



The role of testosterone in men's health: is it time for a new approach?

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Abstract

Purpose Because of many unanswered questions regarding men's health, a literature review was performed to better understand the role of testosterone and testosterone replacement therapy (TRT) in the management of hypogonadism and aging related prostate gland diseases (ARPGD) including prostate cancer (PCa) and benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS).

Methods The PubMed database was screened for pertinent peer reviewed articles published during the last four decades that culminated in the positions and recommendations in this paper.

Results Hypogonadism seriously impacts men's health, and the diagnosis remains controversial. The incidence of ARPGD is projected to increase worldwide and treatment still has significant limitations. There is compelling evidence that lower, not higher, testosterone levels trigger the development of PCa and BPH through androgen receptor over-expression. TRT was found to be safe and effective in treating hypogonadism including in PCa survivors and those harboring PCa. There is also evidence that TRT might reduce the incidence and prevalence of ARPGD.

Conclusions and recommendations This review synthesizes a wide-ranging compendium of basic science and clinical research that strongly encourages altering the present approach to diagnosing and treating men with hypogonadism and ARPGD. These findings underscore the importance of avoiding significant testosterone decline and support the use of TRT. Ten recommendations are offered as a framework for the way forward. It is now time for clinicians, payers, researchers, funding agencies, professional associations, and patient advocacy groups to embrace this new paradigm to increase longevity and improve the quality of life.

Keywords Testosterone · Hypogonadism · Prostate cancer · Benign prostatic hyperplasia (BPH) · Lower urinary tract symptoms (LUTS)

Introduction

Huggins and Hodges first identified the benefit of androgen ablation therapy for the treatment of metastatic prostate cancer in 1941 [1]. Charles Huggins was subsequently awarded a Nobel Prize in Medicine and his observations have remained urologic dogma. Since then, there have been significant improvements in the diagnosis of prostate diseases (PSA, needle biopsy, Gleason Score, MRI, etc.). Treatment of significant intracapsular and localized extracapsular

prostate cancer now includes surgical and/or radiation therapy which are often curative. However, despite the development of new drugs that focus on androgen deprivation therapy (ADT) for patients with advanced prostate cancer, a cure remains elusive. Furthermore, the prolongation of life requires enduring the many untoward signs and symptoms of hypogonadism and the many discomforts caused by metastatic disease. As androgens stimulate prostate growth and as testosterone supplementation has been associated with other systemic side effects, there has been reluctance to employ testosterone replacement therapy (TRT) in hypogonadism and aging related prostate gland diseases (ARPGD) that include prostate cancer (PCa) and benign prostatic hyperplasia (BPH) with associated lower urinary tract symptoms (LUTS).

The public health burden of these conditions is formidable. Based on prevalence data in US. men 40–69 years

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of age, Araujo estimated that approximately 2.4 million men are androgen deficient [2]. Globally, PCa is the most common diagnosed cancer in men with an estimated annual incidence of 1.6 million and an annual estimated death rate of 366,000 [3]. In 2017, the burden of disease measured in Years Lived with Disease reported for BPH/LUTS and PCa was approximately 2.4 million and 843,227, respectively [4]. Thus, there remains a great opportunity to improve men's health and reduce the accompanying public health burden, not only by treating, but also by preventing these diseases [5].

Over the past decades, data has accumulated from the bench and the bedside suggesting that the conventional wisdom regarding the role of testosterone in the diagnosis and management of these illnesses has been overly restrictive. An extensive PubMed review provides compelling evidence that the judicious use of testosterone can alleviate the many untoward consequences of these maladies [6, 7]. In the light of the unrelenting challenges associated with hypogonadism and ARPGD, it is time to alter our longstanding approach to the diagnosis and treatment of these conditions.

Serum testosterone and hypogonadism

Testosterone is a hormone that modulates many of the physiologic functions that significantly impact men's health. Produced by the Leydig cells in the testes, testosterone directly interacts with the androgen receptors (AR) in reproductive organs, muscle, bones, brain, and skin as well as in the prostate gland. Low testosterone is not only associated with hypogonadism, but also with ARPGD including PCa and BPH with associated LUTS. The highest level of circulating testosterone in man is reached at about the age of 30 after which there is a gradual decline as man ages [8]. When a certain decline occurs, men may manifest the signs and symptoms of hypogonadism.

Definitions of hypogonadism

Clinical hypogonadism

Late onset hypogonadism (LOH) correlates with aging. The main causes are reduced production of testosterone by Leydig cells, reduced activity of hypothalamic pituitary function or a combination of both. Regardless of the etiology, clinical hypogonadism can markedly decrease the quality of life and longevity. Symptoms of LOH include sexual dysfunction (loss or decreased libido, morning erection and erectile function), lack of energy, impaired concentration, depression, and a decreased sense of vitality or well-being. There are three well known screening questionnaires for hypogonadism in older men, the St. Louis Androgen Deficiency in Aging Male (ADAM), the Aging Male Survey (AMS) and

the Massachusetts Male Aging Study (MMAS). Of these questionnaires, Morley et al. concluded that when correlated with bioavailable testosterone, ADAM and AMS may be useful screening tools (sensitivity 97% and 83%, respectively), but both are relatively nonspecific (specificity 30% & 39%, respectively) [9]. Signs of LOH include osteopenia, osteoporosis, anemia, decreased muscle mass, abdominal obesity, and the many untoward systemic sequelae of the metabolic syndrome and Type 2 diabetes mellitus [10]. The influence of testosterone on men's well-being is extensive and the potential benefits of TRT should not be minimized.

Biochemical/laboratory hypogonadism

There is no consensus as to what level or rate of decline of systemic testosterone is necessary to diagnose and treat hypogonadism. Despite decades of clinical experience, there is no unified guideline as to when a testosterone level should be obtained nor is there a consensus regarding the testosterone level that merits clinical intervention, even in the presence of the clinical signs or symptoms mentioned above. Many insist upon a defined low level of serum testosterone before one can be diagnosed and treated [11]. Others believe that it is not a certain fixed level, but the rate of decline that predicts the diagnosis [12]. The controversy is further complicated by the fact that there is a very wide range of reported normal levels of testosterone in men. The normal range of testosterone in young healthy non-obese men 19–39 years of age was reported by Travison [13]. The harmonized 2.5th, 25th, 50th, 75th, 97.5th percentile values of total testosterone were 267, 424, 531, 643 and 929 ng/dl, respectively.

In the evaluation of biochemical hypogonadism, the standard approach is to measure Total Testosterone (TT) and the Sex Hormone Binding Globulin (SHBG) with the specimen collected before 11 am. Free testosterone can then be estimated by subtracting SHBG from TT. A free testosterone level can be measured directly, but this requires more sophisticated technology such as tandem mass spectrometry. While valuable in certain clinical situations, increased cost and limited availability make direct measurement less suitable for routine use. Obtaining an estradiol level might provide additional useful information [14].

Testosterone replacement therapy criteria: the debate continues

To date, there remains controversy regarding the management of men with suspected hypogonadism [15]. American and European guidelines oppose universal screening for androgen deficiency in middle aged and older men [11] and in the general population [16]. These guidelines recommend that a predetermined level of serum testosterone is

necessary before providing TRT, even in the presence of hypogonadism symptoms [11, 16]. This level is approximately 11–12 nmol/L (317–345 ng/dl). As noted above, others believe that the change in testosterone concentration over time is a better predictor for the development or diagnosis of hypogonadism [12]. The natural rate of testosterone decline is approximately 1–2%/year [17]. This rate of decline corresponds to a reduction of 3.2–3.5 ng/dl (0.110–0.121 nmol/L) [18]. By the age of 75, a man has already lost 30% of his circulating quota of testosterone measured at the age of 25 years [19].

Unfortunately, as most men do not have a peak testosterone level reference point, there is no way to determine the individual rate or degree of decline that could correlate with asymptomatic or symptomatic hypogonadism. The American and European guidelines do not recommend the routine measurement of testosterone as a universal screening tool or the establishment of a normal peak level for healthy men during early adulthood [11, 16]. Considering the wide range of normal values, the lack of a reference point makes it difficult to determine the timing and target level of replacement therapy. Should a man with a peak testosterone level of 700 ng/dl need to drop his level of testosterone to less than 345 ng/dl before treatment is initiated, even if he has classic symptoms of hypogonadism? Based on the rate of decline, would it be possible to predict who will develop clinical hypogonadism and initiate preventive therapy? What is a safe and effective level of serum testosterone in aging males?

Experience with testosterone replacement therapy: safe and effective

Hypogonadism

Over the last few decades, there has been abundant peer reviewed research demonstrating the effectiveness of TRT in patients with hypogonadism [20, 21]. Although there have been concerns regarding the negative effects of TRT on the cardiovascular and hematopoietic systems, reports show that with proper selection and monitoring, testosterone can be administered safely [22]. The beneficial effects of the long-term use of TRT in improving cardiometabolic function and reducing the risk of cardiovascular disease in men has been reported [23] as has improvement in the quality of life [8, 24].

Hypogonadism with prostate cancer and lower urinary tract symptoms

One of the major concerns with TRT in men is that testosterone might aggravate or cause ARPGD, including prostate intraepithelial neoplasia (PIN), PCa, BPH or LUTS, such that TRT is deemed inappropriate for men with, PCa, or

at high risk for PCa and those with BPH with LUTS [11, 16]. However, many publications during previous decades provide noteworthy evidence to the contrary. Recent reports indicate that men with PCa have a lower level of testosterone compared to those with BPH [25], and in those with high grade PCa and lymph nodal metastasis, the level is even lower [26]. Perhaps the most intriguing contradiction is the well documented inverse relationship between the declining level of testosterone and the increasing incidence of ARPGD in aging men [27]. Utilizing the International Prostate Symptoms Score and the size of transitional prostate volume, Shim also reported an inverse relationship with prostate enlargement and LUTS [28]. In a group of patients with LUTS, TRT was associated with a clinical improvement [29, 30].

There are now reports that the long-term use of testosterone does not increase the incidence of PCa [31] and possibly reduces the incidence of PCa when compared to those who did not receive TRT [32]. Over a 12-year follow-up period in men with hypogonadism, Saad reported a significantly lower incidence of PCa among those receiving TRT [29]. Shoskes reported the prostate biopsy results in 96 men with symptomatic hypogonadism. He noted that 47.5% of 61 patients not receiving TRT had PCa whereas PCa was identified in only 14.3% of the 35 patients who received TRT (0% of 14 treated < 2 years and 23.8% of 21 treated at least 2 years). The accompanying histologic reports also revealed lower grade carcinoma in the TRT group when compared to the untreated patients [33]. Walburton reported that TRT did not induce recurrence among PCa survivors who were successfully treated with surgery or radiation [34]. Morgentaler reported that TRT can also be given safely to men harboring PCa who are under surveillance [35]. The prevalence of PCa declined by 54% in 13 men who received TRT ranging from 1 to 8.1 years (median 2.5 years) after 2 (mean) post therapy biopsies [35]. Although the decline could be due to missed sampling, the fact that the reduction is over 50% suggests that this is more likely due to biological changes in the diseased prostatic cells.

The use of TRT in the treatment of advanced PCa has been the subject of few reports, all including a small number of patients. Szmulewitz determined that the use of testosterone gel was feasible and reasonably well tolerated [36]. Using a different testosterone gel protocol, Morris opined that TRT could be safely utilized in a future clinical trial [37]. Prout and Brewer noted varying responses in men receiving parenteral testosterone and could not determine a substrate predictive of success [38]. In a group of asymptomatic castrate resistant PCa patients receiving supraphysiologic doses of testosterone, Schweizer noted that progression free survival for at least a year is possible [39].

Could testosterone supplementation improve the environmental milieu of the malignant prostate cells and reverse the

oncogenic process? Could the variability of response be due to insufficient dosing of testosterone? Is the dose response dependent on the tumor bulk and/or the Gleason score?

While the above publications utilized exogenous TRT, there is also research suggesting a possible benefit of endogenous testosterone. Sartor reported that 19% of cases experienced progression free survival for over a year when ADT was discontinued [40]. Nam [41] found that in most patients after cessation of ADT, testosterone recovers to over 300 ng/dl in the range of 6.8 months for those treated for less than 18 months and a mean of 9.7 months for those with longer treatment beyond 18 months.

Could the cessation of ADT allow production of endogenous testosterone and alter the biological behavior of the highly malignant prostate cells?

To summarize, the long-held belief that testosterone can cause prostate cancer is at variance with many reports suggesting that ARPGD is associated with low, not high, levels of testosterone. These peer reviewed publications raise important questions. Why does the incidence of ARPGD increase when serum testosterone is declining? Why doesn't the incidence of PCa increase with TRT? Why does the withdrawal of ADT or treatment with supraphysiologic testosterone in some patients with castrate resistant prostate cancer delay the progression of disease?

The prostate cell and tumorigenesis

During the past 2 decades, reports from various disciplines point to androgen receptor over-expression in the presence of low or declining level of testosterone as a tumorigenic culprit. Once the prostate gland matures, the androgen sensitive prostate cells actively alter metabolic processes in order to maintain necessary levels of testosterone and dihydrotestosterone. When the androgen level declines, there is upregulation of androgen receptors (AR) with increased AR-androgen binding, resulting in additional testosterone uptake. While this enables the cell to replete the diminished level of testosterone, it may also be associated with various genomic, DNA and cellular alterations that amplify oncogenes and delete tumor suppression genes [42–57]. Support for this hypothesis has been found at the bench, in the animal laboratory and at the bedside.

Costello noted that low cellular testosterone was associated with the downregulation of ZIP1 zinc transporter resulting in a deficiency of intraprostatic zinc and citrate. This cellular metabolic disturbance is associated with prostate oncogenesis [49]. Beilin reported that a shorter CAG (cytosine, adenine, guanine) repeat length that codes the polyglutamine tract was associated with greater AR activity. It has also been correlated with a higher risk and increased severity of the common prostate aging diseases, BPH and PCa [50]. Meng [51] reported that testosterone deprivation increases

the risk of carcinogenesis by increasing cellular inflammation and the immune response to prostatic proteins.

Experiments by Song & Khera, using prostate cancer cells in vitro, demonstrated that low levels of testosterone are essential for the initial growth of PCa cells, whereas physiologically normal levels of androgen inhibit proliferation [52]. Li supported these findings after studying the role of Sex Hormone Binding Globulin (SHBG) on testosterone uptake, metabolism, and action in the androgen sensitive LNCaP cell line. Testosterone treatment did not promote the growth of cancer cells. Instead, a dose dependent inhibition of tumor cell growth was demonstrated after 38 h in culture. Coincubation with SHBG that binds and inactivates testosterone prevented this inhibition. The author concluded “the inhibition of cell growth by testosterone warrants further investigation” [53].

In the castrate model of rats receiving low, normal or supra-normal doses of exogenous testosterone, Zhou found that the level of testosterone and DHT in the prostate tissue remained constant regardless of the systemic level of testosterone. [54]. This finding demonstrates the ability of the androgen sensitive prostate cells to adjust to deliver only necessary testosterone inside the prostate cells. It also offers additional support to the saturation theory advanced by Morgentaler [55], who noted that prostate growth is exquisitely sensitive to low levels of cellular androgen. Low testosterone concentration triggers AR over-expression, a known recipe for tumorigenesis. Once maximal androgen-AR binding is achieved and cellular testosterone is repleted (saturation), additional androgen produces little effect and contrary to low testosterone levels, would not stimulate PCa growth.

In a mice model, Banach-Petrosky reported that prolonged exposure to reduced levels of androgen (tenfold lower than normal) resulted in a marked acceleration of prostate tumorigenesis compared to those exposed to normal levels [56]. This study supported the possible link between declining androgen in aging males and prostate cancer. The authors suggested further studies in humans to evaluate and develop strategies to reverse this process, “perhaps via androgen supplementation” [56]. A decade earlier, Goldenberg proffered, “maintaining a normal testosterone level throughout life may be beneficial from a survival point of view” [57].

Indeed, increasing the level of prostate cell testosterone is associated with AR underactivity which is deemed to be anti-tumorigenic. Widely prescribed 5 alpha reductase inhibitors, finasteride and dutasteride, increase cellular testosterone to the “normal” range with a resultant decrease in AR activity. A large clinical experience with both drugs has shown a reduction in the incidence of low-grade prostate cancer [58–60].

Additional clinical support for this hypothesis has been found in eunuchs and those with Klinefelter syndrome. Prostate carcinoma is exceedingly rare in these populations. In

these people with lifetime low or absent testosterone levels, the prostate never matures, and the cellular testosterone requirement remains low. This obviates the need for AR overexpression and its accompanying tumorigenic risk. [61]

Androgen deprivation therapy (ADT) and tumorigenesis in advanced PCa

Initially, androgen deprivation results in prostate cell apoptosis [62] resulting in approximately 90% tumor involution [63] and clinical remission. The duration of remission appears to be inversely proportional to the volume and severity of cancer at the onset of therapy, [64, 65]. However, to survive in this extremely low testosterone environment, cells adapt and eventually become castrate resistant. The means by which this adaptation occurs remains uncertain. Attar [64] proposed 5 mechanisms involving genetic transformation and AR upregulation, the latter associated with low testosterone levels and tumorigenesis as described in the preceding section. Sun showed that androgen deprivation induces epithelial–mesenchymal transition (EMT) in both normal and prostate cancer cells, which is implicated in cancer metastases and therapeutic resistance [66].

A clinical risk factor: the rate and degree of testosterone decline

The incidence and the timing of the occurrence of PCa varies amongst individuals. The difference appeared to be dependent on the degree and rate of testosterone decline. Wang reported a faster age-related reduction rather than an absolute level of serum testosterone as a risk for PCa [67]. For every 10 ng/dl increment in annual reduction of testosterone, the risk of PCa increased by 14%. Compared to patients with a relatively stable testosterone, patients with an annual testosterone reduction of more than 30 ng/dl were found to have a fivefold increase in PCa risk. Based on published reports, Xu proposed a dynamic model hypothesis that the magnitude of testosterone decline may trigger and promote the development of PCa. [68]. These reports support the need to regularly monitor the level of testosterone in men. This will help determine the appropriate time for therapeutic or preventive intervention.

The rate or degree of testosterone decline may also explain the higher PCa risk among black men. In a study based on National Health and Nutritional Examination Survey (NHANES) data, when compared to white males, black males had significantly higher peak levels of testosterone during young age, but the difference completely disappeared after the age of 60 suggesting a more rapid decline with aging [69]. The significantly higher testosterone level among young black men compared to young white men was also reported among college students in California. Even after

adjustment by analysis of covariance, blacks still had a 15% higher testosterone level and a 13% higher free testosterone level [70]. In another study, the magnitude of the decrease in testosterone concentrations over time rather than the actual concentration was also found to be a better predictor for symptoms of late onset hypogonadism [12].

Based on the above observations, could preventing serum testosterone decline decrease the incidence of ARPGD (PCa & BPH with LUTS)?

Recommendations based on the review findings

The above review highlights 6 important issues:

- (1) Hypogonadism in men (both clinical and biochemical/laboratory hypogonadism) is a major public health burden that can markedly reduce the quality of life and longevity.
- (2) Declining systemic testosterone predisposes to the development of hypogonadism, PCa and BPH with LUTS.
- (3) Preventing a decline of systemic testosterone (biochemical/laboratory hypogonadism) could prevent ARPGD.
- (4) Clarifying guidelines regarding monitoring clinical hypogonadism, the measurement of the level of serum testosterone and the rate or degree of decline offers the opportunity to better treat and prevent ARPGD.
- (5) TRT is safe and effective in patients with hypogonadism including PCa survivors, those harboring PCa under surveillance, and those with LUTS.
- (6) Testosterone might be beneficial in certain patients with prostate cancer.

The following recommendations are offered to address these issues.

- (1) Annual monitoring for the signs and symptoms of late onset hypogonadism utilizing user friendly questionnaires should be encouraged [9].
- (2) Guidelines pertaining to the diagnosis of hypogonadism should be reassessed.
- (3) A policy should be established recommending that males have a serum testosterone level measured by age 30. The level should then be measured serially to monitor the rate of decline. For men who do not have a peak baseline testosterone level, a harmonized reference level of 531 ng/dl (50th percentile) can be utilized [13].
- (4) When a significant rate of testosterone decline is established, or hypogonadism symptoms are associated with lower serum levels, treatment with exogenous testosterone should be initiated. The physician

and the patient can choose from the many available options [71] (Khodamoradi).

- (5) Alternative or traditional medicines that have been demonstrated to stimulate production of endogenous testosterone [72] might be explored as an alternative to exogenous replacement.
- (6) Treatment of hypogonadism with TRT in the presence of PIN, low risk PCa, BPH, LUTS and PCA survivors [73, 74] should be considered.
- (7) The accumulated data demonstrating the safety and effectiveness of TRT should be enough to supplant the need for a long term randomized clinical trial in low-risk cases. However, diligent registry enrollment can provide valuable information.
- (8) Regardless of indication or therapeutic intervention, the issue of potential serious side effects (cardiovascular, hematopoietic, fertility) must remain an important part of the pretreatment process with continued vigilance during and following therapy.
- (9) There remain numerous multidisciplinary basic science and clinical research opportunities relating to the cellular metabolism, prevention, diagnosis, and therapies associated with ARPGD.
- (10) Well-planned prospective randomized controlled trials should be established to determine the role of TRT in the prevention of ARPGD and the treatment of advanced PCa.

Conclusion

Despite decades of significant diagnostic and therapeutic advances, hypogonadism and ARPGD (PCa and BPH with LUTS) remain a serious challenge to men's health and well-being. This review cites a limited number of the many basic science and clinical publications from respected thought leaders that correlated declining levels of testosterone, not only to hypogonadism, but also to ARPGD. These publications also explain and justify the use of testosterone replacement therapy for the treatment of hypogonadism, even in patients with cancer of the prostate and BPH with LUTS. It is also possible that the diligent monitoring of declining testosterone levels will better enable disease prevention. Though a number of these studies were underpowered or retrospective, in toto, the consistency of these findings over decades merits serious consideration. The chance to significantly improve men's quality of life and longevity at a lower financial cost is an opportunity that must not be ignored. Ten recommendations are offered as a framework for the way forward. It is now time for clinicians, payers, researchers, funding agencies, professional associations, and patient advocacy groups to consider this new paradigm and proceed in a timely manner.

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