Atherosclerosis 233 (2014) 278–283

Contents lists available at ScienceDirect

Atherosclerosis

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

Testosterone deficiency: A determinant of aortic stiffness in men

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ARTICLE INFO

Article history:
Received 28 October 2013
Received in revised form
14 December 2013
Accepted 16 December 2013
Available online 18 January 2014

Keywords:
Total testosterone
Carotid-femoral pulse wave velocity
Testosterone deficiency

ABSTRACT

Objective: Low testosterone levels and increased aortic stiffness are predictors of cardiovascular events. The influence of androgen level on the age- and blood pressure-related increase in aortic stiffness is unknown.
Methods: From January 2007 to June 2011 we enrolled 455 consecutive men with no evidence of cardiovascular disease from a large cohort followed in our Department for arterial function studies. Their total testosterone (TT) levels were measured and carotid-femoral pulse wave velocity (PWVc-f) was measured as an index of aortic stiffness.
Results: In multivariable analysis, PWVc-f values were inversely correlated to TT after adjustment for confounders ($\beta = -0.365$, $P < 0.001$). In younger age categories (<50 yrs and 50–59 yrs), patients with testosterone deficiency (TD) had higher blood pressure-adjusted PWVc-f ($P < 0.001$ and $P = 0.005$, respectively) compared to subjects with normal TT, indicating an "aging effect" of 10 years, whereas in older age categories such a difference was not observed. Furthermore, in men with a higher mean pressure (102–108 mmHg and >108 mmHg), patients with TD had higher age-adjusted PWVc-f ($P < 0.001$) compared to subjects with normal TT, indicating a synergistic unfavorable effect of testosterone deficiency and blood pressure on aortic stiffness.
Conclusions: TT levels are independently associated with aortic stiffening. The effect of low testosterone concentration on aortic stiffness is more prominent in young men and in subjects with higher blood pressure levels. These findings identify testosterone as a marker of arterial damage with special emphasis on young and hypertensive individuals and support its role as predictor of events.

1. Introduction

Increasing attention is focused on the adverse effects of testosterone deficiency on cardiovascular (CV) health. Men with lower testosterone levels tend to have higher incidence of cardiovascular risk factors and coronary artery disease [1,2]. As we and others have shown, testosterone deficiency has emerged as an important predictor of future cardiovascular events and all-cause mortality both in the general population and in patients with disease states [3–5]. On the other hand, the levels of testosterone undergo age-related decline [6], while there is also evidence suggesting that risk factors such as hypertension may hasten the age-related fall in testosterone levels [7].

Carotid-femoral (aortic) pulse wave velocity (PWVc-f) is the gold-standard index for assessment of aortic stiffness [8]. Its implementation in clinical practice is based on its reliability, ease of use [9], and predictive value for future CV events and all-cause mortality independent of classic CV risk factors [10,11] both in the general population [12] and in patients with disease states [13,14]. It has been included as a recommended test in the recent European Society of Cardiology/European Society of Hypertension guidelines for the management of arterial hypertension [15]. Aortic PWV is strongly dependent on age and blood pressure (BP) [8,16].

Low testosterone has been associated both through causal and associative relationships with functional and structural changes in the properties of the arterial wall. Studies that investigated the association between testosterone and arterial elastic properties involved diverse populations, such as either elderly [17] or young [18] subjects, as well as patients with diabetes [19], prostate cancer [17,20] or hemodialysis [21]. In the present study, we sought to investigate whether testosterone levels are associated with aortic

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0021-9150/$ – see front matter © 2014 Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.atherosclerosis.2013.12.010

stiffness in a population with a broad range of age and risk factors without overt cardiovascular disease. We also assessed the influence of androgen level on the age- and blood-pressure related increase in aortic stiffness.

2. Patients and methods

2.1. Study population

From January 2007 to June 2011 we enrolled consecutive men from a large cohort followed in our Department for arterial function studies. All participants were screened for sociodemographic data and risk factors for cardiovascular disease and comprehensively evaluated using medical history, physical examination and electrocardiogram. In the present study, patients with a history of coronary artery disease, stroke or peripheral artery disease and subjects with untreated sleep apnea, chronic obstructive pulmonary disease, or on chronic opiate therapy were excluded, because testosterone levels can be substantially modified in such patients [1]. Subjects currently or previously taking any hormonal treatment were also excluded. Also, patients with acute inflammatory diseases, collagen diseases, or malignant neoplasms were excluded, because levels of inflammation can be greatly enhanced by such diseases.

Diagnosis of hypertension was set if resting BP was ≥140 (systolic) and/or ≥90 (diastolic) mmHg, of hypercholesterolemia if total cholesterol level was ≥190 mg/dl and LDL cholesterol level was ≥115 mg/dl, and of diabetes if plasma glucose level was ≥125 mg/dl (fasting) and ≥200 mg/dl (2 h after a 75 mg oral glucose load) [22].

2.2. Study design

Subjects had fasted for at least 6 h and had abstained from caffeine, ethanol and flavonoid-containing beverages intake for at least 12 h before each session. All vascular studies were performed in the morning between 8 and 10 a.m., in a quiet, temperature-controlled room at 23 °C. Before the vascular examination, brachial BP measurements were taken using an oscillometric device (Omron M4-I, CE 0197; Hoofddorp, the Netherlands). BP was measured twice on the right arm and the average of the two BP values was used in the analyses. After a 20-min rest period, measurements for evaluation of aortic stiffness were taken in the supine position. At the completion of vascular studies blood was drawn. The study complies with the Declaration of Helsinki. The study protocol was approved by our Institutional Research Ethics Committee and all subjects gave informed consent.

2.3. Evaluation of aortic elastic properties

Pulse travels at a higher velocity in a stiff aorta. Carotid-femoral pulse wave velocity (PWVc-f), an established index of aortic stiffness, was calculated from measurements of pulse transit time and the distance traveled between 2 recording sites (PWVc-f equals distance in meters divided by transit time in seconds) with a validated noninvasive device (Complior, Artech Medical), as previously described [8,9]. Two different pulse waves were obtained simultaneously at 2 sites (at the base of the neck for the right common carotid and at the groin over the right femoral artery) with 2 transducers. Distance was defined as the distance from the suprasternal notch (manubrium sternum) to femoral artery minus the distance from the carotid artery to the suprasternic notch [23].

2.4. Laboratory measurements

High sensitivity C-reactive protein (hsCRP) was measured by immunonephelometry (Dade Behring, Marburg, Germany). The serum TT level was measured in the fasting state by enzyme immunoassay from a blood sample taken between 8 and 11 a.m. (testosterone enzyme immunoassay test kit, LI7603; Linear Chemicals). The intra- and inter-assay coefficients of variation were 2.7 and 5.6% respectively. Biochemical testosterone deficiency (TD) was defined when TT levels were below 340 ng/dl [24]. Blood sampling and testosterone measurements were made by a researcher unaware of the study hypothesis. Total cholesterol, HDL-cholesterol, triglycerides and fasting blood glucose were measured with standard methods.

2.5. Statistical analysis

Continuous variables are expressed as mean value ± standard deviation. Normality was tested using the Kolmogorov–Smirnov criterion. Skewed variables are expressed as the median value (interquartile range). Between patients with TD and subjects with normal TT levels, the Student's *t*-test for unpaired measures or the Mann–Whitney *U*-test was used to compare normally distributed and skewed continuous variables, respectively. Categorical variables were compared using the chi-squared test.

Correlations between PWVc-f and clinical characteristics were evaluated by calculation of the Pearson correlation coefficient. The unadjusted association between PWVc-f and total testosterone may have been confounded by clinical and biochemical parameters that are important determinants of large artery stiffness. Therefore, we applied a stepwise multivariable linear regression model in which total testosterone was considered as the main independent variable while PWVc-f was considered as dependent variable. Parameters that determine arterial elastic properties were also introduced in the model as independent variables (covariates). In particular, age, mean BP, height, BMI, fasting blood glucose, total cholesterol, high density lipoprotein, high sensitivity CRP, smoking status and use of statins and ACE inhibitors/ARBS were forced in the multivariable model as covariates.

The influence of testosterone levels on the association between age and PWVc-f was examined by categorizing patients in subgroups according to (i) age decade (<50 yrs, 50–59 yrs, 60–69 yrs and >70 yrs) and (ii) presence/absence of TD. The influence of testosterone levels on the association between blood pressure and PWVc-f was examined by categorizing patients in subgroups according to (i) mean pressure quartile (<94 mmHg, 94–102 mmHg, 102–108 mmHg and >108 mmHg) and (ii) presence/absence of TD. Significant differences between men with TD and subjects without TD across age and mean pressure categories were determined using the Student independent-samples *t*-test after checking for equality of variances using the Levene's test. Analysis of covariance was performed in order to detect significant differences in PWVc-f between men with TD and subjects without TD after adjustment for confounders that were significantly different between men with TD and subjects without TD. Finally, a 2-way between-groups analysis of variance was conducted to explore the impact of age (or mean pressure) categories and TT categories on PWVc-f.

Statistical significance was defined as $P < 0.05$. All statistical analyses were performed with the use of SPSS 15.0 (SPSS, Chicago, IL).

3. Results

3.1. Population characteristics

The baseline clinical characteristics of the 455 participants are given in Table 1. One-hundred and nine (24%) patients had biochemical TD, while 23 of those (5%) had TT levels below 2.5 ng/ml (severe TD). Compared to patients with normal TT levels, subjects with TD were older ($P < 0.001$) and had higher BMI ($P < 0.05$), waist