Testosterone replacement therapy and prostate cancer: the collapse of a paradigm?

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Abstract

For six decades, it has been a part of the conventional medical wisdom that higher levels of testosterone increase the risk of prostate cancer. This belief is mostly derived from the well-documented regression of prostate cancer after surgical or pharmacological castration. However, there is an absence of scientific data supporting the concept that higher testosterone levels are associated with an increased risk of prostate cancer. Moreover, men with hypogonadism have substantial rates of prostate cancer in prostatic biopsies, suggesting that low testosterone has no protective effect against the development of prostate cancer. Moreover, prostate cancer rate is higher in elderly patients when hormonal levels are low. These results argue against an increased risk of prostate cancer with testosterone replacement therapy.

Resumen

Por casi seis décadas ha sido parte de la cultura médica en general, que los niveles altos de testosterona incrementan el riesgo de padecer o agravar un cáncer de próstata. Esta creencia se ha derivado fundamentalmente de la bien documentada regresión del cáncer de próstata luego de la castración médica o quirúrgica. Sin embargo, no existe evidencia científica que apoye la idea de que niveles altos de testosterona están asociados con un incremento del riesgo de cáncer de próstata. Más aún, los hombres con hipogonadismo tienen una tasa substancialmente alta de cáncer de próstata detectado por biopsia, lo que sugiere que los niveles bajos de testosterona no tienen un efecto protector en el desarrollo de cáncer de próstata y, además, la tasa de cáncer de próstata es más alta en los pacientes de edades avanzadas cuando sus niveles hormonales son más bajos. Estos argumentos tienden a demostrar que no existiría un incremento del riesgo de padecer un cáncer de próstata asociado a la terapia de reemplazo con testosterona.
Introduction

It has been over 60 years since Huggin et al. reported their research proving that castration led to metastatic prostate cancer regression, establishing a perpetual relationship between prostate cancer and testosterone[1]. The recognition that this type of tumor is mainly androgen-dependent has resulted in trying to avoid testosterone replacement even in patients with symptoms and signs of hypogonadism.

Moreover, surgical or pharmacological castration is still the gold standard treatment for advanced prostate cancer. Therefore, if testosterone reduction induces prostate cancer cell apoptosis, increasing testosterone levels should produce the opposite effect.

Even more, there is a growing recognition within the medical community that hypogonadism is an especially significant treatable medical condition that increases with aging. In this sense, the benefits of testosterone replacement are well documented, including an improvement in libido, erectile function, cognitive function, as well as body mass distribution and reduced bone loss [2]. Hence, how can we balance the benefits of testosterone replacement with the potential risk of developing prostate cancer?

After all these years, there is no solid evidence that testosterone replacement poses a real risk for developing a new cancer or induces prostate cancer progression. Therefore, our aim is to perform a systematic review about testosterone replacement and its relationship to prostate cancer. Also, to try to clarify whether this hormone replacement is related to the risk of increasing the severity of prostate cancer or possibly modifying its aggressiveness.

Methods

A systematic review of the literature was conducted using the Medline/PUBMED and Cochrane databases. Search terms included “prostate cancer, testosterone, hypogonadism and risk”. A total of 134 articles were assessed by the same author including those publications up to 2014, in English and with the highest level of evidence [3].

Evidence

Testosterone effect over benign prostate tissue

In males, 90% of testosterone is produced by Leydig cells in the testicle and the remaining 10% by the adrenal glands. Once inside the prostate cell, testosterone is irreversibly transformed into its active metabolite named dihydrotestosterone by 5-reductase. It joins to an intracytoplasmic receptor to produce complex information-stimulating androgen regulatory genes as a final pathway [4]. Although testosterone is required for prostate development and the normal prostate has shown to be androgen-dependent, it does not follow that elevated testosterone levels result in larger prostatic growth. Morgentaler and Traish, demonstrated that beyond a given testosterone concentration, there is a limit to its ability to stimulate prostate growth. This means that higher levels of testosterone do not necessarily produce increased prostate stimulation [5]. This phenomenon is due to intracytoplasmic receptor saturation demonstrated initially in animal studies [6],[7].

In men, this phenomenon can be also reflected by prostatic specific antigen (PSA) and prostate gland volume. Testosterone replacement in patients with hypogonadism resulted in elevated prostate specific antigen and prostate volume although not significantly [8],[9], or only 15% such as Rodh and Morgentaler reported[10]. Furthermore, it is shown that even increasing testosterone concentration to supraphysiological levels in eugonadic patients does not produce changes in these parameters [11],[12].

Even more, several communications have reported that patients with prostate cancer, where growth and epithelial mitosis are increased, have lower testosterone compared to patients with benign prostatic hyperplasia [13]. Besides, low levels of free testosterone are associated with more aggressive prostate cancer[14]. Although Morgentaler and Morales referred to the studies that support the concept of “saturation model” which were conducted in animals or in vitro, and that the evidence is purely theoretical and clinically tested [15]; recently one meta-analysis has demonstrated that short-term testosterone supplementation would not lead to an increased risk of prostate cancer [16].

Clinical cases

Many studies have reported clinical cases describing prostate cancer development after testosterone replacement for hypogonadism [17], for example, Loughlin y Richie communicated a total of 20 cases [18]. The time between testosterone replacement onset and prostate cancer diagnosis was up to eight years.

These communications of only clinical cases have been used as an argument to demonstrate the relationship between testosterone replacement and prostate cancer; albeit they only propose an association, not cause-effect. Because prostate cancer is diagnosed with more frequency and testosterone deficiency syndrome is increasing significantly, with an estimated incidence of more than 500,000 new cases in men between 45 and 69 years in the United States [19],[20],[21],[22], it is critical to demonstrate that testosterone replacement in these patients has any relationship to prostate cancer initiation or progression.

It is common in daily practice for urologists to detect a sudden PSA increase or abnormal prostatic density in rectal examination that will trigger a biopsy. Since most of these changes occur without a precipitating event, any idea that testosterone replacement induces prostatic changes, requires some evidence that this hormone can increase cancer rate in these men. Without this information, publications or clinical case series do not provide useful information or have statistical significance.
**Testosterone replacement in men at high-risk of prostate cancer development**

Since the relationship between prostate cancer and testosterone is controversial, the greatest dilemma appears in those patients at high risk of developing prostate cancer. High-grade intraepithelial prostatic neoplasia (HGPIN) has been classified in several publications as a preneoplastic lesion [23]; therefore, it would be a good scenario to evaluate the effect of testosterone replacement.

Rhoden and Morgentaler evaluated prostate changes after one year with hormone replacement therapy in patients with hypogonadism [24]. Seventy-five patients were enrolled and divided into two groups: those with previously diagnosed benign prostatic lesion as Group 1 (n=55) and those with HGPIN (n=20) as Group 2. After twelve months; total and free testosterone, prostate specific antigen and digital rectal examination were assessed. In those patients with a PSA elevation greater than 1 ng/dL or any digital rectal examination abnormality, a new biopsy was performed. There were no statistically significant differences in PSA in both groups (1.82 ± 1.1 vs 1.78 ± 1.6 ng/dL; p > 0.05). Only one patient with HGPIN demonstrated an increased PSA and rectal examination abnormality after one year of testosterone replacement. The patient underwent prostate biopsy showing at the final histological exam an upgrade to Gleason 7 (3+4). The authors concluded that hormone replacement therapy for 12 months in patients with hypogonadism and HGPIN diagnosis does not lead to an increased risk of developing prostate cancer; hence, HGPIN should not contraindicate testosterone replacement. This retrospective publication demonstrates that might be safe to use testosterone replacement therapy even in patients with increased risk of developing prostate cancer as well as those with a previous diagnosis of HGPIN.

**Testosterone replacement in patients with prostate cancer**

More and more men with prostate cancer choose active surveillance as an alternative treatment, and some of them could present symptoms of testosterone deficiency [25]. This scenario allowed Morgentaler et al. to evaluate testosterone replacement in hypogonadal patients with untreated prostate cancer [26]. The authors communicate outcomes from prostate biopsies, prostate specific antigen and prostate volume in 13 patients with testosterone deficiency syndrome who were treated at least 12 months with testosterone, while on active surveillance for prostate cancer. Initially, Gleason Scores were 6 (3+3) in 12 patients and 7 (3+4) in the other. The average testosterone replacement period was 2.5 years (range from 1 to 8.1 years) and the follow up was to measure PSA every 3 months and perform a prostate biopsy annually. Testosterone replacement effectiveness was demonstrated by elevating the mean serum total testosterone from 238 ng/dL to 668 ng/dL (p <0.001). In all patients the value of prostate specific antigen and prostate volume remained unchanged with testosterone replacement. In 54% prostate cancer was not found in biopsies during follow-up. Two patients showed disease progression at prostate biopsy. One of them, with Gleason Score 6 (3+3), presented an upgrade to Gleason Score 7 (3+4) in 5% of one prostate sample; therefore, the patient continues under active surveillance with two subsequent annual biopsies presenting Gleason 6 prostate cancer. In the other patient the upgrade was to Gleason 7 (4+3) and he underwent radical prostatectomy. The final histological exam revealed a Gleason 6 (3+3) prostate cancer, which was the same as the initial biopsy. While this study enrolled few cases (n=13), prostate cancer was low risk, retrospective and uncontrolled; the authors demonstrated that testosterone replacement in patients with prostate cancer under active surveillance was not associated with cancer progression within the medium-term follow up. This is the first report to provide a direct evidence of testosterone effects in a group of patients with testosterone deficiency syndrome associated with untreated prostate cancer. Recently, Cui et al. published a meta-analysis of 22 randomized controlled studies demonstrating the short-term safety of testosterone replacement, without promoting prostate cancer development and progression [16], which confers Level 1A of evidence.

**Longitudinal studies of endogenous testosterone levels and prostate cancer risk**

Longitudinal studies represent one of the most powerful tools to investigate the potential effect of serum hormone levels in developing prostatic cancer. There have been population-based longitudinal studies, looking at the relationship between testosterone endogenous levels and prostate cancer risk, enrolling hundreds of patients [27],[28]. Blood samples were taken at baseline and then were followed for 10 or more years. At the end of the study, a cohort of patients developed prostate cancer. Blood samples collected several years before in this group of patients with prostate cancer were analyzed and compared for differences in testosterone levels with the group without evidence of prostate cancer. None of the studies demonstrated differences in testosterone levels among men who developed cancer and those who did not. Moreover, in men with high testosterone levels, there was no increased risk of cancer when compared to men with low testosterone levels. Although a study with \textit{Physician Health Study} data demonstrated a relationship between prostate cancer to elevated testosterone levels and low levels of sex-hormone binding globulin [29], current evidence has not allowed to establish differences in testosterone levels between normal and cancer group. Although these studies do not assess the role of testosterone replacement directly, they show repeatedly, consistently and with high level of evidence that elevated testosterone levels are not associated with an increased cancer risk [30],[31],[32],[33],[34].

Also, it is known that obese patients have worse prognosis after primary treatment for prostate cancer [35]; these patients present with lower testosterone levels compared to patients with normal weight [36]. Again, the relationship between low testosterone levels and prostate cancer is demonstrated.
What happens to men with low testosterone?
If elevated testosterone levels are a risk for developing prostate cancer; then, it should be assumed that low testosterone would be protective. Is this correct? Interestingly, there are studies that have shown a relationship between low testosterone levels and prostate cancer [37],[38]. Morgentaler y Rodhen [37], determined prostate cancer prevalence in patients with hypogonadism and PSA at or below 4 ng/ml. A total of 345 patients were enrolled and evaluated by digital rectal examination and prostate biopsy before initiating testosterone replacement. Total testosterone less than 300 ng/dL and free testosterone than 1.5 ng/dL were considered as inclusion criteria. Prostate biopsy reveals 15.1% prostate cancer. The prostate cancer rate was 5.6%; 17.5%; 26.4%; and 36.4% for PSA values less or equal than 1, 1.1 to 2, 2.1 to 3 and 3.1 to 4 ng/ml; respectively (p = 0.05). Prostate cancer detection was 21% for patients with less or equal to 250 ng/dL testosterone compared with 12% whose testosterone levels were greater than 250 ng/dL (p = 0.04). The authors concluded that prostate cancer occurs in more than one of seven patients with hypogonadism and prostate specific antigen less or equal to 4 ng/ml. Furthermore, an increased prostate cancer risk was associated with lower testosterone, i.e. an inverse association. Additionally, other studies have shown that low testosterone is associated with advanced pathologic stage, worse Gleason score and biochemical recurrence after radical prostatectomy [30],[39]. Even with this evidence, testosterone replacement remains controversial.

The testosterone and prostate cancer paradox
As has been discussed in this review, literature review clearly fails to demonstrate a competent evidence that high testosterone levels, either endogenous or by testosterone replacement, increases prostate cancer risk. But this is still an open question, since by reducing testosterone levels to castrationi ranges has a beneficial effect on prostate cancer causing most cells to enter apoptosis; why then, high testosterone levels do not cause prostate cancer growth and represent a demonstrable risk for men with hidden cancers? This paradox appears to be best explained by the fact that testosterone replacement in hypogonadal men is not the opposite of medical castration. Whereas castration decreases testosterone levels to very low values, most men during testosterone replacement have substantially lower circulating levels of testosterone. It seems that, even in a man with hypogonadism, circulating testosterone levels would exist to satisfy the metabolic requirements of any preexisting prostate cancer.

The other part of the explanation is the concept of how testosterone affects prostate growth. We tend to think that this relationship is a dose/response curve, where high levels of testosterone lead to increased prostate growth. But most biological systems reach a plateau at a given growth factor concentration, this fact probably being related to the relationship between testosterone and prostate cancer. Therefore, high serum testosterone does not provide additional prostatic growth (Saturation Model) [5].

What do clinical guidelines say about testosterone replacement and prostate cancer?
Currently, there are different clinical guidelines about testosterone deficiency syndrome management [40],[41]. There is no evidence that high total testosterone increases the risk of developing prostate cancer, neither that it converts a subclinical or indolent cancer into a more aggressive cancer. However, the guidelines clearly contraindicate testosterone replacement in patients with prostate cancer. Therefore, prostate cancer risk should be investigated with digital rectal examination and prostate specific antigen before initiating testosterone replacement in all patients. On the other hand, testosterone replacement in patients with prostate cancer already successfully treated, a guideline from the European Urological Association (EUA) recommends that it can be considered after no clinical or biochemical recurrence [40]. Although it is not known which is the period that must elapse from primary treatment and testosterone replacement because there is no evidence from randomized studies that demonstrate when is the appropriate moment.

Conclusion
Despite multiple attempts to demonstrate that high testosterone levels lead to an increased prostate cancer risk, there is no competent scientific evidence that validates this hypothesis. Physicians should take this into account when considering testosterone replacement in hypogonadal men. However, the current concepts regarding hormones and cancer, make it imperative that men receiving testosterone replacement are subject to monitoring prostatic gland with digital rectal examination and prostate specific antigen, two to three times the first year and then at least annually. In case of prostate cancer suspicion such as an elevated PSA or an abnormal digital rectal exam, a prostate biopsy should be performed prior to testosterone replacement. However, this recommendation applies to all men, regardless of whether they receive testosterone replacement therapy or not.

As physicians, it is our duty to make decisions for each patient, assessing risks and benefits. With proper monitoring, testosterone replacement seems to be safe and can be an effective treatment for many men with testosterone deficiency syndrome.

While the final chapter regarding the potential risk of testosterone replacement for prostate cancer has not yet been written, currently we know that there is insufficient evidence to support the belief that testosterone replacement increases prostate cancer risk.

Notes
Potential conflicts of interest
The authors have completed the Uniform Disclosure Form for Potential Conflicts of Interests from ICMJE and declare not having received any financial support for writing this article and not having any conflict of interests with its subject.
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