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Original Article

Testosterone as a marker of coronary artery disease severity in middle aged males

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ABSTRACT

Historically, higher levels of serum testosterone were presumed deleterious to the cardiovascular system. In the last two decades, studies have suggested that low testosterone levels are associated with increased prevalence of risk factors for cardiovascular disease (CVD), including dyslipidemia and diabetes. This is a cross sectional study. The aim of our study was to determine the relationship between serum testosterone levels and angiographic severity of coronary artery disease (CAD). Serum testosterone levels were also correlated with flow mediated dilation of brachial artery (BAFMD) – an indicator of endothelial function. Consecutive male patients, aged 40–60 years, admitted for coronary angiography (CAG) with symptoms suggestive of CAD, were included in the study. Out of the 92 patients included in the study, 32 patients had normal coronaries and 60 had CAD on coronary angiography. Severity of CAD was determined by Gensini coronary score. The group with CAD had significantly lower levels of total serum testosterone (363 ± 147.1 vs 532.09 ± 150.5 ng/dl, $p < 0.001$), free testosterone (7.1215 ± 3.012 vs 10.4419 ± 2.75 ng/dl, $p < 0.001$) and bioavailable testosterone (166.17 ± 64.810 vs 247.94 ± 62.504 ng/dl, $p < 0.001$) when compared to controls. Adjusting for the traditional risk factors for CAD, a multiple linear regression analysis showed that low testosterone was an independent predictor of severity of CAD ($\beta = -0.007$, $p < 0.001$). This study also showed that levels of total, free and bioavailable testosterone correlated positively with BAFMD %.

1. Introduction

Cardiovascular diseases (CVD) are the leading cause of death world wide and coronary artery disease (CAD) is the most significant contributor to this mortality.[1] In addition, CVD contributes to significant morbidity and loss of disability adjusted life years (DALYS).[1] A wealth of information exists on the association of traditional coronary risk factors with CAD.[2–4] In the last two decades, there has been an emergence of several non-traditional risk factors which are associated with an inflammatory and pro-coagulant states in patients with CAD.[5] Studies in hypogonadal males have shown an increased prevalence of the traditional coronary risk factors and CAD.[6,7] Furthermore, androgen replacement therapy has been shown to improve risk factor profile and symptoms of ischemia in hypogonadal males.[8–10] Phillips et al.[11] was the first to report an inverse correlation between angiographically proven CAD and testosterone levels after adjustment for adiposity and age. Yeap et al.[12] found that the highest quartile for serum testosterone was associated with the lowest mortality and the lowest 2 quartiles with higher mortality. Additional studies too indicated an association between incidence of CAD and testosterone concentrations.[13–20] However, a recent study showed no significant correlation between serum testosterone levels and CAD severity.[21] Nevertheless, testosterone levels were lower in CAD patients as compared to those with normal coronaries in this study. Above evidences suggest involvement of testosterone in the pathogenesis of CAD; that of a potentially protective role against development and progression of CAD. Additionally, patients with low testosterone levels have been found to have impaired endothelial function which may contribute to the increased cardiovascular risk in them.[22,23]

In this cross sectional observational study, we aimed to determine the relationship between serum testosterone levels and angiographic severity of CAD in middle-aged Indian men.

Abbreviations: FBS, fasting blood sugar; BMI, body mass index; BAFMD, brachial artery flow mediated dilatation; CAD, coronary artery disease; CAG, coronary angiography; CVD, cardiovascular disease; CLIA, chemiluminescence; DALYS, disability adjusted life years; HDL-C, high density lipoprotein cholesterol; IHD, ischemic heart disease; LDL-C, low density lipoprotein cholesterol; PP, post-prandial blood sugar; SHBG, sex hormone binding globulin; TG, triglyceride.

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Secondary objective was to evaluate the association between serum testosterone levels and flow mediated dilation of brachial artery (BAFMD) – an indicator of endothelial function.

2. Materials and methods

This cross sectional study was performed in consecutive male patients aged 40–60 years admitted for coronary angiogram, in the department of Cardiology from 1/10/2013 to 30/9/2014. The exclusion criteria were: previous revascularization procedure, patients not giving consent, history of hypogonadism, patients of prostate cancer taking anti-androgens, liver/renal dysfunction, recent myocardial infarction, and recent or current infection. Written informed consent was obtained from all patients before sample collection and angiography. The study was approved by the Institutional Review Board and the Ethics committee of Christian Medical College Vellore. The study conformed to Good Clinical Practice and the ethical principles guiding human research. Out of all the patients who had angiography, 92 middle-aged males were recruited, and were divided into two groups according to coronary angiography (CAG) findings – 32 patients had normal coronaries and 60 had presence of CAD on CAG. Coronary artery disease was defined by the presence/absence of atherosclerotic plaques, regardless of the degree of diameter stenosis.

2.1. Baseline data

Detailed socio-demographic and clinical characteristics were recorded for each patient including age, gender, lifestyle, hypertension, diabetes, dyslipidemia, smoking, history of ischemic heart disease (IHD) and family history of IHD. Smoking habits were categorized as current smoker-individuals who currently smoked or quit <3 months prior to CAG or non-smoker. Weight and height were recorded after admission and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

2.2. Sample collection and laboratory measurements

Blood samples were drawn in the morning, prior to the coronary angiogram and after 8 h overnight fasting. The blood glucose, serum lipid and creatinine levels were measured by enzymatic methods on an automated analyser. Serum fasting testosterone was measured by automated chemiluminescence method, using Siemens Immulite 2000 Xpi machine (Siemens, Munich, Germany) (normal levels for men aged 20–49 years: 270–1030 ng/dl; >50 years: 212–755 ng/dl).

Serum sex hormone binding globulin (SHBG) was measured by automated electro-chemiluminescence method, using Roche E170 Modular machine (Roche Diagnostics, Basel, Switzerland). Free and bio-available testosterone levels were calculated from serum total testosterone and SHBG using an online calculator.

2.3. Coronary angiography and Gensini coronary score

Severity and extent of CAD was determined by the Gensini scoring system, an index that assesses severity based on the number of vessels affected, localization of segment, and grading of the stenosis.[24] Gensini score has been shown to correlate with CAD progression and overall as well as CVS mortality.[25] The Gensini score was calculated as follows: grading of narrowing of a coronary artery determined by eyeballing as; 1 for ≤25% narrowing, 2 for 26–50% narrowing, 4 for 51–75% narrowing, 8 for 76–90% narrowing, 16 for 91–99% narrowing, and 32 for total occlusion. Next, this primary score is multiplied by a factor that takes into account the importance of position of lesion in the coronary arterial tree: five for the left main, 2.5 for proximal left anterior descending or proximal left circumflex artery and 1.5 for mid-region, 1 for the distal left anterior descending and 1 for mid-distal region of the left circumflex or right coronary artery. Gensini score was expressed as the sum of the scores for all three coronary arteries to evaluate the entire extent of coronary artery disease. Angiographic scoring was done by cardiologist who was unaware of biochemistry values in order to avoid bias.

2.4. BAFMD assessment

The examination was carried out in a quiet air conditioned room with patient in a supine position. A longitudinal section of the brachial artery was analyzed with B mode ultrasound using a Philips iE 33 Ultrasound machine and a linear array transducer (Philips Medical Systems, Andover, MA, USA). After baseline measurement, a cuff which was placed above the transducer position, was inflated to supra systolic pressure to produce ischemia in the forearm. The cuff was deflated after 5 min. BAFMD was calculated as percentage increase in diameter from baseline to maximum value which is obtained after cuff deflation, BAFMD % = [(diameter, maximum-diameter, baseline)/diameter, baseline] × 100.

2.4.1. Data collection and statistical analysis

Continuous variables were expressed as mean value ± stan-standard deviation (SD). Categorical variables were presented as absolute values (percentages). The study population was divided into two groups according to angiographic finding: CAD subjects and normal coronaries (controls). Baseline characteristics of the two groups were noted and compared. Comparisons between the two groups pertaining to categorical data were done by chi-squared test or Fisher's exact test, wherever appropriate. Comparisons pertaining to quantitative data were done by *t*-tests. Correlations between serum total, free and bio-available testosterone levels and Gensini scores as well as BAFMD were assessed using Pearson's correlation test. Similarly, correlations between serum testosterone and traditional risk factors for CAD were also assessed. A multivariate regression analysis was done to assess whether serum testosterone was independently associated with CAD after adjusting for age, BMI, smoking history, hypertension, diabetes mellitus, dyslipidemia and history and treatment of IHD. A two sided p values <0.05 were considered significant for all tests. All statistical analyses were performed using SPSS 19.0 (IBM SPSS, Chicago, IL, USA).

3. Results

3.1. Baseline, clinical and biochemical characteristics

Baseline and clinical characteristics of the two study groups are displayed in Table 1. Age, diabetes mellitus and history of ischemic heart disease (IHD) differed among the two study groups significantly (all $p < 0.05$). As expected, CAD group had greater age, higher incidence of diabetes mellitus and history of IHD than controls. However, there were no statistically significant difference between the two groups for hypertension, obesity, smoking and dyslipidemia ($p > 0.05$). The values of fasting (FBS) and post-prandial sugars (PPBS) were significantly higher in patients with CAD when compared to those with normal coronaries (Table 2). Serum lipid levels did not differ between the two groups significantly.

The mean values of serum total, free and bioavailable testosterone were significantly lower inpatients with CAD when compared to controls ($p < 0.001$ for all).

CAD group also had significantly lower BAFMD values in comparison to subjects with normal coronaries ($p < 0.001$).

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