table 2). After adjustment for age, sex, and race/ethnicity, the trend of diabetes across quartiles of serum BTP levels was significantly decreased ($P_{trend} < 0.001$). Compared with quartile 1, all other quartiles were associated with lower odds of diabetes with multivariable ORs (95% CI) of 0.50 (0.32–0.79), 0.29 (0.14–0.57) and 0.23 (0.13–0.42) for quartiles 2–4, respectively. However, the association became insignificant after further adjustment in model 2 that further adjusted for lifestyle factors (physical activity, smoking, drinking), inflammatory markers (CRP, serum albumin), cardiometabolic risk factors (BMI, serum total cholesterol, triglycerides, HDL cholesterol, mean arterial pressure), eGFR, and liver enzymes (Table 2, $P_{trend} = 0.099$). Stratification by sex showed similar results, although a stronger association was observed in women (Supplementary Table 1).

3.3. Association of serum BTP with MetS

In the unadjusted model, there was a marginally significant association between serum BTP and MetS (Table 2, $P_{trend} = 0.044$). After adjustment for age, sex and race/ethnicity, serum BTP levels were associated with lower odds of MetS ($P_{trend} = 0.006$) in quartiles 2–4; when compared with quartile 1, the multivariable ORs (95% CI) of MetS were 0.61 (0.44–0.84), 0.45 (0.28–0.71) and 0.49 (0.27–0.89) for quartiles 2–4, respectively. Further adjustment in model 2 for lifestyle factors (physical activity, smoking, drinking), inflammatory markers (CRP, serum albumin), cardiometabolic risk factors (BMI, serum total cholesterol), eGFR, and liver enzymes did not attenuate the associations. Stratification by sex showed similar results, although a stronger association was observed in women (Supplementary Table 2). Using the International Diabetes Federation definition of MetS revealed similar or even stronger associations (Supplementary Table 3). Among the five components of MetS, BTP was associated with hypertriglyceridemia with a $P_{trend} < 0.001$, while a small but insignificant association was observed between BTP and elevated fasting glucose ($P_{trend} = 0.099$) (Supplementary Table 3). When both BTP and dependent variables were modeled as continuous variables, significant associations were observed between BTP and blood pressure or triglycerides (Supplementary Table 4).

4. Discussion

This is the first study to demonstrate a definite correlation between serum BTP and MetS. In this nationally representative sample, serum BTP levels were negatively associated with MetS, and these associations were not dependent on any known metabolic risk factor.

Our novel findings are consistent with previous studies in mice. L-PGDS knockout mice showed accelerated glucose intolerance and insulin resistance when they were fed a diabetogenic diet [10]. Several studies had shed light on the role of BTP in the pathophysiology of MetS. L-PGDS is a carrier of lipophilic biomolecules, some of which are associated with adipogenesis and MetS, such as thyroid hormone [11] and retinoids [12]. Moreover, the metabolites of L-PGDS are involved in the regulation of inflammation [3]. L-PGDS and its downstream products, such as PGD_2 and PGJ_2s, are involved in adipogenesis [13,14]. During pre-adipocyte differentiation, there is a decrease in expression of PGD_2 and PGJ_2, whereas L-