The Relationship between Total Testosterone Levels and Prostate Cancer: A Review of the Continuing Controversy

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Purpose: For many years it was believed that higher total testosterone contributed to prostate cancer and caused rapid cancer growth. International guidelines consider that adequate data are not available to determine whether there is additional risk of prostate cancer from testosterone replacement. Numerous studies with multiple designs and contradictory conclusions have investigated the relationship between total testosterone and prostate cancer development. To establish current knowledge in this field we reviewed the literature on total testosterone and the subsequent risk of prostate cancer as well as the safety of exogenous testosterone administration in patients with a history of prostate cancer.

Materials and Methods: We searched the literature to identify articles from 1994 to 2014 related to the relationship between total testosterone and prostate cancer. Emphasis was given to prospective studies, series with observational data and randomized, controlled trials. Case reports were excluded. Articles on testosterone replacement safety were selected by patient population (under active surveillance or with a prostate cancer history). We organized our results according to the relationship between total testosterone and prostate cancer, including 1) the possible link between low total testosterone and prostate cancer, 2) the effect of high levels and 3) the absence of any link. Finally, we summarized studies of the risk of exogenous testosterone administration in patients already diagnosed with prostate cancer, treated or on active surveillance.

Results: We selected 45 articles of the relationship between total testosterone and prostate cancer, of which 18 and 17 showed a relationship to low and high total testosterone, respectively, and 10 showed no relation. Total testosterone was defined according to the definition in each article. Contradictory findings have been reported, largely due to the disparate methodologies used in many studies. Most studies did not adhere to professional society guidelines on total testosterone measurements. One of 18 series of low total testosterone and prostate cancer adhered to published guidelines while none of 17 showing a relationship of high total testosterone to prostate cancer and only 1 of 10 that identified no relationship between total testosterone and prostate cancer adhered to measurements recommended in the guidelines. In 11 studies the risk of exogenous testosterone was examined in patients with a prostate cancer history. Many studies were limited by small cohort size and brief followup. However, overall this literature suggests that the risk of exogenous testosterone replacement in patients with prostate cancer appears to be small.

Conclusions: The relationship between total testosterone and prostate cancer has been an area of interest among physicians for decades. Conflicting results have been reported on the relationship between total testosterone and subsequent prostate cancer. Much of this controversy appears to be based on

Abbreviations and Acronyms

AR = androgen receptor
DHT = dihydrotestosterone
DRE = digital rectal examination
FT = free testosterone
PCa = prostate cancer
PSA = prostate specific antigen
SHBG = sex hormone-binding globulin
TRT = testosterone replacement therapy
TT = total testosterone

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Supplementary references 51 to 82 for this article can be obtained at http://jurology.com/.

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conflicting study designs, definitions and methodologies. To date no prospective study with sufficient power has been published to unequivocally resolve the issue. The preponderance of studies of the safety of exogenous testosterone in men with a prostate cancer history suggests that there is little if any risk. However, because the risk has not proved to be zero, the most prudent course is to follow such men with regular prostate specific antigen measurements and digital rectal examinations.

Key Words: prostatic neoplasms; testosterone; hypogonadism; neoplasm recurrence, local; prognosis

PROSTATE cancer is the most commonly diagnosed cancer in males with an estimated 233,000 new cases in 2014.[1] During the most recent 5 years for which data are available the PCa death rate decreased as a result of improved early detection and treatment.[1] Therefore, more patients are living with a history of PCa.

The prevalence of symptomatic hypogonadism in men 30 to 79 years old has been reported to be 5.6%.[2] It is estimated that by 2025 approximately 6.5 million American men 30 to 80 years old will be diagnosed with androgen deficiency.[2] Moreover, clinical evidence supports TRT in hypogonadal patients with erectile dysfunction, which is a frequent complication of PCa treatment.[3]

According to the recommendations of ISA (International Society of Andrology), ISSAM (International Society for the Study of the Aging Male), EAU (European Association of Urology), EAA (European Academy of Andrology) and ASA (American Society of Andrology) late onset hypogonadism is "a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels."[4] The diagnosis of hypogonadism in older men is complicated by the fact that its clinical presentation is nonspecific and overlaps with that of other illnesses and with the aging process. Many older men (more than 20% in some studies) have testosterone levels that are lower than the normal range in younger men. This is why a combination of symptoms and low testosterone is required to confirm a diagnosis of hypogonadism.[5] Thus, relevant TT measurement is mandatory.

It was believed for a long time that higher TT contributed to PCa development and caused rapid cancer growth. International guidelines show that adequate data are not available to determine whether TRT carries an additional risk of PCa.[4] Thus, it seemed appropriate to study the relationship between TT and subsequent PCa as well as the risk of TRT in men with a history of PCa.

MATERIAL AND METHODS

We searched the literature using the PubMed® database to identify English language articles related to the relationship between TT and PCa. The search was extended using the key words prostate cancer, testosterone, hypogonadism, recurrence and prognosis. All articles from 1994 to 2014 were reviewed and emphasis was given to those that were prospective, contained observational data or were randomized, controlled trials. Articles on the safety of testosterone replacement were selected according to patient population (on active surveillance or with a PCa history).

RELATIONSHIP OF TT TO PCa

Low TT

Incidence. A prospective study of 206 consecutive patients with benign prostatic hyperplasia or PCa recently showed that low TT (less than 2.4 ng/ml) was an independent predictor of PCa with statistical significance on multivariate analysis (88.3% vs 85.4%, $p = 0.001$, table 1).[6] The PCa incidence was significantly higher in the low testosterone group (less than 3.85 ng/ml) comprising 568 patients who underwent prostate biopsy compared to the high testosterone group (38.9% vs 29.5%, $p = 0.018$).[7] In a prospective multicenter study of 718 men in a prostate screening program using a cutoff PSA of 3.0 ng/ml or greater patients with PSA less than 10.0 ng/ml and lower TT (mean 3.6 ng/ml) were at increased risk for PCa (OR 0.13, 95% CI 0.05–0.35, $p = 0.0001$).[8] In a population of 345 hypogonadal men (less than 4 ng/ml) PCa was detected in 21% of those with lower TT (less than 2.5 ng/ml) compared to 12% in those with normal testosterone ($p = 0.04$).[9]

In contrast, in the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) trial, which was limited by prior negative biopsy as an entry criterion, 596 men (18%) with the lowest baseline TT in the placebo group with low baseline TT and PSA 2.5 to 10 ng/ml were at lowest risk for PCa.[10] Thus, the association between TT and PCa risk on initial biopsy was not tested.

Biopsy. García-Cruz et al prospectively evaluated 137 men diagnosed with PCa.[11] TT was inversely related to PCa bilaterality ($p < 0.01$) and percent of tumor in the biopsy ($p = 0.006$).

Grade. On multivariate analysis of 137 positive prostate biopsies lower TT was related to a higher D'Amico risk of progression ($p = 0.038$).[11] A recent