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Original article

The testosterone conundrum: The putative relationship between testosterone levels and prostate cancer

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Abstract

Background: The controversy surrounding the relationship between testosterone and prostate cancer has existed for decades. The literature surrounding this topic is confusing and at times contradictory. There is no level-one quality evidence that confirms or refutes the relationship between either high or low serum testosterone levels and the subsequent development of prostate cancer. This commentary aims to review the issues involved and to provide an interpretation as to the causes of the confusion and to provide a framework for ongoing discussion and investigation.

Materials and methods: A Medline and PubMed search was conducted using search terms: testosterone levels and prostate cancer to identify pertinent literature.

Results: There is no consistent evidence that a single testosterone level is predictive of prostate cancer risk.

Conclusion: The development of prostate cancer is a complex biologic process potentially involving genetics,dietary, life style and hormonal factors. Serum testosterone levels do not accurately reflect the internal prostatic milieu. Finally, if testosterone levels are to be considered in the etiology of prostate cancer they should be measured and interpreted on a chronic basis with multiple measurements over a period of years.

Keywords: Testosterone; Prostate cancer; Relationship

1. Introduction

The putative relationship between serum testosterone and prostate cancer was first described by Charles Huggins over 7 decades ago [1]. It has remained controversial since that time. This ongoing controversy is because of multiple factors that we will review. First, throughout the literature, there have been variable methodologies employed for testosterone measurement. Second, there is compelling evidence that serum testosterone levels do not reflect intraprostatic testosterone levels. Third, the role of the androgen receptor has not been considered in the interpretation of serum testosterone results. Fourth, the potential of the contribution of chronic testosterone levels over years rather than a single or several recent testosterone levels, and the subsequent development of prostate cancer has been largely ignored. Finally, a more thorough examination of intraprostatic androgen levels in benign and malignant prostate tissue has received only cursory examination in the literature.

A review of the literature regarding the possible causal relationship between a single often random, testosterone level, and the diagnosis of prostate cancer appears stochastic at best. An apt analogy would be that of a single glucose level in a diabetic or a single blood pressure reading in a hypertensive patient. No physician would extrapolate the status of the coronary endothelium based on a single or even several serum glucose readings, nor would one make conclusions regarding the vascular tree on the basis of a few blood pressure values. In a similar fashion, it is tenuous to surmise any causal relationship based on a paucity of data such as one or several serum testosterone levels and the development of prostate cancer. In most cases, the prostate cancer that is diagnosed has been present for months or years and is likely because of both systemic and local factors as well as heredity, environmental, and dietary contributions. To posit a

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relationship between a single, sometimes random, testosterone level is unlikely, taken in isolation, to provide significant insight into the complex pathophysiology of prostate cancer.

As part of the Massachusetts Male Aging Study, Feldman et al. [2] reported on longitudinal serum testosterone levels in 1,156 men who were followed for 7 to 10 years as part of the Massachusetts Male Aging Study. They found that total T declined at 0.8%/y of age over time, whereas both free-bound and albumin-bound T declined at approximately 2%/y. Sex hormone–binding globulin increased at 1.6%/y so that the biologically available testosterone was demonstrated to decrease with aging.

A more recent report by Araujo et al. [3] estimated the crude prevalence of androgen deficiency at baseline in the 40 to 69-year-old U.S. male population to be 12.3%. Prevalence increased significantly with age and the authors estimated that there were approximately 2.4 million hypogondal men in the age group in the United States.

What remains unanswered is what effect, if any, do chronic testosterone levels over decades have on the subsequent development of prostate cancer. Does a faster or slower decrease of serum testosterone over decades influence the ultimate development of prostate cancer? That answer is unknown. We only know that prostate cancer is typically diagnosed when men are older and their serum testosterone levels are at their nadir. The contribution of chronic testosterone levels to the development of prostate cancer remains unclear.

2. Methodology issues

A recent systematic review identified 45 studies that examined the link between serum testosterone levels and prostate cancer [4]. Of these studies, 18 showed a link between low serum T and prostate cancer, 17 demonstrated a link between high serum T and prostate cancer, and 10 identified no relationship between serum T level and prostate cancer. Of these 45 studies, only 2 adhered to the methodology recommended in professional society guidelines [5].

The methodological differences in these studies were significant. They varied in the time of specimen collection, the number of samples collected and the assays used. Brambilla et al. [6] reported a 10% intraindividual variation in morning vs. afternoon testosterone levels and Collier et al. [7] found similar results. The intraindividual biological variation in morning testosterone was 18.7% whereas intraindividual biological variation on the same day was 12.9% [7]. Therefore, a single testosterone level which was used by many of these studies can be inadequate to accurately characterize levels in an individual.

3. Discordance between serum T and intraprostatic T

The serum testosterone level has been shown by several investigators not to be a reflection of intraprostatic testosterone levels. Marks et al. [8] reported a randomized double-blind, placebo-controlled trial of 44 hypogonadal men (screening serum T less than 300 ng/dl) age 44 to 78 years randomly assigned to receive 150 mg of testosterone enanthate or placebo every 2 weeks for 6 months.

The testosterone replacement therapy increased serum testosterone levels to the normal range, (282–640 ng/dl), whereas there was no significant change in the serum levels of the placebo group. However, the median prostate levels of testosterone and dihydrotestosterone did not change significantly from baseline (0.9) to 1.55 ng/g (p0.29), 6.79 to 6.82 ng/g (p0.51), respectively.

Additional evidence suggesting that serum testosterone does not accurately reflect intraprostatic testosterone levels is provided by Page et al. [9] In this small study of healthy volunteers, despite a 94% drop in serum T following medical castration, intraprostatic T, and DHT levels remained at 20% to 30% of control values.

4. Role of the androgen receptor

The controversy regarding the possible link between serum testosterone levels and prostate cancer has largely ignored the role of the androgen receptor (AR). The AR gene is located on the X-chromosome at the locus Xq11 to Xq12. The AR gene encodes a 110 kDa protein consisting of 919 amino acids. The AR consists of 3 major functional domains —(1) N-terminal domain (NTD), (2) the DNA binding domain (DBD), and (3) the C-terminal ligand binding domain (LBD). It has been reported that 159 mutations of the AR can predispose males to prostate cancer [10].

It has been suggested that the length of the CAG repeats in the first exon of the gene (N-terminal domain) correlates with the risk of prostate cancer [11]. An association exists between the fewer androgen receptor gene CAG repeats and the higher risk of prostate cancer [12].

In addition to the early data, there is animal data to suggest a change in the AR with aging. Gallon et al. [13] reported a change in cytosolic androgen receptor levels in the epididymis, vas deferens, and seminal vesicles of mice with aging. Ono et al. [14] demonstrated that there were no significant age-related changes in binding sites and affinity of the glucocorticoid receptor in cultured pubic skin fibroblasts, whereas the binding sites of AR significantly decreased as men aged.

A further caveat regarding the interplay of serum testosterone and the androgen receptor was reported by Mostaghel et al. [15] They measured androgen levels and androgen-regulated gene expression in prostate samples from a clinical trial of short-term castration (1mos) using a gonadotropin-releasing hormone antagonist, Acycline vs. placebo in healthy men. Gene expression measurements were evaluated at baseline and after 3, 6, and 9 months of neoadjuvant ADT in prostatectomy samples from men with localized prostate cancer. Although medical castration reduced tissue androgens by 75% and reduced the