Clinica Chimica Acta 469 (2017) 26–30

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Plasma proANP$_{1–98}$ levels are positively associated with central obesity: A cross-sectional study in a general population of China

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ARTICLE INFO

Keywords:
Plasma proANP
Waist circumference
Central obesity
Chinese
Cross-sectional study

ABSTRACT

Background: Atrial natriuretic peptide (ANP) and its prohormone activating enzyme are associated with central obesity, suggesting there may be a potential relationship between proANP$_{1–98}$ and central obesity. However, the association is still lack of population-based evidence. We explored the association in a general population of China.

Methods: We measured plasma proANP$_{1–98}$, waist circumference and other traditional biomarkers in 2203 participants aged ≥ 30 y. Multivariate logistic regression models were used to determine the association between plasma proANP$_{1–98}$ and central obesity, and odds ratio (OR) and 95% confidence interval (CI) were calculated.

Results: High proANP$_{1–98}$ was significantly associated with increased risk of central obesity in participants, and the multivariate adjusted OR (95% CI) of central obesity associated with the second, third and fourth quartiles of proANP$_{1–98}$ were 1.33 (1.03–1.72), 1.69 (1.31–2.19) and 1.76 (1.35–2.29), respectively, compared with the lowest quartile of proANP$_{1–98}$. There was a dose-response relationship between proANP$_{1–98}$ and risk of central obesity among the participants (P$_{trend}$ AMPlt; 0.001). Sensitivity analyses further confirmed these associations. Adding proANP$_{1–98}$ to a model containing conventional risk factors improved discriminatory power of central obesity (as shown by significant improvement in continuous NRI and IDI).

Conclusions: Contrary to known reduced ANP levels in central obesity, we found that plasma proANP$_{1–98}$ was positively associated with central obesity, suggesting that elevated plasma proANP$_{1–98}$ may be a marker or a risk factor for central obesity.

1. Introduction

Obesity is a global pandemic and its prevalence has more than doubled in the last 30 y, resulting in a staggering disease burden around the world [1]. It is widely accepted that central obesity is more closely related to metabolic and cardiovascular complications than general obesity [2,3], and visceral adipose tissue is associated with a greater atherosclerotic risk profile than subcutaneous fat when present in excess [4–6]. Although existing strategies to prevent central obesity through lifestyle improvements and medical intervention have achieved some success, but there is still room for further improvement [7]. Some unknown risk factors for central obesity need to be studied to improve central obesity prevention and control.

Atrial natriuretic peptide (ANP) plays a key role in maintaining extracellular fluid volume and normal blood pressure [8]. In the past decade, accumulating evidence has demonstrated that circulating ANP was reduced in individuals with central obesity [9–11]. As we all know, corin is the only activating enzyme of proANP$_{1–126}$ which is the prohormone of ANP [12,13] and it has been suggested to be associated with central obesity in cell- and animal-based studies [14–16]. Furthermore, our previous epidemiological study found a higher serum soluble corin concentration in individuals with central obesity compared to those without central obesity [17]. Cleavage of proANP$_{1–126}$ releases equimolar amounts of the biologically active peptide ANP and inactive proANP$_{1–98}$ into the circulation [13,18]. These evidences suggest that there may be a potential association between plasma proANP$_{1–98}$ and central obesity.

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http://dx.doi.org/10.1016/j.cca.2017.03.019
Received 28 October 2016; Received in revised form 16 March 2017; Accepted 17 March 2017
Available online 19 March 2017
0009-8981/

2. Methods

2.1. Study participants

We conducted a cross-sectional study in a traditional but economically developed district of Suzhou from January to May, 2010. The participants were selected via multiphase cluster random sampling. From the total 20 urban communities and 19 rural villages in the district, 4 urban communities, and 4 rural villages were randomly selected as the research fields. The residents aged ≥ 30 y living in the 4 urban communities and 4 rural villages were selected as subjects. The exclusion criteria were to meet one of the followings: (1) having clinical suspicion of diseases which may cause secondary hypertension (e.g., renal artery stenosis, coarctation, glomerulonephritis, pyelonephritis, phaeochromocytoma, Cushing's syndrome, Conn's syndrome), (2) self-reported history of coronary heart disease, stroke, or tumors, (3) self-reported thyroid or parathyroid diseases, (4) being pregnant. There were a total of 3061 eligible residents in the study fields, but only 2706 (participating rate: 88%) persons participated in this study. Among 2706 participants, 503 were excluded because they refused to offer blood samples, or some collected samples were hemolyzed in transport or storage, or failed to measure plasma $proANP_{1–98}$ levels, a total of 2203 participants were finally included in current analysis. This study was approved by the Soochow University Ethics Committee. Written informed consent was obtained from all study participants.

2.2. Data collection

Data on demographic information, lifestyle risk factors, and personal medical history were collected with standard questionnaires in Chinese language administered by trained staff. Cigarette smoking was defined as having smoked at least 1 cigarette per day for 1 year or more and reported current smoking. Alcohol consumption was defined as consuming any type of alcohol beverage at least once per week during the last three years. Body weight and height were measured using a regularly calibrated stadiometer and balance-beam scale with subjects wearing light clothing and no shoes. Waist circumference (WC) was measured at the level of 1 cm above the umbilicus. For this analysis, central obesity was defined as WC ≥ 85 cm for men and as WC ≥ 80 cm for women based on the recommendations of the Working Group on Obesity in China [19]. Three consecutive sitting blood pressure (BP) measurements (30 s interval between each) were measured by trained staff using a standard mercury sphygmomanometer according to a standard protocol [20], after the subjects had been resting for at least 5 min. The first and fifth Korotkoff sounds were recorded as systolic BP (SBP) and diastolic BP (DBP), respectively. The mean of the three records was used in analysis. Hypertension was defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg or use of antihypertensive medication in the last 2 weeks [21].

Blood samples were collected in EDTA-containing tubes by venipuncture in the morning after a requested overnight fast (at least 8 h). All plasma and serum samples were frozen at − 80 °C until laboratory testing. Total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol, low density lipoprotein cholesterol, and fasting plasma glucose (FPG) were measured for all participants. All the biochemical indexes were analyzed enzymatically on Hitachi 7020 automatic biochemical analyzer using commercial reagents. Intra- and inter-assay CVs were AMPlt;2% and AMPlt;4%, respectively. Diabetes was defined as FPG ≥ 7.0 mmol/l or use of hypoglycemic medication in the last 2 weeks [22]. Dyslipidemia was defined as TC ≥ 6.22 mmol/l or LDL-C ≥ 4.14 mmol/l or TG ≥ 2.26 mmol/l or HDL-C $AMP $lt; 1.04 mmol/l or use of lipid-lowering drugs in the last 2 weeks [23]. ProANP (1–98) ELISA No. BI-20892 kits (BIOMEDICA, AUSTRIA) was used to examine soluble $proANP_{1–98}$ concentration in plasma samples. All the samples were processed in a duplicate assay. A standard curve was constructed and from which $proANP_{1–98}$ concentrations of unknown samples were determined. Intra- and inter-assay coefficients of variation were AMPlt;2% and AMPlt;4%, respectively.

2.3. Statistical analysis

Baseline characteristics were presented and compared between the participants with central obesity and those without central obesity. Comparisons in rates for categorical variables were performed by using the χ^2 test. Comparisons in means of continuous variables (normal distribution) and in medians of continuous variables (skewed distribution) were analyzed by using Student's *t*-test and Wilcoxon rank-sum test, respectively. Multivariate non-conditional logistic regression models were used to assess the association of plasma $proANP_{1–98}$ with central obesity. All participants were divided into 4 groups according to the quartiles of plasma $proANP_{1–98}$ concentration in men and women, respectively. The quartile values of plasma $proANP_{1–98}$ were 0.63, 1.04, and 1.51 nmol/l in men and 0.68, 1.15, and 1.69 nmol/l in women. Odds ratios (OR) and 95% confidence intervals (CI) of central obesity were calculated for upper quartiles of $proANP_{1–98}$ with the lowest quartile as a reference. Trends for the ORs of central obesity across increasing $proANP_{1–98}$ categories were determined, having $proANP_{1–98}$ category as an ordinal variable. In addition, the potential covariates such as age, sex, current smoking, alcohol consumption, family history of hypertension, SBP, DBP, TC, TG, LDL-C, HDL-C and FPG were included in the multivariate models. We further used nonparametric restricted cubic splines to explore the shape of relationship between plasma $proANP_{1–98}$ and central obesity, with 4 knots defined at the 5th, 35th, 65th, and 95th percentiles of $proANP_{1–98}$ [24].

Some studies have found that hypertension, diabetes and dyslipidemia can affect the plasma $proANP_{1–98}$ [25–27]. Therefore, in order to weaken or even eliminate the confounding effects of these diseases on the relationship between plasma $proANP_{1–98}$ and central obesity, we performed sensitivity analyses which repeated the multivariate non-conditional logistic regression models after excluding the subjects with hypertension, diabetes and dyslipidemia, respectively. We also used the continuous net reclassification index (NRI) and integrated discrimination improvement (IDI) statistics [28] to assess whether inclusion of high plasma $proANP_{1–98}$ concentration (alone or together) improved discriminatory abilities for risk of central obesity. A 2-tailed *P* $AMP $lt; 0.05 was considered statistically significant. SAS statistical software (ver 9.4) and R statistical software (ver 2.15) were used for data analysis.

3. Results

3.1. Baseline characteristics of study participants

A total of 2203 participants, including 842 males and 1361 females, were included in the present analysis and average age was 53 y (from 30 to 80 y). Among them, 1165 (52.88%) participants were central obesity. The baseline characteristics of study participants were presented in Table 1. Participants with central obesity were more likely to be older, males, hypertensive, have higher levels of SBP, DBP, TC, TG, LDL-C, and FPG, and have a lower level of HDL-C compared with those with a normal WC (all *P* values AMPlt; 0.05). The median concentration of plasma $proANP_{1–98}$ was significantly higher in the participants with central obesity than that in those with normal WC (0.99 vs. 1.18 nmol/l, *P* AMPlt; 0.05).

3.2. Association between plasma $proANP_{1–98}$ and central obesity

The association between plasma $proANP_{1–98}$ and central obesity was shown in Table 2. After adjustment for age, sex, current smoking, alcohol consumption, family history of hypertension, SBP, DBP, TC, TG, LDL-C, HDL-C and FPG, the participants in the second (OR = 1.33,