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REVIEW ARTICLE

Hypogonadism and its treatment among prostate cancer survivors

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Abstract
Adult-onset hypogonadism (AOH) is associated with sexual dysfunction, poor bone mineralization, decreased muscle mass, metabolic syndrome disorder, and cognitive suppression. Historically, testosterone has been contraindicated in men with a history of prostate cancer. However, there has been a modern resurgence in re-evaluating this belief. Not only can testosterone be safely utilized to alleviate AOH symptoms in prostate cancer survivors, it has been also touted as a treatment option for aggressive prostatic cancer. While much work remains in understanding the relationship between testosterone and prostate cancer, those who survive this disease should not be automatically turned away from an opportunity to be treated and restored.

Introduction

Adult-onset hypogonadism (AOH) is characterized by the low levels of testosterone in conjunction with symptoms of androgen deficiency, which includes sexual dysfunction, reduced libido, hot flashes, gynecomastia, diminished muscle mass, bone density loss, depressed mood, and sleep disturbances [1–4]. Furthermore, metabolic disorders, such as type 2 diabetes mellitus, hypertension, and obesity, are significantly associated with decreased testosterone levels [5, 6]. AOH and its complications are chronic processes with large population studies reporting that the average adult male experiences an annual decline of 0.8–1.6% in their total testosterone (TT) and, more dramatically, a 2–3% drop in free testosterone (FT) [7, 8]. The Massachusetts Male Aging Study (MMAS) found the prevalence of AOH to be 6.0% among men 40–69 years old, rising to 12.3% after 8.8 years of follow-up [8]. Inferring from the MMAS, the incidence of AOH approaches 481,000 annually in the United States [9]. In a similar vein, the risk of prostate cancer also coincides with aging as 0.005% of men younger than 39 years are at risk, while 13.7% of men between 60 and 79 years of age will develop prostate cancer [10]. Thus, with aging, a greater proportion of men will be diagnosed with AOH in conjunction with prostate cancer [11].

Since the early 1990s, prostate cancer-specific mortality rates have steadily fallen coinciding with the introduction of widespread prostate-specific antigen (PSA) screening and improved surgical technique [12–14]. In the United States, it is estimated that in 2020 there will be 191,930 new cases of prostate cancer, 33,330 related deaths, and ~3.1 million men currently alive with the diagnosis [15]. In light of this, modern management has begun to incorporate quality and longevity of life after definitive therapy to assist patients in managing decreased libido and sexual dysfunction secondary to treatment [11, 16]. Historically, testosterone replacement therapy (TRT) has been contraindicated in men with prostate cancer due to fears of exacerbating their disease [17, 18]. However, modern studies on the application of TRT in survivors of prostate cancer has vastly transformed our understanding [19, 20]. In this review, we aim to discuss the historical significance of testosterone in prostate cancer, the studies that led to the introduction of the "saturation model", and the current application of testosterone in prostate cancer survivors.

Testosterone physiology and the prostate

Androgens are a group of sex hormones, which include testosterone and its more potent metabolite, dihydrotestosterone (DHT) [21]. Approximately 90% of circulating testosterone is produced in the testes by Leydig cells, while the remaining 10% are from the adrenal glands [21, 22]. DHT is synthesized locally by the conversion of circulating testosterone within the

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prostate, testes, hair follicles, and adrenal glands [21, 23]. During puberty, a surge in androgens causes the prostate to swell in volume 10-fold, while, in adulthood, DHT continues to promote linear prostatic growth—implicated as the pathophysiology of benign prostate hypertrophy [24–26]. While inhibition of local DHT production has been proven to reduce cancer progression, exogenous androgen administration has not been clearly linked to increased risk of prostate malignancy [27–29].

Early understanding of testosterone and prostate cancer

In 1941, Drs Charles Huggins and Clarence Hodges demonstrated that surgical or hormonal castration resulted in the regression of metastatic disease [30]. In a subset of men with metastatic prostate cancer, they reported that tumor markers rose after testosterone administration and quickly dropped when withheld [30]. Their work paved the way for androgen deprivation therapy (ADT), which continues to be utilized today for men with more advanced disease [31–33]. In 1966, Dr Huggins received the Nobel Prize for this work, which helped create the first systemic approach for the treatment of cancer [34]. However, their extrapolation that excess androgens promote prostate cancer growth was based on interpreting levels of prostatic acid phosphatase, an older and less specific tumor marker, found to be elevated in one out of three patients with metastatic disease injected with testosterone [30]. For the next 60 years, the findings from one patient cemented the association of testosterone as the fuel to the fire of prostate cancer in the minds of physicians, researchers, and the public alike [34].

Modern understanding of testosterone and prostate cancer

This fear based on historical evidence eventually came under scrutiny in the 1990s and 2000s with the introduction of the "saturation model", which was born to reconcile the emergence of publications reporting no increased risk for prostate cancer development among patients receiving TRT [19, 35]. This model posited that the androgen receptors on prostate cells are only responsive to fluctuations in serum testosterone within significantly low ranges of androgen, close to that of hormone castration levels [35]. Beyond a certain androgen receptor saturation point, however, any additional rises in serum testosterone would not confer any added risk for malignant prostatic proliferation [35].

Testosterone levels and prostate cancer

Prior to 2008, the majority of studies on androgen levels associated with prostate cancer risk were single-center or regional studies. The Endogenous Hormones and Prostate Cancer Collaborative group were the first to analyze >95% of all prospective data available at that time, involving 18 studies for a total of 3866 men with prostate cancer compared to 6438 controls [36]. They found no association between the risk of prostate cancer and androgen levels, including TT, calculated FT, and DHT [36]. Furthermore, in the placebo arm of the Reduction by Dutasteride of Prostate Cancer Events trial, men with normal to elevated levels of testosterone had no association between their testosterone concentrations and rates of cancer detection or aggressiveness of grade [37]. In another analysis of 345 men with PSA levels ≤4.0 ng/mL, those with lower testosterone (≤250 ng/dL) had higher rates of prostate cancer compared to men with testosterone levels ≥250 ng/dL (21% vs. 12%, $p = 0.04$) [38]. In patients already diagnosed with high-grade prostatic intraepithelial neoplasia, men with lower calculated FT had significantly higher rates of prostate cancer cores upon re-biopsy compared to eugonadal men [39].

Not only do men with low testosterone experience greater rates of prostate cancer, they are more likely to suffer from more aggressive and larger volume disease [40–44]. The AndroCan clinical trial prospectively analyzed 1343 patients with prostate cancer from four French medical centers and found that hypogonadal men, defined as having TT <300 ng/dL or bioavailable testosterone <80 ng/dL, were more likely to suffer from more aggressive Gleason pathology compared to their eugonadal counterparts [42]. Studies have also reported that men with lower total [43, 44], bioavailable [40], and free [40, 41] testosterone levels were all more likely to have extraprostatic disease (tumor stage 3/4). Salonia et al. suggested a nonlinear, U-shaped model of increased risk for high-grade prostate cancer for those at the lowest and highest ranges of endogenous testosterone, while men with physiologic levels of testosterone did not experience increased risk [45].

Testosterone levels and prostate-specific antigen (PSA)

When examining endogenous concentrations of testosterone in the general population, there has not been clear evidence of a linear association with PSA [46, 47]. Bhasin et al. administered Luteinizing Hormone Releasing Hormone antagonists in 54 healthy men, aged 18–35 years, and then treated them with various doses of testosterone [48]. After 20 weeks, differences in PSA levels between treatment groups were not statistically different, even when testosterone levels widely ranged from hypogonadal to supratherapeutic ranges [48]. While some studies report that PSA is unlikely to change secondary to testosterone administration, Khera et al. found that hypogonadal men with testosterone levels <250 ng/dL had a significant rise in PSA of

0.32 ng/mL at 6 months after TRT [49]. While hypogonadal men demonstrate increases in PSA when initiating TRT, there has been no association with short-term increase in cancer risk [50–52].

Healthy men injected with exogenous testosterone should expect a rise in PSA without lasting changes after discontinuing TRT, even after reaching supratherapeutic levels of testosterone (>1000 ng/dL) [53, 54]. Oral [55] and topical administration of testosterone via patches [56] do not appear to significantly influence changes in PSA during therapy. These differences may be explained by the varying pharmacokinetics between testosterone delivery systems. Intramuscular injections of testosterone cypionate and enanthate have been shown to cause significant fluctuations in serum testosterone levels and are associated with adverse rise in hematocrit, estradiol, and PSA [57, 58]. To mitigate these risks, a subcutaneous testosterone enanthate-autoinjector was designed with a lower testosterone peak-to-trough ratio of 1.8 [59]. Transdermal testosterone gels can also provide steady levels of serum testosterone, but have the undesirable side-effect of accidental spread to other people by contact [60]. When deciding between TRT modalities, patients should be counseled on the possibility for fluctuating levels of testosterone and the implications it may have on PSA. Prior to initiating TRT in hypogonadal men, both the American Urological Association (AUA) and European Association of Urology (EAU) recommend screening for prostate cancer via PSA [2, 61]. Routine PSA's should be followed at 6 months, 12 months, and then annually afterwards [2, 61].

Hypogonadism in prostate cancer survivors

By 2024, it is estimated that there will be over 4 million survivors of prostate cancer in the United States alone [62]. The 5-year survival rate for local and regional disease approaches 100%, while 10-year survival rates are ~98% [15]. For these men, the causes of death are non-cancer related with cardiovascular disease being the most frequent cause [63]. Pulmonary embolisms and venous thromboembolisms are also commonly seen in men treated with ADT after prostate surgery [64]. Reflective of what prostate cancer survivors with AOH endure, men treated with ADT suffer from hot flashes [65], sexual dysfunction [66], poor bone mineralization [67, 68], decreased muscle mass [69], metabolic syndrome disorder [70–73], cognitive suppression [74], and thromboembolisms [75, 76]. The complex relationships between testosterone and metabolic syndrome continue to be elucidated. Men with greater fat mass are more likely to have higher levels of estrogen due to increased aromatase activity in adipocytes [77]. It is also theorized that uninhibited lipoprotein lipase activity due to low testosterone levels result in increased conversion of circulating triglycerides into absorbable fatty acids [78]. Furthermore, testosterone drives muscle mass by promoting myocyte differentiation in pluripotent stem cells [79]. In the presence of low testosterone, there is inhibition of mitochondrial oxidative phosphorylation in skeletal muscle, which may explain the increased rate of insulin insensitivity in AOH [80]. As prostate cancer is sensitive to metabolic derangements in AOH, men with low testosterone have been shown to suffer from more aggressive pathology as well as higher rates of positive surgical margins and biochemical recurrence (BCR) postradical prostatectomy [81–84].

Treating hypogonadism in prostate cancer survivors

With the "saturation model" and numerous confirmatory studies, there has been a modern renaissance in evaluating TRT in prostate cancer survivors to mitigate the overlapping comorbidities between prostate cancer and AOH [20, 85]. With testosterone's overarching impact on men's health, especially with adipose reduction and maintenance of the cardiovascular system, men suffering from low testosterone face increased rates of early mortality [86–88]. TRT has demonstrated to be protective in men with metabolic syndrome by improving body fat, glycemic control, and severity of atherosclerosis [89, 90]. A population study of the Prostate Cancer Database Sweden stratified 118,543 men based on Charlson Comorbidity Index (CCI) scores and found that those with greater CCI suffered from more severe prostate disease in both grade and tumor stage [91]. After adjusting for Gleason grade, volume, and type of oncologic treatment received, CCI lost its effect on cancer-specific mortality while maintaining effect for other-cause mortality [91]. This phenomenon has been replicated in multiple other studies [92–96]. It stands to reason that in survivors of prostate cancer, control over their metabolic syndrome holds paramount to extend their lives.

Prostate cancer recurrence with testosterone replacement therapy

In 2004, Kaufman and Graydon were the first to publish on TRT for seven men who had already undergone radical prostatectomy for low-risk cancer (Gleason score 6–7) [97]. None of these patients had BCR after a median of 12-month follow-up. Since then, multiple studies repeated these findings for men postradical prostatectomy [98, 99], brachytherapy [100–102], and external beam radiation [101]. Kaplan et al. analyzed a population database and reported no increase in cancer-specific mortality as well as rates of salvage ADT among 1181 survivors who received TRT [103]. More recently in 2019, Parizi et al. performed a meta-analysis of 21 studies and found virtually no effect size between TRT and BCR in prostate cancer survivors ($d =$

0.01, 95% CI: 0.00–0.02) [104]. A systematic literature review published in 2020 analyzed 54 manuscripts on TRT in prostate cancer survivors and found that BCR after definitive treatment was rare, even after 12 years of follow-up [85]. While ultrasensitive PSA tests can detect levels <0.07 ng/mL, current guidelines continue to label BCR as PSA levels >0.2 ng/mL with a second confirmatory value [105]. After radical prostatectomy, the AUA and EAU recommend TRT to be initiated 1 year after surgery and to be reserved for men with favorable disease profiles, such as Gleason score <8, preoperative PSA <10 ng/mL, negative surgical margins, and negative seminal vesicle invasion [2, 61]. Guidelines also report that no studies have not shown increase BCR or progression of disease with TRT after brachytherapy or external beam radiation, though long-term studies are lacking [2, 61].

Protective benefits of testosterone replacement therapy

In stark contrast to the "androgen hypothesis", there have been reports on the protective effects of TRT in prostate cancer survivors. In vitro and in vivo animal models have shown that testosterone can induce apoptosis in prostatic cancer cells via androgen receptors found on the cells' outer membrane layer [106]. Yassin et al. compared biopsies in men with AOH and found that those who received TRT had favorable pathology compared to men who were untreated [107]. Ahlering et al. recently published a study in 2020 detailing a 54% reduction in BCR for men who received testosterone after prostatectomy of low-grade disease [108]. However, these emerging findings are restricted to only a few retrospective studies and remain to be replicated further.

Treating prostate cancer with testosterone

Krakowsky and Morgentaler reported on seven men with advanced prostate cancer (Gleason 7–9) who decided to receive TRT for severe AOH symptom management [109]. Two patients discontinued therapy once their PSA rose greater than 20 ng/mL, two patients died from causes unrelated to prostate cancer, and three had continued with TRT [109]. There were no reports of disease flare, pain, or vertebral compromise [109]. Drs Samuel Denmeade and John Isaacs were the first to describe "bipolar androgen therapy" (BAT), which utilizes supraphysiologic levels of testosterone to treat castrate-resistant prostate cancer [110]. This therapy was in response to the rapid resistance that castrated men would develop to even second-line ADT [110, 111]. In vitro studies have demonstrated that prostate cancer cells expressing androgen sensitive receptors do surprisingly well in media with castrate levels of androgens, but can be inhibited once exposed to supraphysiologic testosterone levels [112, 113].

Fourteen men with leuprolide resistant prostate cancer underwent a BAT regimen of 400 mg testosterone injections every 4 weeks, resulting in 2 weeks of supraphysiologic testosterone levels and 2 weeks of hormonal castrate status [111]. Men were also treated with etoposide for the first 2 weeks of each 4-week cycle [111]. 50% (7/14) of the cohort experienced PSA decline with 28.6% (4/14) seeing a PSA decline ≥50% [111]. 50% (5/10) had radiographic improvements and four men remained on BAT for ≥1 year [111]. Furthermore, all (10/10) patients treated with ADT post-BAT experienced improvements in PSA, indicating that they were re-sensitized to ADT [111]. In 2016, the same group reported on the Phase II results of their BATMAN trial in which 29 men with either asymptomatic metastases or BCR were pretreated with 6 months of ADT and then two cycles of BAT and ADT in alternating fashion [114]. All patients experienced some PSA reduction with 59% (17/29) having levels drop below 4 ng/mL by 18 months [114]. 80% (8/10) demonstrated radiographic regression, while three patients were eventually removed from the study due to radiographic progression [114]. In 2018, Teply et al. reported on a phase II study for BAT in men with metastatic prostate cancer resistant to enzalutamide [115]. They reasoned that those resistant to such a potent anti-androgen likely have overexpression of androgen receptors readily susceptible to testosterone [115]. Thirty men were treated with BAT and 21 re-challenged with enzalutamide. By the end of study, 52% (15/29) of the patients had achieved PSA < 50% from baseline [115]. During the BAT cycle, three patients developed hypertension as well as one case of pulmonary embolism, myocardial infarction, urinary obstruction, gallstone, and sepsis [115].

Conclusions

AOH causes a devastating burden on the quality of life for survivors of prostate cancer. Furthermore, AOH and its comorbidities further contribute to the risk for oncologic recurrence and progression. While testosterone levels have been historically associated as the driver of prostate cancer, there has been a modern resurgence in re-evaluating this belief. Not only has TRT been safely utilized to alleviate AOH symptoms in select groups of prostate cancer survivors, but exposure to supraphysiologic levels of testosterone has been on the forefront as a treatment option for aggressive prostatic disease. While much work remains in understanding the relationship between testosterone and prostate cancer, those who survive this disease should not be automatically turned away from an opportunity to be treated and restored.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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