Serum PSA as a Predictor of Testosterone Deficiency

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DOI: 10.1111/jsm.12266

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.

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 recognize 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].

Other specific items used were (i) frequency of sexual intercourse, assessed using a standard question (“During the last three months how many sexual attempts per month did you have?”), rating 0 = equal to or higher than 7 times for month, 1 ≤ 7 times per month; (ii) relationship span, investigated using a standard question (“How long is the relationship with your partner?”) rating 0 ≤ 6 years; 1 = equal to or higher than 6 years as previously reported [13,31–33].

Table 1  Characteristics of the sample

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 2,967</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.5 ± 12.4 (range 18–85)</td>
</tr>
<tr>
<td>Marital status (%)</td>
<td></td>
</tr>
<tr>
<td>Not stable relationship</td>
<td>10.9</td>
</tr>
<tr>
<td>Stable relationship</td>
<td>89.1</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
</tr>
<tr>
<td>None/primary school</td>
<td>13.9</td>
</tr>
<tr>
<td>Secondary school</td>
<td>33.3</td>
</tr>
<tr>
<td>Secondary higher</td>
<td>34.4</td>
</tr>
<tr>
<td>University</td>
<td>18.3</td>
</tr>
<tr>
<td>Morbidities (%)</td>
<td></td>
</tr>
<tr>
<td>Delayed puberty</td>
<td>3.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29.4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20.9</td>
</tr>
<tr>
<td>CVD</td>
<td>28.4</td>
</tr>
<tr>
<td>Clinical and laboratory parameters</td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>98.2 ± 10.6</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>135.0 (120–140)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>80.0 (80–90)</td>
</tr>
<tr>
<td>Mean testis volume (mL)</td>
<td>18.9 ± 4.5</td>
</tr>
<tr>
<td>Gynecomastia (%)</td>
<td>4.4</td>
</tr>
<tr>
<td>Glycemia (mg/dL)</td>
<td>105.6 ± 37.6</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>115.0 (83–164)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>48.1 ± 12.4</td>
</tr>
<tr>
<td>LH (mU/L)</td>
<td>3.8 (2.6–5.6)</td>
</tr>
<tr>
<td>FSH (mU/L)</td>
<td>4.6 (3.1–7.9)</td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>15.5 ± 6.3</td>
</tr>
<tr>
<td>Sex hormone binding globulin (nmol/L)</td>
<td>35.6 ± 18.7</td>
</tr>
<tr>
<td>Calculated free testosterone (pmol/L)</td>
<td>307.5 ± 132.3</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>0.8 (0.5–1.3)</td>
</tr>
<tr>
<td>SIEDY scale score</td>
<td></td>
</tr>
<tr>
<td>Scale 1 (organic domain)</td>
<td>2.9 ± 2.3</td>
</tr>
<tr>
<td>Scale 2 (relational domain)</td>
<td>1.9 ± 2.0</td>
</tr>
<tr>
<td>Scale 3 (intrapsychic domain)</td>
<td>3.3 ± 2.1</td>
</tr>
<tr>
<td>ANDROTEST score</td>
<td>7.7 ± 3.4</td>
</tr>
<tr>
<td>PsychoANDROTEST score</td>
<td>10.0 ± 3.6</td>
</tr>
<tr>
<td>Metabolic syndrome (NHLB/AHA) (%)</td>
<td>39.0</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation when normally distributed, median (quartiles) when not normally distributed, and as percentages when categorical.

CVD = cardiovascular diseases; FSH = follicle stimulating hormone; HDL = high-density lipoprotein; LH = luteinizing hormone; NHLB/AHA = National Heart, Lung, and Blood Institute; American Heart Association; PSA = prostate-specific antigen; SIEDY = Structured Interview on Erectile Dysfunction

Main Outcome Measures

All patients underwent a complete physical examination, including measurement of blood pressure, waist circumference, and testis volume (Prader orchidometer, Educational+Scientific Products Ltd., Littlehampton, UK). Blood samples were drawn in the morning, after an overnight fast, for determination of PSA, total T, follicle stimulating hormone (FSH), luteinizing hormone (LH), sex hormone-binding globulin (modular E170 platform electrochemiluminescence immunoassay; Roche Diagnostics, Mannheim, Germany), blood glucose (by glucose oxidase method; Aerocet Abbott, Rome, Italy), high-density lipoprotein (HDL) cholesterol, and triglycerides (by automated enzymatic colorimetric method; Aerocet Abbott, Rome, Italy). Levels of calculated free T (cFT) were derived using Vermuelen formula as previously described [34]. MetS was defined according to the National Heart, Lung, and Blood Institute/American Heart Association definition [35]. During follow-up, pathological hormonal (including testosterone) and/or other biochemical values were retested to further confirm abnormalities. However, as this report is essentially dedicated to hypogonadism screening at the first visit, follow-up values were not reported.

Statistical Analysis

Data were expressed as mean ± standard deviation when normally distributed, and as median (quartiles) for parameters with non-normal distribution. For continuous variables, correlations were assessed using Pearson’s or Spearman’s method, whenever appropriate. Kolmogorov–Smirnov test was used to test the parameter distribution. Stepwise multiple logistic analysis was used for multivariate analyses. Receiver operating characteristic (ROC) analysis was used to select possibly optimal models and essentially represent the sensitivity vs. (1 – specificity) plot. Each prediction result or instance of a confusion matrix represents one point in the ROC space. The accuracy represents conformity to truth or to a standard or model. From a statistical point of view, accuracy of a measurement system is the degree of closeness of measurements of a quantity to that quantity’s actual (true) value. Accuracy is measured by the area under the ROC curve and an area of 1 represents a perfect test. All analyses were carried out with SPSS 19.0.0 statistical package and a P < 0.05 was considered statistically significant.

Results

Relationship Between PSA and Testosterone

Figure 1 (panels A and C) describes the relationship between circulating total T (nmol/L) and
calculated free testosterone and PSA (ng/mL). The curve in panel A shows a plateau for testosterone levels above 8 nmol/L, where a further increase of T level does not correspond to a substantial increment in PSA. A similar trend was observed for calculated free T, when available (N = 1,554, panel C).

Hence, we tested the efficacy of PSA in detecting severe hypogonadism, defined as total T < 8 nmol/L (see ref. [2]) or cFT < 180 pmol/L (see ref. [36]) in symptomatic subjects (SD complaints). ROC curve analysis for PSA levels showed an accuracy (area under the ROC curve) of 0.612 ± 0.022, P < 0.0001, in predicting severe hypogonadism (i.e., T < 8 nmol/L; see Figure 1, panel B). In particular, when a threshold of 0.65 ng/mL was chosen, sensitivity and specificity for severe hypogonadism were 65.2% and 55.5%.

Table 2 reports the categorization of severe hypogonadism according to the PSA threshold of 0.65 ng/mL. The corresponding negative and positive predictive values were 94.0% and 13.0%.

Table 2 Categorization of patients according to hypogonadism and according to PSA levels

<table>
<thead>
<tr>
<th>PSA ≥ 0.65 ng/mL</th>
<th>PSA &lt; 0.65 ng/mL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>T ≥ 8 nmol/L</td>
<td>1,770</td>
<td>943</td>
</tr>
<tr>
<td>T &lt; 8 nmol/L</td>
<td>113</td>
<td>141</td>
</tr>
<tr>
<td>Total</td>
<td>1,883</td>
<td>1,084</td>
</tr>
</tbody>
</table>

Sensitivity (1,770/2,713 x 100) and specificity (141/254 x 100) for severe hypogonadism were 65.2% and 55.5%. The corresponding negative (1,770/1,883 x 100) and positive (141/1,084 x 100) predictive values were 94.0% and 13.0%.

PSA = prostate specific antigen; T = testosterone
positive predictive values were 94.0% and 13.0%, respectively. When subjects with elevated visceral adiposity (waist circumference ≥102 cm) were excluded from the analysis, a similar sensitivity and specificity for detecting severe hypogonadism was observed for low PSA (accuracy = 0.591 ± 0.031; sensitivity = 65.1%; specificity = 54.9%; negative predictive value = 95.6% and positive predictive value = 9.5%). When the same threshold was applied for cFT, ROC curve analysis showed an overall accuracy of 0.573 ± 0.023 (P = 0.001) and a sensitivity of 61.3% and a specificity of 50.0% with negative and positive predictive values of 88.7% and 16.6%, respectively, for a cFT < 180 pmol/L.

Among the patients studied, 63.5% and 36.5% had PSA levels higher and lower than 0.65 ng/mL, respectively. As PSA and age were positively associated at univariate analysis (r = 0.293, P < 0.0001), all the following analyses were adjusted for age.

**PSA as a Marker of Hypogonadism-Related Comorbidities**

When hypogonadism-related comorbidities were considered (Figure 2, upper panel), subjects with low PSA (<0.65 ng/mL) more often reported a history of delayed puberty, as well as of any other testicular disease. In addition, they more often had a positive history for cardiovascular diseases (CVD) and T2DM (Figure 2, upper panel). Accordingly, patients with lower PSA levels showed a higher risk of MetS (Figure 2, middle panel). In particular, elevated glycemia and waist circumference, as well as reduced HDL-cholesterol levels, were independently associated with a low PSA level (Figure 2, middle panel). FSH, but not LH levels, retained a significant, negative association with lower PSA levels (hazard ratio [HR] = 1.367 [1.078; 1.733]; P = 0.010). Accordingly, subjects with low PSA had lower testis volume and more often gynecomastia, as compared with subjects with higher PSA levels (Figure 2, lower panel).

When sexual symptoms were considered, subjects with lower PSA levels more frequently reported an impairment in both sex- and sleep-related erections, as well as a reduction of intercourse frequency (see Figure 2, lower panel). Moreover, they were more often engaged in a long-lasting, stable relationship and fathered a higher number of children (Figure 2, lower panel). Patients with the lowest PSA levels had higher SIEDY scale 1 (organic domain of ED) scores and lower SIEDY scale 2 (relational domain of ED) and scale 3 (intrapsychic domain of ED) scores (Table 3). As expected, both ANDROTEST and Psycho-ANDROTEST scores, investigating physical and psychological symptoms and signs of T deficiency, respectively, were significantly higher in subjects with lower PSA levels (Table 3).

We next tested the effect of the introduction of measured total T as a further covariate in a logistic model in order to assess the robustness and independence of the association between the hypogonadal symptoms and PSA. Interestingly, we found that even after adjusting for total T, low PSA was still associated with the severity of ANDROTEST score (HR = 1.041 [1.004–1.078]; P = 0.029). In addition, other physical signs of hypogonadism, such as the presence of gynecomastia (1.562 [1.076–2.269]; P = 0.019) or testis volume (0.780 [0.655–0.930]; P = 0.005), was independently associated with low PSA. Finally, subjects with low PSA showed a higher prevalence of MetS, even after adjusting for total T (1.374 [1.126–1.677]; P = 0.002).

**PSA as a Marker of Hypogonadism**

As expected, the prevalence of hypogonadism according to both biochemical (total T < 8 nmol/L) and clinical definition (total T < 8 nmol/L + any major sexual symptom, including ED, hypoactive sexual desire, and reduced spontaneous erection), was increased by a factor of two in patients with lower PSA levels, either in the whole population or in subjects with hypogonadism-associated morbidities, such as MetS or elevated fasting glucose (Table 4).

In order to investigate the accuracy of the PSA threshold of 0.65 ng/mL in predicting severe hypogonadism, we performed three separate ROC curve analyses according to age tertiles (I tertile = 17–47; II tertile = 48–59; and III...
tertile = 60–85 years). As shown in Figure 3, the accuracy in predicting severe hypogonadism was 69.8% (62.5–77.1%), $P < 0.0001$; 62.2% (54.7–69.6%), $P < 0.0001$; and 57.6% (50.8–64.4%), $P = 0.014$ for I, II and III tertiles, respectively. In addition, applying the value of 0.65, throughout the age tertiles, resulted toward a trend in increasing sensitivity (55.4%, 65.0%, and 76.2%) and positive predictive value (11.5%, 12.3%, and 16.9%) for I, II, and III tertiles, respectively, whereas specificity (72.0%, 57.5%, and 41.8%) and negative predictive value (96.1%, 94.7%, and 91.9%) were decreased according to increasing age tertiles. Figure 3 also shows age-specific optimal sensitivity and specificity for low PSA in predicting hypogonadism according to age tertiles. Based on ROC curves shown in Figure 3, in younger individuals, the optimal sensitivity and specificity were 66.4 and 61.3% for PSA = 0.56; in middle-aged subjects were 66.8 and 57.5% for PSA = 0.63; and in older subjects were 56.5 and 56.1% for PSA = 0.97. According to these

Figure 2 Hazard ratio (HR) and 95% confidence interval (CI) for prostate-specific antigen <0.65 ng/mL as a function of several hypogonadism-related comorbidities (upper panel), metabolic syndrome (MetS) components (middle panel) and several hypogonadism-related clinical features and sexual symptoms (lower panel). All data have been adjusted for age. CVD = cardiovascular diseases; HDL = high-density lipoprotein; mellitus; severe ED = erectile dysfunction; SREs = sleep-related erections; T2DM = type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed puberty</td>
<td>1.176</td>
<td>[1.030-1.344]</td>
<td>0.017</td>
</tr>
<tr>
<td>History of testicular diseases</td>
<td>1.848</td>
<td>[1.139-3.000]</td>
<td>0.013</td>
</tr>
<tr>
<td>History of CVD</td>
<td>1.275</td>
<td>[1.006-1.617]</td>
<td>0.045</td>
</tr>
<tr>
<td>History of T2DM</td>
<td>2.044</td>
<td>[1.675-2.494]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Elevated glycaemia</td>
<td>1.479</td>
<td>[1.245-1.758]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Elevated waist circumference</td>
<td>1.242</td>
<td>[1.042-1.479]</td>
<td>0.016</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>0.958</td>
<td>[0.787-1.167]</td>
<td>NS</td>
</tr>
<tr>
<td>Reduced HDL-cholesterol</td>
<td>1.407</td>
<td>[1.179-1.680]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Elevated triglycerides</td>
<td>1.076</td>
<td>[0.908-1.273]</td>
<td>NS</td>
</tr>
<tr>
<td>MetS</td>
<td>1.506</td>
<td>[1.241-1.827]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testis volume</td>
<td>0.967</td>
<td>[0.961-0.973]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>1.732</td>
<td>[1.200-2.499]</td>
<td>0.003</td>
</tr>
<tr>
<td>Severe ED</td>
<td>1.368</td>
<td>[1.023-1.828]</td>
<td>0.034</td>
</tr>
<tr>
<td>Severity SRE's reduction</td>
<td>1.085</td>
<td>[1.008-1.179]</td>
<td>0.034</td>
</tr>
<tr>
<td>Reduced frequency of intercourse</td>
<td>1.299</td>
<td>[1.023-1.659]</td>
<td>0.032</td>
</tr>
<tr>
<td>Stable relationship</td>
<td>1.292</td>
<td>[1.066-1.659]</td>
<td>0.044</td>
</tr>
<tr>
<td>Long lasting relationship (&gt;4 years)</td>
<td>1.265</td>
<td>[1.049-1.524]</td>
<td>0.014</td>
</tr>
<tr>
<td>Number of children</td>
<td>1.088</td>
<td>[1.000-1.183]</td>
<td>0.05</td>
</tr>
</tbody>
</table>

age-specific thresholds, the negative predictive values were 95.5%, 94.7%, and 91.9% and the positive predictive values were 12.8%, 12.9%, and 17.2% for younger, middle-aged, and older subjects, respectively.

Discussion

In this study, we demonstrated that low PSA can be considered a reliable biochemical marker of reduced bioactive circulating androgens in subjects consulting for SD, providing an index of low androgenization, which includes T-activated post-receptor downstream events. In particular, low PSA can predict hypogonadism-related symptoms and signs, even independently from total T levels. The androgen dependency of PSA is most probably related to the ARE present in the promoter of the PSA gene [17]. The accuracy (area under the ROC curve) of low PSA in screening potential hypogonadal subjects is decreasing as a function of age, being less sensitive but more specific in younger individuals. However, even in elderly subjects, a low PSA should raise the suspicion of a hypogonadal state. In aged subjects, high PSA might, in fact, have different determinants and therefore it retains less specificity.

According to Morgentaler and Traish [18,22], the human prostate is sensitive to massive androgen ablation (at castrate levels), but rather insensitive in normal or even in subnormal conditions (as in LOH). According to their hypothesis, the human prostate AR is indeed “saturated” by the

Table 4  Prevalence of hypogonadism, according to biochemical (Total T < 8 nmol/L) and/or clinical (Total T < 8 nmol/L + any major sexual symptom, including erectile dysfunction, hyperactive sexual desire and reduced spontaneous erection) definition, in subjects with prostate specific antigen (PSA) lower and higher than 0.65 ng/mL.

<table>
<thead>
<tr>
<th>PSA &lt; 0.65 ng/mL</th>
<th>PSA ≥ 0.65 ng/mL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total T &lt; 8 nmol/L</td>
<td>13.0%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Total T &lt; 8 nmol/L + symptoms</td>
<td>10.1%</td>
<td>5.1%</td>
</tr>
<tr>
<td>NHLB/AHA-defined MetS</td>
<td>Total T &lt; 8 nmol/L</td>
<td>18.3%</td>
</tr>
<tr>
<td>Total T &lt; 8 nmol/L + symptoms</td>
<td>15.2%</td>
<td>8.6%</td>
</tr>
<tr>
<td>History of impaired fasting glucose and/or T2DM</td>
<td>Total T &lt; 8 nmol/L</td>
<td>15.3%</td>
</tr>
<tr>
<td>Total T &lt; 8 nmol/L + symptoms</td>
<td>12.7%</td>
<td>7.4%</td>
</tr>
</tbody>
</table>

MetS = metabolic syndrome; NHLB/AHA = National Heart, Lung, and Blood Institute; American Heart Association; T = testosterone; T2DM = type 2 diabetes mellitus

Figure 3 Receiver operating characteristic curve for prostate-specific antigen (PSA) in the identification of total T < 8 nmol/L according to age tertiles. The black arrows indicate the threshold of 0.65 ng/mL, identified as the PSA value with the best sensitivity and specificity in detecting severe hypogonadism in the overall population. The red arrows indicate the thresholds with the best sensitivity and specificity in detecting severe hypogonadism as a function of age tertiles.
circulating androgens and therefore is rather insensitive to further T increase, such as those derived from T replacement therapy in cases of mild hypogonadism. We here reported that above the threshold of 8 nmol/L, PSA does not rise as a function of increasing total testosterone levels. Thereafter, PSA appears to become indifferent to higher concentrations of T. It might be inferred that T therapy in men with values above this point would not be expected to result in a rise in PSA, whereas men with T values below this point may very well experience a rise in PSA.

In our subjects, reduced PSA levels are associated with hypogonadism-related clinical features. ANDROTEST [27] and PsychoANDROTEST [30] are validated structured interviews for the screening of hypogonadism, which investigate physical and psychological symptoms associated with reduced T levels. In the present sample, we found that subjects with PSA levels lower than 0.65 ng/mL have higher ANDROTEST and PsychoANDROTEST scores, further suggesting the ability of low PSA in detecting relevant patient-related outcomes. According to this view, low PSA levels are also associated with a clinical history consistent with severe hypogonadism. In fact, we found a significant association with delayed puberty and history of testis diseases as well as with reduced testis volume and gynecomastia, which are typical clinical features of severe T deficiency [13,37,38]. In fact, subjects with low PSA have higher FSH levels, further suggesting testicular dysfunction. We did not find any difference in LH levels between subjects with higher and lower PSA levels, consistent with a mixed pathogenesis of hypogonadism. In accord with this hypothesis, subjects with lower PSA levels more frequently reported a positive history of MetS, T2DM, and CVD, disorders that are known to be associated with LOH [6–11]. Among the MetS components, we found that low PSA levels were associated with impaired glycemia and increased waist circumference, factors previously demonstrated to be specifically associated with hypogonadism [7]. In particular, we showed that waist circumference is the metabolic parameter most closely associated with hypogonadism [7,13,39]. Conversely, the association between reduced HDL-cholesterol and T levels is controversial [8,13,39–41]. When evaluating sexual symptoms, low PSA levels were associated with higher SIEDY scale 1 score and lower SIEDY scale 2 and 3 scores, suggesting that a low PSA identifies subjects with an SD involving the organic domain, rather than the marital or intrapsychic ones. Consistent with the view that T is important in regulating penile erection, we found a close association between low PSA and reduced sleep-related erection, a parameter that well reflects androgenicity in cohorts from the European general population [13] and from SD subjects [42]. Low PSA was associated only with severe ED, a finding in line with previous observations in our cohort [13]. Subjects with low PSA levels were more often engaged in a stable and long-lasting relationship. The decrease in T levels in men involved in a committed relationship has been demonstrated in several studies that analyzed the difference in androgen levels between paired and unpaired men [43]. Even fatherhood, and also a number of children, has been previously associated with the decrease of T [44,45], and in our study, we found that low PSA, as a mirror of a hypogonadal status, is a associated with a higher number of children.

The finding of an independent association of symptoms (ANDROTEST score), typical signs (reduced testis volume, gynecomastia), and metabolic correlates (MetS) of hypogonadism with a PSA value <0.65, even after adjusting for measured total T, indicates that low PSA can give insights on hypogonadism-related events that might not be captured by the total T itself. Hence, we speculate that a low PSA might reflect a lower AR stimulation, even though further studies should be performed to test possible association between CAG repeats and PSA. It is important to note that some, but not all, the studies indicate that a more transcriptional efficient AR (shorter CAG repeats) is associated with higher PSA levels and aggressiveness in subjects with prostate cancer [46]. The association between low PSA and gynecomastia is also quite unexpected because breast per se have been described as a prostate-independent source of PSA [47]. For this reason, in subjects with gynecomastia, the relationship with low PSA might be attenuated. Hence, the finding of a strong significant relationship between low PSA and gynecomastia is consistent with severe hypogonadism in these subjects, reinforcing our hypothesis.

Prostate development and size, and consequently PSA levels, are known to be androgen-dependent. In fact, a full prostate development during embryonic life requires a normal AR [48] and an efficient synthesis of dihydrotestosterone [49] so that a severe pre-pubertal hypogonadism [50] or a genetic defect of AR [48] or type 2 5α-reductase [49] results in an impairment of
prostate growth. In later life, the correlation between androgen levels and prostate size is attenuated, and both prostate volume and PSA increase with aging [19]. In fact, in this study, the accuracy of PSA in detecting hypogonadism decreases as a function of age. Based on the results described earlier, in the elderly, the finding of a low PSA is a strong indicator of hypogonadism, and it should prompt specific investigation; conversely, a normal or high PSA does not exclude hypogonadism in older subjects. The opposite is apparently true for youngest individuals.

Several limitations of the present study should be recognized. These results are derived from patients consulting an Italian Andrology Clinic for ED, which could have different characteristics from those consulting general practitioners or not seeking medical care. Furthermore, it should be recognized that results obtained in specific clinical settings cannot be easily generalized to wider populations. Conversely, phenomena observed in samples from the general population cannot always be extended to patients seeking treatment for a specific condition. In addition, the median PSA level was relatively low. However, it should be recognized that, in order to prevent possible bias in the analysis, only subjects without history of prostate disease and with PSA levels \(< 4\) ng/mL were included. Finally, testosterone levels used in this article derive from hormonal levels obtained in the morning of the first screening. Although abnormal values were usually re-tested during follow-up, we recognize that the lack of two morning testosterone levels is a limitation of the present study.

Conclusions

Our data demonstrate that a low PSA is a marker of reduced bioactive T concentrations and suggest that low PSA levels may represent a new tool in confirming severe hypogonadism, at least in SD subjects, having both a biochemical and a clinically relevance. As PSA levels summarize the biological activity of T at the level of one of the main androgen target tissue, i.e., the prostate, it is possible that its determination might give insights not only on the circulating levels of total T but also on its active fractions and, most importantly, in AR transcriptional activity. The efficacy of PSA as a screener for hypogonadism is modest and decreases as a function of aging, when PSA levels are affected by other factors, besides androgen activity. From a clinical standpoint, our data support the “saturation hypothesis,” suggesting that above 8 nmol/L total testosterone does not substantially contributes to further increase in PSA levels.

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Conflict of Interest: The authors report no conflicts of interest.

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