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Cross-sectional and longitudinal associations between serum testosterone concentrations and hypertension: Results from the Fangchenggang Area Male Health and Examination Survey in China

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ABSTRACT

Background: Low testosterone concentrations have been suggested as a risk factor for hypertension, but their contribution to the development of hypertension is not well studied. We carried out a cohort study based on the results of an earlier cross-sectional investigation. We established the association between testosterone concentrations and hypertension.

Method: Data on 2427 healthy male subjects, aged from 17 to 88 y, were collected for the cross-sectional study. A representative sample of 853 individuals who did not suffer from hypertension at baseline was followed up for 4 y. Differences between the tertiles groups of sex hormones were analyzed, relative risks (RR) were estimated using binary logistic regression model.

Results: In the cross-sectional analysis, the serum total testosterone (TT), free testosterone (FT), and bioavailable testosterone (BT) concentrations of the hypertensive population were lower than those of the non-hypertensive population. Binary logistic regression analysis showed that TT, BT, and FT were inversely associated with hypertension. Moreover, decreasing odds ratio (OR) was observed from the lowest tertile group to the highest tertile group. After multivariate adjustment, the correlation between FT, BT, and hypertension was attenuated. Statistically significant differences remained only in the middle tertile group of TT and in the highest tertile group of TT, FT, and BT. In the longitudinal analysis, the 4-y incidence of hypertension was higher in participants with lower TT than in those with higher TT. Subjects in the middle and highest tertile groups of TT had an RR of 0.35 (0.22–0.57) and 0.30 (0.18–0.50), respectively (P for trend < 0.001). After further adjustments, these associations still remained statistically significant.

Conclusions: Serum TT, FT, and BT concentrations were inversely associated with blood pressure in man, and TT independent of age and body mass index (BMI) influences the development of hypertension. Furthermore, TT can be employed as a risk marker for hypertension in the identification of high-risk individuals.

1. Introduction

Hypertension, a major risk factor for cardiovascular disease (CVD), is a growing public health concern worldwide. In China, the prevalence of hypertension among adults is high [1]. Testosterone plays an important role in males as it regulates reproductive function and lipid and

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protein metabolism. Aside from obesity, hypertension, dyslipidemia, metabolic syndrome, and type 2 diabetes mellitus (T2DM), low testosterone concentrations in men have been suggested to be a novel risk factor for CVD [2,3]. Pietri found that plasma TT is independently and inversely associated with central blood pressure (BP) and wave reflections [4]. The same result was obtained by Svartberg, stating that lower concentrations of testosterone in men are associated with higher BP, left ventricular mass, and left ventricular hypertrophy [5].

Low testosterone concentrations in men have been suggested to be an independent risk factor for hypertension or CVD, but its contribution to hypertension development is not well studied. Prior longitudinal studies have suggested that TT can be used as a potential biomarker for increased CVD risk. Torkler et al. conducted a 5-y prospective cohort study and found that men with TT concentrations in the lowest quartile group had an increased risk of incident hypertension relative to men with higher TT concentrations [6]. Congruently, other studies have shown that low plasma testosterone/low sex hormone-binding globulin (SHBG) concentrations are correlated with or predict the occurrence of metabolic syndrome or atherosclerosis [7,8]. Men with low testosterone are advised to take testosterone replacement therapy (TRT) as an early preventive measure for cardiovascular events. However, whether or not testosterone replacement helps decrease the morbidity rate from CVD is still under controversy. Testosterone affects men's body composition by decreasing visceral fat deposition and increasing adipocytokine and pro-inflammatory cytokine secretion, which are helpful in lowering BP [9,10]. However, many studies suggested that TRT treatment as the sole intervention will not help in decreasing BP. Hoyos et al. reported that 18 weeks of TRT in obese men with severe obstructive sleep apnea decreases arterial stiffness but has no effect on BP [11]. Another study on Asian Indian men with T2DM and hypogonadism also concluded that testosterone treatment exerts a neutral effect on insulin resistance and glycemic control and fails to improve dyslipidemia, control BP, or reduce visceral fat [12]. Furthermore, the protective cardiometabolic effect of long-term TRT is not yet known [13].

2. Materials and methods

2.1. Participants

The participants were recruited from the Fangchenggang Area Male Health and Examination Survey (FAMHES), which was initiated in 2009 in Fangchenggang City, Guangxi, China. We carried out a cohort study based on the results of an earlier cross-sectional investigation (Fig. S1). Briefly, 4303 male participants in the study completed a physical examination at the Medical Centre of Fangchenggang First People's Hospital from September 2009 to December 2009. In 2013, subjects of the cohort study underwent physical examination in the same hospital, wherein the physiological and biochemical indexes of the sample population were measured once again.

Subjects who met the following criteria that might influence BP or whose sex hormone concentrations were not measured will be excluded: (1) currently diagnosed with diabetes mellitus, coronary heart disease, stroke, rheumatoid arthritis, or cancer; (2) taking any kind of medication; (3) with impaired hepatic function (alanine transaminase > 2.0 times the normal upper limit); (4) with impaired renal function (serum creatinine > 178 μmol/l); (5) without sex hormone results. A total of 2427 participants were included in the baseline survey.

We excluded the participants who met the following criteria: (1) diagnosed with baseline hypertension and (2) no communication. 995 participants were selected for the 4-y follow-up cohort study. After 4-y follow-up, we excluded 102 participants due to incompleteness data, eventually, 853 participants were included in cohort study. All subjects provided written informed consents, and the study was approved by the Ethics and Human Subject Committee of Guangxi Medical University.

2.2. Epidemiological survey

Information including demographic characteristics (age, education, etc.), lifestyle (smoking, alcohol consumption, and physical activity), health status, and history of disease and medication was obtained by well-trained physicians using a standard questionnaire during a face-to-face interview. Alcohol consumption was considered positive if the participant drinks one or more alcoholic beverages, including beer, wine, or hard liquor, per week. Current smokers were defined as participants who smoked at least once a day for > 6 months. Physical activity was categorized as either yes (exercising > 60 min per week) or no (exercising < 60 min per week).Weight and height were measured without coat and shoes to the nearest 0.1 kg and 0.1 cm, respectively. BMI was calculated as weight (in kilograms)/height (in square meters). Waist circumference (WC) was measured at the midpoint between the inferior costal margin and the superior border of the iliac crest on the midaxillary line. After resting for > 15 min, BP was measured twice with a mercury sphygmomanometer by well-trained nurses, and the average values were then taken.

2.3. Laboratory measurement

Blood sampling was performed in the morning after a 12 h fast. Serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and glucose (GLU) concentrations were measured enzymatically with a Dimension-RxL Chemistry Analyzer (Dade Behring, Newark, DE, USA) in the Department of Clinical Laboratory at the Fangchenggang First People's Hospital. Fasting concentrations of serum total testosterone (TT) were also measured. The interassay coefficient of variation for TT was 3.6%. Bioavailable testosterone (BT) and free testosterone (FT) concentrations were calculated based on the serum concentrations of TT [14].

2.4. Definition of hypertension

Hypertension is defined as having a systolic BP (SBP) of ≥140 mmHg and/or a diastolic BP (DBP) of ≥90 mmHg on more than three measurements. Hypertension was defined twice, once at baseline examination, and the second at the end of the 4-y follow-up period.

2.5. Outcome measurement and comorbidities

The outcome of interest in this study was the development of hypertension. Participants with new-onset hypertension after the 4-y follow-up were regarded as new hypertension patients.

2.6. Statistical analysis

For the cross-sectional analysis, first, spearman partial correlation coefficients was used to assess the proportion between serum testosterone concentrations and age, blood pressure. Second, the baseline data between the hypertensive and non-hypertensive groups were compared using independent samples *t*-test or chi-square test, where suitable. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as number (n) and percentage (%). Third, the sex hormone concentrations (TT, FT, and BT) were divided into 3 groups from the lowest tertiles to the highest tertiles. The SBP and DBP of each group were compared using variance analysis and trend line analysis. Fourth, we estimated the association between sex hormones and hypertension using binary logistic regressions. The OR was calculated to test for the presence of hypertension in the middle and highest tertiles of sex hormone. The lowest tertiles of sex hormone were considered as the reference group. Potential confounders included age, BMI, education, alcohol drinking, physical activity, glucose, cholesterol, triglyceride, and LDL.

For the longitudinal analysis, we used binary logistic regressions to