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Serum testosterone improves the accuracy of Prostate Health Index for the detection of prostate cancer

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ABSTRACT

Objective: Prostate cancer (PCa) detection suffers from low specificity when using the prostate-specific antigen (PSA) alone. The aim of this study was to investigate the applicability of total testosterone (tT), free testosterone (fT), the fraction (%) of fT to tT (%fT), and bioavailable testosterone (bioT) in serum to improve the diagnostic validity of the serum (−2)pro-PSA-based Prostate Health Index (PHI).

Design and methods: Total and free PSA (tPSA, fPSA), (−2)pro-PSA, testosterone, and sex-hormone-binding globulin were measured by automated immunoassays from serum of 193 men scheduled for prostate biopsy (99 PCa, 94 without PCa). fT and bioT were calculated using an online calculator. Statistical analyses were performed by non-parametric tests (Wilcoxon signed rank, Mann–Whitney, Kruskal–Wallis), binary logistic regression, and receiver operating characteristic (ROC) analyses.

Results: Compared with the non-malignant controls, PCa patients had significantly higher tPSA concentrations and PHI values, but lower %fPSA values and lower concentrations of tT, fT, and bioT. PCa could be differentiated from controls by PHI, tT, fT, bioT, and %fPSA. PHI showed the largest area under the ROC curve (AUC = 0.73) that was increased further by the inclusion of bioT or tT in a binary logistic regression model. The AUC of PHI in patients with tT concentrations of <8 nmol/L (indicating biochemical hypogonadism) was significantly larger than that in patients with higher tT values (0.86 vs. 0.70; P = 0.024).

Conclusions: The PHI-based discrimination between PCa patients and non-malignant controls could be improved by the simultaneous determination of testosterone. Patients with testosterone concentrations of <8 nmol/L have the greatest benefit.

Introduction

In prostate cancer (PCa) screening, the detection rate is associated with the concentration of prostate specific antigen (PSA) in serum [1,2]. Unfortunately, this relationship is limited by the low specificity of this biomarker for PCa. Additional parameters such as percent free PSA (%fPSA) and other PSA subforms improve the diagnostic accuracy [3,4]. However, only %fPSA has been routinely used to improve the specificity beyond PSA alone [3,4]. The inclusion of further clinical parameters – such as prostate volume, age, and status of the digital rectal examination – into multivariate models increases the diagnostic power [3].

Recently, the two new FDA-approved biomarkers, urinary PCA3 (Progensa, Hologic) and the serum (−2)pro-PSA-based Prostate Health Index (PHI, Beckman Coulter), showed promising results and an advantage compared with PSA or %fPSA [5–7]. A multicenter study in 1362 men demonstrated PHI's superior clinical performance compared with PSA and %fPSA [8]. A comparison of the newly FDA-approved biomarkers showed no difference between PHI and PCA3 and confirmed the further improved PCa detection compared with %fPSA [6]. Currently, these two markers can be considered as strongest biomarkers for early PCa diagnosis. In spite of this diagnostic progress, further efforts must be directed to search for new biomarkers and validate them, in order to reduce diagnostic procedures with lower positive predictive values like transrectal ultrasound or digital rectal examination and the number of prostate biopsies [3].

Recent studies have considered total, free, and bioavailable testosterone, as well as the sex-hormone binding globulin (SHBG), a carrier protein of testosterone in the blood, as potential biomarkers for PCa [9–17]. This increasing interest in testosterone resulted above all from the fact that emerging data contradict the long-established assumption that PCa is a carcinoma triggered by testosterone, with high testosterone

Abbreviations: AUC, area under the curve; bioT, bioavailable testosterone; %CV, percent coefficients of variation; fPSA, free PSA; fT, free testosterone; %fT, fraction (%) of free testosterone; NEM, no evidence of malignancy; %fPSA, % free PSA; PCa, prostate cancer; PCA3, prostate cancer antigen 3; PHI, Prostate Health Index; PSA, prostate-specific antigen; ROC, receiver operating characteristic; SHBG, sex-hormone binding globulin; tT, total testosterone; tPSA, total PSA.

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concentrations promoting PCa and low concentrations being protective [9,18,19]. It has been shown that testosterone concentrations within the physiological range are not related to the development of PCa [20]. In contrast, lower testosterone concentrations have been found to be associated with a higher rate of positive prostate biopsies and elevated Gleason scores, although this relationship could not always be confirmed [10–12,14,21–30]. Moreover, some studies have shown a positive correlation between SHBG concentrations and the presence of PCa on prostate biopsy [16,26,31]. The usefulness of testosterone and its components as PCa biomarkers has been partly proven in comparison to the diagnostic validity of the conventional parameters, total PSA and %fPSA [10,11,13,15,26,32]. To date, no studies have compared the diagnostic validity of testosterone or its components to the PHI as part of diagnostic algorithm for PCa detection. It is quite conceivable that the integration of testosterone and its components into the diagnostic procedure could improve diagnostic accuracy and the assessment of tumor aggressiveness.

The goal of this study was to investigate whether total testosterone (tT), free testosterone (fT), bioavailable testosterone (bioT), or their derivatives such as percent free testosterone (%fT) and percent bioavailable testosterone (%bioT), or SHBG are useful as single biomarkers, or in combination with the PHI, to improve the detection of PCa or to identify patients with potentially aggressive tumors.

Material and methods

Study population

This study was approved by the hospital ethics committee. All patients provided written informed consent for this research study. Serum samples were collected from 193 men scheduled for prostate biopsy (10–22 cores) between 2009 and 2012.

Study exclusion criteria included receipt of medications or surgical interventions that might alter PSA before blood sampling, a PSA concentration above 20 ng/mL, or urinary infections. Based on the prostate biopsy, patients were classified as either having PCa or no evidence of malignancy (NEM) (Table 1). The Gleason scores were estimated according to the 2005 consensus conference of the International Society of Urological Pathology [33].

Table 1
Characteristics of the patients stratified by diagnosis.[a]

Characteristics	PCa patients (n = 99)	NEM patients (n = 94)	P value[b]
Age, years	67 (61–71)	65 (59–70)	0.020
DRE, positive (%)	42.6; n = 97[c]	20; n = 90[c]	0.001
Prostate volume, cm^3	38 (29–56); n = 94[c]	50 (35–70); n = 90[c]	0.004
Gleason score, bioptic	<7, n = 49 7, n = 30 >7, n = 20		
PSA, ng/mL	7.10 (4.80–15.1)	5.70 (3.70–7.60)	0.0004
%fPSA	13.5 (8.86–17.7)	16.4 (11.0–19.5)	0.0006
PHI	59.9 (39.8–92.8)	36 (27.6–49.2)	<0.0001
Total testosterone, nmol/L	10.8 (7.32–14.5)	13.0 (9.26–15.6)	0.012
SHBG, nmol/L	38.2 (28.7–51.1)	39.8 (30.9–48.8)	0.947
fT, pmol/L	193 (147–226)	227 (175–272)	0.0005
bioT, nmol/L	4.26 (3.18–5.37)	5.44 (4.02–6.45)	0.0002
%fT	1.84 (1.54–2.10)	1.84 (1.59–2.10)	0.812
%bioT	41.4 (34.1–47.0)	42.2 (36.2–47.5)	0.564

PCa, prostate cancer; NEM, no evidence of malignancy; DRE, digital rectal examination; PSA, prostate specific antigen; %fPSA, percentage free PSA of total PSA; PHI, Prostate Health Index; SHBG, sex hormone-binding globulin; fT, free testosterone; bioT, bioavailable testosterone; %fT, percentage fT of total testosterone; %bioT, percentage bioT of total testosterone.

[a] Data are given as medians and interquartile ranges in parentheses except for the percentage of positive numbers of DRE.

[b] P values were calculated using the Mann–Whitney *U* test, except the DRE data that was analyzed with the test of difference for two proportions.

[c] Data available only from the indicated "n" patients.

Measurements of biomarkers

Prior to prostate biopsy, a fasting blood sample was collected from all patients between 8:00 AM and 11:00 AM. Serum was used for the assessment of PSA, free PSA (fPSA), (−2)pro-PSA, testosterone, and SHBG (Access 2, Beckman Coulter, Brea, CA) as previously described [8]. PSA values were based on the WHO-calibrated assays. The PHI was calculated according to the equation (−2)proPSA / fPSA * √PSA. The concentrations of fT and bioT were calculated according to the formula of Vermeulen et al. [34] using an online calculator (http://www.issam.ch). The two analytes were calculated with both the provided default albumin value of 43 g/L and the measured albumin concentration, using a bromcresol green method (mti-Diagnostics, Idstein, Germany).

The analytical performance was controlled by within-run and between-run measurements of control materials. Serum pools of two different concentrations of the five analytes (except for SHBG) were used for the within-run controls (n = 10). The percent coefficients of variation (%CV) were 1.4% and 1.2% for mean tPSA concentrations of 1.17 and 6.29 ng/mL, 3.7% and 1.9% for mean fPSA concentrations of 0.18 and 0.53 ng/mL, 7.2% and 5.5% for mean (−2)pro-PSA concentrations of 6.12 and 13.9 pg/mL, 2.8% and 1.9% for mean testosterone concentrations of 9.58 and 11.9 nmol/L, and 3.0% for mean SHBG concentrations of 36.9 nmol/L. The between-run precision and analytical accuracy were performed using control materials from Beckman Coulter for all PSA analytes and SHBG and using Lyphocheck Immunoassay control material from Bio-Rad Laboratories (Irvine, CA). The %CV values obtained in 8 measuring series using control materials of two different concentrations were 4.2% and 2.5% for mean tPSA concentrations (with target values of the control materials in parentheses) of 0.85 (0.84) and 11.5 (11.7) ng/mL, 5.7% and 2.8% for mean fPSA concentrations of 0.79 (0.77) and 10.6 (10.4) ng/mL, 4.9% and 4.4% for mean (−2)pro-PSA concentrations of 18.5 (19.2) and 158 (176) pg/mL, 6.3% and 8.0% for mean testosterone concentrations of 3.02 (3.23) and 27.5 (29.4) nmol/L, and 5.9% and 4.4% for mean SHBG concentrations of 9.2 (10.1) and 93.8 (101) nmol/L. All the values determined in the control materials were within the limits (mean target values ± 1 standard deviation) declared by the suppliers of the control materials.

Statistical analysis

Statistical analyses were performed with SPSS 21 (IBM Corporation, Somers, NY) and MedCalc 12.7.7.0 (MedCalc Software bvba; Ostend, Belgium). Several non-parametric tests (Mann–Whitney *U* test, Kruskal–Wallis test, Spearman rank correlation coefficient, and Wilcoxon matched pairs test) were performed and are indicated at the corresponding passages in the text. Receiver operating characteristic (ROC) analysis was used for estimating the area under the curve (AUC) according to DeLong et al. [35]. A P value <0.05 (two-side) was considered statistically significant.

Results

Characteristics of the study groups

The clinicopathological characteristics of the study groups and the median values of the measured and calculated analytes and their significant values are provided in Table 1. Prostate volume, %fPSA, tT, fT, and bioT were significantly lower in cancer patients than in non-malignant controls, whereas PSA and PHI were significantly higher in cancer patients. SHBG, %fT, and %bioT were not significantly different between the two groups.