Atherosclerosis 238 (2015) 415–419

Contents lists available at ScienceDirect

Atherosclerosis

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

Erectile dysfunction is associated with low total serum testosterone levels and impaired flow-mediated vasodilation in intermediate risk men according to the framingham risk score

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ARTICLE INFO

Article history:
Received 31 May 2014
Received in revised form
26 November 2014
Accepted 1 December 2014
Available online 9 December 2014

Keywords:
Erectile dysfunction
Endothelial function
Flow mediated vasodilation
Serum testosterone levels

ABSTRACT

Background: The role erectile dysfunction (ED) coupled with low testosterone levels as early markers of atherosclerosis is not well understood. **Objectives**: To analyze the relationship between serum testosterone levels with both ED and brachial artery flow-mediated vasodilation (FMD), in a primary prevention sample of men. **Methods**: We enrolled 802 asymptomatic, intermediate CV risk patients, according to the Framingham Risk Score, aged 40–80 years, who underwent the ultrasound examination of FMD, the evaluation of ED and the assessment of total serum testosterone levels. **Results**: Testosterone levels correlated both with FMD ($r = 0.85$; $p < 0.0001$) and IIEF-5 score (rs = 0.65; $p < 0.0001$). Multivariable logistic regression analyses revealed that lower serum testosterone levels were strongly associated ($p < 0.001$) with severe (OR 0.78; 95% CI: 0.62–0.86), and moderate ED (OR 0.85; 95% CI: 0.72–0.97), while impaired FMD percentages were strongly associated ($p < 0.001$) with severe (OR 0.68; 95% CI: 0.59–0.79), moderate (OR 0.76; 95% CI: 0.63–0.83) and mild to moderate ED (OR 0.8; 95% CI: 0.69–0.94). Mild ED resulted statistically associated with lower FMD (OR 0.94; 95% CI: 0.82 – 1.07; $p = 0.03$) but not with serum testosterone levels. These relations were not substantially affected by adjustments for further potential confounders including smoking status, hypertension, diabetes mellitus and body mass index. **Conclusions**: lower total serum testosterone levels are associated with impaired FMD and ED in this sample of intermediate CV risk men according to the Framingham Risk Score.

1. Introduction

The evaluation of brachial artery flow-mediated vasodilation (FMD) through duplex ultrasounds is a noninvasive tool used for the assessment of endothelial function (EF) [1], and in recent years, an increasing body of evidence suggested that endothelial dysfunction can be an etiological factor for erectile dysfunction (ED) [2–6]. Moreover, many authors also stated that endothelial dysfunction could be considered as an early marker for silent coronary disease [7,8].

Recently, much interest has focused on the impact of serum testosterone levels on cardiovascular (CV) diseases and mortality and on the effects of testosterone replacement therapy [9–14]. The normal reference range for total serum testosterone levels in adult men is approximately 300–1000 ng/dL [14]. Low testosterone levels are associated with CV risk factors such as dyslipidemia, hypertension, obesity, and diabetes [15,16], and some studies have shown an association with changes in carotid intima-media thickness (IMT) and ankle/brachial index (ABI) as a measure of peripheral atherosclerotic disease [17–19]. Other studies have also reported that low testosterone levels are associated with increased CV and all-causes mortality in older men [12,13,20–22]. However, the true CV benefits of testosterone supplementation are still not fully understood, although some evidence showed positive results [10].

To the best of our knowledge, only few studies investigated the relationship between testosterone levels and FMD [23,24]. In these

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http://dx.doi.org/10.1016/j.atherosclerosis.2014.12.007
0021-9150/

outpatients there was an association of low serum testosterone levels with decreased FMD percentages, independently of major CV confounders.

Our study aimed to analyze the association of total serum testosterone levels, with both erectile function and FMD in a large sample of 802 intermediate-risk patients, according to the Framingham Risk Score (FRS).

2. Methods

We screened 1542 men afferent to our Centre for the early diagnosis of preclinical and multifocal atherosclerosis.

Individuals aged between 40 and 80 years, with a stable marital relationship, Intermediate CV risk according to the FRS and without clinical evidence of atherosclerotic disease were enrolled.

We excluded patients with suspected or manifest CV disease (such as coronary artery disease, cerebrovascular arterial disease or peripheral arterial disease), uncontrolled arterial hypertension, impaired renal function (eGFR < 30 mL/min/1.73 m^2), history of pelvic surgery, previous history of clinical neoplasm, past organ transplantation, active liver disease, hypo- or hyperthyroidism; finally, patients unable to give the informed consent were also excluded. We excluded also patients treated with β-blockers, to reduce possible confounding factors for ED. Those who met the inclusion criteria were invited to participate and provide signed informed consent. Erectile function was assessed by the International Index of Erectile Function-5 (IIEF-5) score questionnaire, which was preferentially filled in by the patient himself or, if required, by a trained interviewer. The possible score for the IIEF-5 ranges from 5 to 25, and ED can be classified into five categories based on the score: severe (5–7), moderate (8–11), mild-to-moderate (12–16), mild (17–21), and no ED (22–25) [25]. Data collection included clinical, laboratory, and anthropometric parameters such as age, weight, height, body mass index (BMI), lipid profile, family history for CV disease and information on others traditional risk factors. We reported also the principal classes of drugs used in our sample of patients. Total serum testosterone levels were measured from stored samples, collected in the early morning, using a chemiluminescent immunometric assay on an Immulite 2500 analyzer.

The anthropometric measurements were performed by a single examiner, in a standardized way, while the ultrasound examinations of the brachial artery were all performed by a trained blinded researcher.

The patients underwent assessment of FMD in the right brachial artery (Siemens Sequoia C512 with linear probe, sound of 7.5/10 MHz). We recommended avoiding physical activities and suspending all vasoactive drugs (nasal decongestants and/or bronchodilators) at least 24 h before the examination and recommended also a 12-h minimum fasting period; each patient was positioned in supine position in a silent room with controlled temperature of 23 Celsius degrees (1 h before the ultrasound evaluation) and systemic blood pressure was measured in both arms, 30 min before performing the ultrasound test.

While the examination was performed, the right arm remained in a comfortable position to identify the brachial artery, assessed in all cases above the ante-cubital fossa in the longitudinal plane. First we measured the brachial artery diameter at rest, and blood flow was estimated by Pulse Doppler Wave. Brachial artery diameter was determined as the mean of two measurements. After determining the baseline diameter of the brachial artery, ischemia was produced by inflating a sphygmomanometer cuff placed in the right arm, with a pressure of 50 mmHg higher than the systemic blood pressure [26]. The cuff was kept for 5 min. The maximum velocity of blood flow was detected by analyzing the Doppler signal immediately after or up to 15 s after releasing the cuff, while the maximum diameter of the brachial artery was determined after 60 s [27]. The FMD was defined as the percentage change in brachial artery diameter, 60 s after deflating the cuff [27].

2.1. Statistical analyses

Categorical variables are presented as absolute frequencies and percentages and compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables are presented as means ± standard deviation (SD). The Student's *t* test was used for the analysis of symmetric variables. Pearson coefficient (r) was used to calculate the correlation between testosterone levels and FMD; Spearman's Rank-Order Correlation was used to calculate the correlation between testosterone levels and IIEF-5 score. Multivariate logistic regression models were performed to calculate odds ratio (OR) for levels of erectile function score, total serum testosterone levels and FMD percentages. Finally, in the subgroup of patients with overt (moderate to severe) ED, we used Analysis of Variance (ANOVA) to test differences between mean FMD percentages, according to testosterone levels. A value of $p < 0.05$ was considered statistically significant.

3. Results

After the evaluation of inclusion and exclusion criteria, only 802 men were enrolled of the 1542 screened. Table 1 shows the baseline characteristics of the whole cohort and Table 2 reports the principal classes of drugs used by the patients. Finally, in Table 3, we listed the prevalence of the main CV risk factors, dividing the population according to testosterone levels, with a threshold of 300 ng/dL. Our study population had mean age of 57 years, and the subjects were mostly hypertensive and overweight. Mean FMD percentage was 9.31 ± 7.05%, while mean serum testosterone level was 398 ± 205 ng/dL; 192 patients (24%) had severe ED (IIEF-5 = 5–7); 152 (19%) moderate ED (IIEF-5 = 8–11); 184 (23%) mild to moderate ED (IIEF-5 = 12–16); 116 (14%) mild ED (IIEF-5 = 17–21) and 158 (20%) no ED (IIEF-5 ≥ 22).

Subjects with lower testosterone levels (≤300 ng/dL) had higher prevalence of hypertension, dyslipidemia, diabetes and also a worse erectile function and lower FMD percentages (Table 3). Testosterone levels correlated both with FMD ($r = 0.85$; $p < 0.0001$) and IIEF-5 score (rs = 0.65; $p < 0.0001$) (Figs. 1 and 2). Multivariable logistic regression analyses revealed an association between each decrement of erectile function with FMD and serum testosterone, with an age-adjusted model (Table 4). Lower serum testosterone levels were strongly associated ($p < 0.001$) only with severe (OR 0.78; 95% CI: 0.62–0.86), and moderate ED (OR 0.85; 95% CI: 0.72–0.97), while lower FMD percentages were strongly associated

Table 1
Baseline population characteristics ($n = 802$).

Age (years) ± SD	57.5 ± 13.9
BMI (kg/m^2) ± SD	27.6 ± 3.1
Waist circumference (cm) ± SD	96.2 ± 5.4
Hip circumference (cm) ± SD	95.4 ± 5.2
Current Smoking (%)	399 (50%)
Dyslipidemia (%)	306 (38%)
Diabetes (%)	332 (41%)
Family History of CVD (%)	392 (49%)
Hypertension (%)	560 (70%)
Total Serum testosterone (ng/dL) ± SD	398 ± 205
FMD% ± SD	9.3 ± 7.1
Erectile function (score) ± SD	15.7 ± 6.0

BMI, body mass index; CVD, cardiovascular disease; FMD, flow mediated vasodilation; SD, standard deviation.