ORIGINAL RESEARCH—ENDOCRINOLOGY

Serum PSA as a Predictor of Testosterone Deficiency

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ABSTRACT

Introduction. The relationship between serum prostate-specific antigen (PSA) and testosterone (T) levels is still controversial. According to the "saturation hypothesis," a significant relationship is apparent only in the low T range.
Aim. To verify whether, in a large sample of male subjects seeking medical care for sexual dysfunction (SD), PSA might represent a reliable marker of T levels.
Methods. A consecutive series of 3,156 patients attending our unit for SD was studied. Among them, only subjects without history of prostate disease and with PSA levels <4 ng/mL (N = 2,967) were analyzed.
Main Outcome Measures. Several hormonal and biochemical parameters were studied, along with structured interview on erectile dysfunction (SIEDY), ANDROTEST, and PsychoANDROTEST.
Results. Receiver operating characteristic curve analysis for predicting severe hypogonadism (T < 8 nmol/L) showed an accuracy of PSA = 0.612 ± 0.022 ($P < 0.0001$), with the best sensitivity and specificity at PSA < 0.65 ng/mL (65.2% and 55.5%, respectively). In the entire cohort, 254 subjects (8.6%) showed T < 8 nmol/L and, among them, more than half (N = 141, 4.8%) had PSA < 0.65 ng/mL. After adjusting for age, low PSA was associated with hypogonadism-related features (i.e., delayed puberty, lower testis volume) and associated conditions, such as metabolic syndrome (hazard ratio [HR] = 1.506 [1.241–1.827]; $P < 0.0001$), type 2 diabetes (HR = 2.044 [1.675–2.494]; $P < 0.0001$), and cardiovascular diseases (HR = 1.275 [1.006–1.617]; $P = 0.045$). Furthermore, low PSA was associated with impaired sex- and sleep-related erections. The association between low PSA and hypogonadal symptoms and signs as well as with metabolic syndrome was retained even after adjusting for T levels. Sensitivity and positive predictive values of low PSA increased, whereas specificity and negative predictive value decreased as a function of age.
Conclusions. PSA is a marker of T concentrations and it may represent a new tool in confirming hypogonadism. The determination of PSA levels might give insights not only on the circulating levels of total T but also on its active fractions. **Rastrelli G, Corona G, Vignozzi L, Maseroli E, Silverii A, Monami M, Mannucci E, Forti G, and Maggi M. Serum PSA as a predictor of testosterone deficiency. J Sex Med 2013;10:2518–2528.**

Key Words. Testosterone; Hormone Action; Androgen; Biomarker

Introduction

Late onset hypogonadism (LOH) is characterized by low testosterone (T) levels, with an unknown etiology and natural history, due to a failure in testis activity resulting from a partial or total communication breakdown between the hypothalamus, the pituitary, and the testis itself [1]. According to major international guidelines, low serum T levels must be associated with consistent symptoms and signs for diagnosing LOH [2–4]. Despite the fact that LOH is a common condition, particularly among patients consulting for sexual dysfunction (SD; [5]), its diagnosis is often overlooked because the symptoms are relatively mild, insidious, and difficult to be

recognized. However, LOH has been associated with metabolic comorbidities, such as type 2 diabetes mellitus (T2DM) [6,7] and metabolic syndrome (MetS) [8], as well as with an increased mortality [9–11]. Furthermore, LOH-associated symptoms and signs have the potential to cause considerable short-term and long-term disabilities, with economic consequences [12]. Hence, it is important to suspect and screen symptomatic men for this condition. Questionnaires and structured interviews developed for the screening of hypogonadism are useful tools, but they often require time to be administered or to be scored, and they have a low specificity (see ref. [13] for review). Hence, the measurement of T levels remains the reference for the screening of hypogonadism. However, T biological effects are known to be mediated not only by hormonal levels but also by the transcriptional efficiency of its cognate receptor, i.e., the androgen receptor (AR), which shows a relevant interindividual variability [14]. In clinical research, the most extensively studied genetic parameter that predicts AR activity is the variable length of a polyglutamine stretch in the N-terminal domain of the receptor, which reflects a variable number of CAG triplets in exon 1 of the *AR* gene [14]. Although interesting, this parameter cannot be routinely used in clinical practice due to its relatively high cost. Therefore, the identification of other, simpler predictors of AR activity could be clinically relevant.

Prostate-specific antigen (PSA) is a serine protease of 261 amino acids, member of the tissue kallikrein family of proteases [15], and it is produced primarily by prostate epithelium [16]. *PSA* gene is located on chromosome 19q13.4 [15] and its transcription is positively regulated by the AR that, after binding with T, migrates into the nucleus and interacts with androgen-responsive elements (AREs) located at -156 to -170 pair of bases from the transcriptional start site of the *PSA* gene [17]. As PSA measurement is frequently obtained in middle-aged and older men, it could be a good candidate as a marker of bioactive T circulating levels in men. However, the relationship between serum PSA and T levels is still not universally accepted: some authors recognizes a positive correlation [18,19] but others did not [20,21]. According to the "saturation hypothesis" [22], a significant relationship is apparent only in the low testosterone range and therefore apparent in studies evaluating testosterone replacement therapy in hypogonadal subjects [23–25] but not in those considering eugonadal subjects [21,22,26].

Aim

The aims of this study are to assess the clinical and biochemical correlates of PSA levels in a huge sample of subjects seeking medical care for SD and to verify whether PSA might represent a marker of bioactive T circulating levels.

Methods

A consecutive series of 3,156 male patients attending our Outpatient Clinic for SD for the first time was retrospectively studied. Among them, in order to prevent possible bias in the analysis, we selected only subjects without a history of prostate disease and with a PSA level <4 ng/mL (N = 2,967). The socio-demographic and clinical characteristics of the sample are summarized in Table 1. All patients enrolled underwent the usual diagnostic protocol applied to newly referred subjects at our Andrology Outpatient Clinic. All the data provided were collected as part of the routine clinical procedure. An informed consent for the study was obtained from all patients. Patients were interviewed before any specific diagnostic procedures and prior to the beginning of any treatment, using ANDROTEST [27] and Structured Interview on Erectile Dysfunction (SIEDY; [28,29]). ANDROTEST is a 12-item structured interview previously validated for the screening of hypogonadism in patients with erectile dysfunction (ED; [27,30]).

SIEDY is a 13-item structured interview composed of three scales, which identify and quantify components concurring with ED [28]. The characteristics of ED were assessed using SIEDY Appendix A, as previously described [28]. In particular, severe ED was evaluated using question 1D of SIEDY appendix A (difficulties in achieving an erection sufficient for penetration in >75%; see in ref. [28] and [29]). Question 1D of SIEDY Appendix A has been recently validated against IIEF 5 and showed an accuracy of 81% in predicting severe ED as defined by IIEF-5 < 8 [29]. Sleep-related erections were specifically evaluated using question #13 of SIEDY ("Does it ever occur to you to wake up with an erection?"), rating 0 = yes, regularly, 1 = less frequently than in the past, 2 = only occasionally, and 3 = never [28]. Engagement in a stable relationship has been assessed using question #5 of SIEDY ("Do you have a stable relationship with a partner?") and answers were codified as a dummy variable 0 = no stable relationship and 1 = stable relationship, living, or not living together [28].