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Original Article

Low levels of serum testosterone in middle-aged men impact pathological features of prostate cancer

Elton Llukani [1, 2], Benjamin F. Katz [1], Ilir Agalliu [3, 4], Andrew Lightfoot [1], Sue-Jean S. Yu [1], Martin Kathrins [1], Ziho Lee [5], Yu-Kai Su [1], Kelly Monahan Agnew [1], Alice McGill [1], Daniel D. Eun [5], David I. Lee [1, *]

[1] Division of Urology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
[2] Department of Urology, New York University School of Medicine, New York, NY, USA
[3] Department of Epidemiology and Population Health, Albert Einstein College of Medicine, New York, NY, USA
[4] Department of Urology, Albert Einstein College of Medicine, New York, NY, USA
[5] Department of Urology, Temple University Health System, Philadelphia, PA, USA

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ABSTRACT

Background: Serum testosterone deficiency increases with aging. Age is also a major risk factor for prostate cancer (PrCa) and PCa tumors are more frequently diagnosed among men >65 years old. We evaluated the relationship between preoperative serum testosterone and clinical/ pathological features of PrCa in middle-aged and elderly patients.

Methods: A total of 605 PrCa patients who underwent robotic-assisted radical prostatectomy between September 2010 and January 2013 at the University of Pennsylvania, and who had serum testosterone levels measured using Elecsys Testosterone II Immunoassay were included in this IRB-approved protocol. Androgen deficiency was determined as serum free testosterone (FT) <47 pg/ml and total testosterone (TT) <193 ng/dl. Demographic, clinical and tumor characteristics of men with low vs. normal TT or FT were compared using t-test or chi-square tests. Logistic regression was used to determine associations of clinical and pathological variables with FT or TT levels.

Results: Among middle-aged men (45–64 years; $n = 367$), those with low FT and low TT had, on average, a higher BMI (29.7 vs. 27.4, $P < 0.01$; and 32.2 vs. 27.6; $P < 0.01$, respectively) and higher proportion of Gleason 8–10 PrCa (13.3% vs. 4.8%, $P = 0.011$; and 19.2% vs. 5.1%, $P = 0.012$) compared to men with normal FT and normal TT values. Patients with low FT had also higher number of positive cores on biopsy (3.9 vs. 3.1 $P = 0.019$) and greater tumor volume (7.9 ml vs. 6.1 ml, $P = 0.045$) compared to those with normal FT. Among men ≥65 years ($n = 135$) there was no difference in prostatectomy specimens of PrCa between patients with low or normal FT or TT.

Conclusion: Among men aged 45–64 years low serum pretreatment FT and TT predicted more aggressive features of PrCa in prostatectomy specimens. In middle-aged patients low testosterone levels measured pre-operatively may indicate more aggressive disease parameters.

1. Introduction

Serum total testosterone (TT) measurements are used to assess the androgen status in men. Free testosterone (FT) is the clinically relevant fraction of TT, and serum levels of FT depend on the interplay between sex hormone binding globulin (SHBG) levels and its affinity for testosterone (T). Alterations in the complex T–SHBG interaction are commonly found in obese[1] and elderly[2] patients. The preferred method for androgen evaluation in these men is the measurement of serum FT levels. In addition, SHBG levels and function can be altered by several comorbidity conditions including liver disorders, thyroid disorders, diabetes mellitus, and hypo- or hyperalbuminemia.

The dependence of prostate cancer (PrCa) on serum androgen levels was demonstrated for the first time in 1941 by Huggins and Hodges[3] when they were treating patients with metastatic disease. Since then, various studies have analyzed the relationship between serum levels of T and risk of PrCa with conflicting results.[4–13] Although the association between T levels and overall PrCa risk is

* Corresponding author. Penn Presbyterian Medical Center, 51 North 39th Street, MOB 300, Philadelphia, PA 19104, USA.
E-mail address: David.Lee@uphs.upenn.edu (DI Lee).

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inconclusive, some studies have reported that low levels of preoperative T increases the risk of higher Gleason score PrCa,[4,5] advanced tumor stage,[6–9] and biochemical PrCa recurrence following radical prostatectomy (RP).[10,11]

Serum T deficiency is a complex multifaceted issue and the prevalence increases with age, making it more frequent in men over 65 years of age in comparison with middle-aged men.[14,15] The incidence of PrCa also increases with aging, and PrCa tumors are more frequently diagnosed in men over the age of 65 years in the USA.[16,17] Current treatment options for low-risk PrCa patients involve surgery, radiation, or active surveillance for the appropriately selected patient. It is imperative to decipher among the men with low-risk clinical stage who will overall benefit from a curative intent.

Currently, there is no study evaluating associations between prediagnostic FT and TT levels and pathological features of PrCa separately in middle-aged and elderly patients. We examined associations between serum T levels, and clinical and pathological features of PrCa in a cohort of PrCa patients who underwent prostatectomy, and then conducted stratified analysis in middle-aged versus elderly patients.

2. Materials and methods

2.1. Patients and data collection

We retrospectively reviewed medical records of 968 patients diagnosed with clinically localized PrCa (cT1–cT2) who underwent robotic-assisted laparoscopic RP performed by a single surgeon (D.I.L.) at the University of Pennsylvania between September 2010 and January 2013. All patients' information was collected in a prospective registry that was approved by our Institutional Review Board. A total of 605 patients who had their TT and FT levels measured using Testosterone II Immunoassay were screened for participation in the study. In order to evaluate the androgen status uniformly, patients were excluded from this study if their T levels were measured using an alternative assay ($n = 324$), were not collected preoperatively ($n = 39$), or if they had incomplete clinical data ($n = 11$). In addition, patients who had preoperative prostate resection (Transurethral resection of the prostate (TURP), $n = 10$), diabetes mellitus ($n = 62$), or hypo- or hyperthyroidism ($n = 20$) were excluded, because of potential T level variations in these diseases. No patient had hypo- or hyperalbuminemia, or prior use of androgen deprivation therapy. A total of 502 patients met the inclusion criteria.

Demographic, clinical, and pathological data that were collected from medical records and analyzed included reports on the age at surgery, body mass index (BMI; kg/m^2), race, preoperative prostate-specific antigen (PSA), clinical stage, serum TT and FT levels, prostate biopsy, and surgical pathology. Clinical stage was determined using the Union for International Cancer Control (UICC) 2002 tumor-node-metastasis (TNM) system. All pathological specimens were reviewed at our institution using standard pathology procedures.

2.2. T measurement

Serum levels of TT and FT were measured as part of the pre-RP evaluation protocol, and the time of collection was between 7 AM and 5 PM (during the work hours of outpatient laboratory testing). Both TT and SHBG were measured with the Elecsys 2010 analyzer by ARUP Laboratories (Salt Lake City, UT, USA) using the electrochemiluminescence immunoassay provided by Roche Diagnostics (Indianapolis, IN, US). The lower limits of detection of SHBG and TT were 1 nmol/L and 3 ng/mL, respectively. FT levels were calculated based on a mathematical model of the TT, SHBG, and albumin-binding equilibria using a novel spreadsheet method,[18] which provides an acceptable assessment compared with the gold standard of equilibrium dialysis. The threshold for hypogonadism was adjusted in accordance with patients' age and defined as FT levels <47 pg/mL and TT levels <193 ng/dL, using the definitions of ARUP Laboratories.

2.3. Statistical analyses

Demographic, clinical, and tumor characteristics between patients with low and normal FT or TT levels were compared using Student t tests for continuous normally distributed variables or Wilcoxon sign-rank test for continuous non-normally distributed variables, and Chi-square tests for categorical variables. We carried out these analyses among all patients as well as among middle-aged (45–64 years) and elderly (65 years or older) patients. For demographic, clinical, and pathological variables that were associated with low FT or TT levels in univariate analysis ($P < 0.05$), we fitted multivariate logistic regression models to examine associations in middle-aged and elderly patients. All tests were two sided using a significance level of $\alpha = 0.05$. Statistical analysis was performed using STATA version 13.0 (Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

3. Results

Of the 502 patients included in the study, 102 (20.3%) and 33 (6.6%) of men had preoperatively low serum FT and TT levels, respectively. In Table 1, we compared middle-aged patients with elderly ones and found that elderly patients presented a greater total Gleason score on biopsy ($P < 0.01$) or in surgical specimens ($P = 0.004$), a higher prostate volume ($P = 0.002$), and a higher pathological stage ($P = 0.03$).

The results of univariate analysis of characteristics among all patients with low T compared with those with normal T are presented in Table 2. Both patients with low FT levels and those with low TT levels were more likely to have an elevated BMI (FT groups: 29.4 vs. 27.4; $P < 0.01$; TT groups: 31.2 vs. 27.6; $P < 0.01$) and a greater percentage of positive lymph nodes (FT groups: 5.7% vs. 1.0%; $P = 0.002$; TT groups: 9.1% vs. 1.5%; $P = 0.003$) in comparison with the normal groups. For all patients, those with low FT levels were significantly more likely to have a greater number of positive cores on biopsy (3.9 vs. 3.1; $P = 0.014$) and a greater tumor volume (TV) in prostatectomy specimens (8.0 vs. 6.4; $P = 0.049$). All other pathologic findings were not substantially different between the two comparison groups.

We further examined demographic and clinical characteristics of patients stratified by age (i.e., middle-aged vs. older men). Table 3 shows a univariate comparison of low versus normal FT and TT levels in middle-aged patients (age 45–64 years). There were statistically significant differences between low ($n = 75$) and normal ($n = 292$) serum FT groups regarding BMI (29.7 vs. 27.4; $P < 0.01$), the number of positive cores (3.9 vs. 3.1; $P = 0.018$), total Gleason score on pathological report ($P = 0.011$), TV (7.9 vs. 6.1, $P = 0.045$), and positive lymph node rates (6.7% vs. 1%, $P = 0.003$). Among patients with low and normal serum TT levels, there were statistically significant differences regarding BMI (32.2 vs. 27.6, $P < 0.01$), total Gleason score on pathological report ($P = 0.012$), and positive lymph node rates (11.5% vs. 1.5%, $P = 0.001$).

Multivariate logistic regression was performed to analyze factors associated with a greater total Gleason score, a higher pathological stage, and positive lymph nodes in surgical specimens. Table 4 shows the predictors of a more aggressive total Gleason score in surgical specimens using a multinomial logistic regression model. Compared with patients with a Gleason score of 6, those with a Gleason score of 7 had increased preoperative PSA [Gleason