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Androgen Replacement Therapy and Prostate Safety

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Abstract

Progress in the understanding of the action of exogenous testosterone has diminished many of the concerns that existed regarding its safety. The major interest is now focused on the effects of androgen supplementation on the prostate gland. Many such concerns have been addressed but others remain to be fully elucidated. It is well established that hypogonadal men receiving adequate androgen therapy develop a prostate with a volume similar to what would be expected from their eugonadal counterparts. Androgen therapy results in modest elevations in the PSA and minor changes in flow parameters. Prostate cancer, on the other hand, remains the most prominent of the safety concerns. Although there is no evidence that normal levels of testosterone promote the development of cancer of the prostate, it is clear that the administration of testosterone enhances a pre-existing prostatic malignancy. Androgen supplementation studies have been, in most cases, of short duration and lacked a control cohort. The current evidence does not support the view that appropriate treatment of hypogonadal elderly men with androgens has a causal relationship with prostate cancer. Larger experience, however, is needed. The same criteria applies to the use of other hormones such as dehydrotestosterone, dehydroepiandrosterone follicle stimulating and growth hormone. A set of recommendations regarding androgen replacement therapy and prostate safety is proposed.

Keywords: Testosterone; Androgens; Prostate safety; Prostate cancer

1. Introduction

It is generally accepted that advancing age is associated with significant changes in the hormonal milieu [1]. In men, despite a significant inter-individual variability, there is a progressive decline in several circulating hormones, including both testosterone (T) and dehydroepiandrosterone (DHEA). This has led to the recommendation for use of exogenous androgens to replenish the levels of serum T. Although T administration in aging men with manifestations of hypogonadism is usually beneficial, androgen replacement therapy (ART) demands, at the very least, working knowledge of its efficacy and drawbacks by the treating physician. A great deal of concern has been expressed regarding the potential for serious side effects resulting from T administration. While alterations in lipid and hematological profile, liver toxicity, sleep apnea and other potential adverse effects are increasingly elucidated with reassuring results, the main and perhaps most worrisome aspect pertains to prostate health.

2. Indications for androgen administration

The prevalence of overt hypogonadism in adult men is low [2] and many individuals with hypotestosteronemia do not exhibit clinical manifestations or show only marginal deficits in one or more organ/systems. The most common signs of adult hypogonadism are shown in Tables 1 and 2. It should be emphasized that only rarely are all the symptoms present in an individual. Frequently, men consult because of sexual dysfunction. The increasing awareness of the androgen decline in the aging male (ADAM) also known as the andropause, is now bringing to the physician men with fatigue, depression and sarcopenia. In the presence of these manifestations or obvious findings on physical examination (atrophic gonads) a thorough assessment

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Table 1
Signs and symptoms of adult hypogonadism[a]

1	The easily recognized features of diminished sexual desire and erectile quality, particularly nocturnal erections
2	Changes in mood with concomitant decreases in intellectual activity, spatial orientation ability, fatigue, depression and irritability
3	Decrease in lean body mass with associated diminution in muscle volume and strength
4	Decrease in body hair and skin alterations
5	Decreased bone mineral density resulting in osteoporosis
6	Increase in visceral fat

[a] These manifestations need not all be present to identify the syndrome.

Table 2
Common hypogonadal states

Hypothalamic-pituitary disorders	Gonadal abnormalities	Defects in androgen action
Panhypopituitarism	Kleinfelter's syndrome	Complete androgen insensitivity
Isolated LH deficiency	Other cromosomal defects	Incomplete androgen insensitivity
LH and FSH deficiency (Kallman's syndrome)	Bilateral anorchia	Type I
		Type II 5α-reductase deficiency
Biologically inactive LH	Leydig cell aplasia	
	Adult Leydig cell failure (ADAM, andropause)	
	Defects in androgen biosynthesis	

is indicated. The physical examination, however, is rarely fruitful. In addition to a complete examination, special note should be made of hair distribution, breast volume, location and size of the testicles and evaluation of the prostate gland by digital rectal examination (DRE). Possible symptoms of hypogonadism need to be sought out. Simple questionnaires are available and they are helpful [3,4] in the initial screening.

As indicated above, establishing the presence of adult hypogonadism on a purely clinical basis is, in most cases, extremely difficult. Only the most severe cases bring up clinical suspicion. Despite this, there is some controversy as to the need for hormonal evaluation of the senescent man. For instance, hormonal evaluation in men with erectile dysfunction (ED) has been questioned on the basis that it is not cost-effective [5]. This skepticism is not shared by most [6]. There are several reasons to justify, at least, basic hormonal assessment of men with ED. It is commonly accepted that the combination of low sexual desire and erectile difficulties may be the result of serious hormonal abnormalities. The reality is not as simple or clear cut as that. Not only may men with significant androgen deficiency be capable of adequate sexual erections but also hormonal supplementation resulting in normal T values does not always translate into restoration of libido and quality of erectile function [7]. More important, however, is the fact that the population seeking advice for ED is in its majority the same group in which hormonal alterations associated with aging is commonly found. It behooves the urologist to be aware of and assume a proactive attitude towards the diagnosis of these deficiencies and treat or refer them depending on his/her interests and expertise. It is recommended therefore, that in-patients at risk or suspected of hypogonadism the following biochemical investigations be done: (a) serum T between 8:00 and 11:00 a.m. The most appropriate parameter to determine hypogonadism is probably the measurement of bio-available T (it includes the free and albumin-bound fractions). In men beyond middle age levels of total T may be misleading due to alterations in SHBG levels and flattening of the circadian rhythm mentioned previously. (b) If T levels are below or at the lower limit of the accepted normal values, it is prudent to confirm the results with a second determination together with assessment of luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin. (c) In the younger male, low levels of T (<12 nmol/l or <350 ng/dl) with chronically elevated gonadotropins makes a clear diagnosis of primary hypogonadism or testicular failure. (d) In an older man, the diagnostic lines are not as clearly defined and additional information may be needed. Thus in these men, as well as the obese, an SHBG determination may be useful in establishing the true clinical significance of total T measurements. (e) Measurement of serum free T by equilibrium dialysis is considered the most accurate measurement of androgenicity. The method for free T determination is, however, more complex to perform and not available in most areas of the world [8]. Another diagnostic possibility for biochemical diagnosis is the calculated free T [9]; this procedure provides a reliable marker of the levels of metabolically

active serum T with methodologies that are widely available. Although secondary (hypogonadotropic) hypogonadism is usually also treated with androgen supplementation, it is recommended that a more thorough endocrinological assessment be carried out in such cases. A correctable cause or a different therapeutic approach may be more appropriate than simple androgen administration. Ideally, the diagnosis is reached by the combination of clinical manifestations and biochemical confirmation. This is not always possible and good clinical sense then would play a critical role in deciding therapy. The indiscriminate use and abuse of androgens for non-medical reasons is to be emphatically condemned [10].

3. Contraindication for the use of androgens

Currently, the only absolute contraindication for ART is the suspicion or the documented presence of carcinoma of the prostate or breast. Prostate and androgens will be discussed, separately, below. The clinician however, must be aware that exacerbation of various other pre-conditions and the development of new health issues may occur as a result of ART. It is also important to emphasize that long-term studies with ART are just a handful and most only extend for a few years. The short follow-up available for most longitudinal studies is a valid concern.

ART should be considered with particular caution in men afflicted by a variety of conditions that can be adversely affected by T administration. Briefly, they include:

- Liver disease. All injectable and transdermal androgens have proven to be free of liver toxicity. Oral androgens, on the other hand, require special consideration. The oral and injectable T undecanoate are free of liver toxicity [11,12] while alkylated forms are recognized for their ability to induce cholangitic hepatitis and even liver tumors [13]. All commercial T manufacturers, however, include warnings on potential hepatic risks with the use of T. Therefore, the benefits brought in by the exogenous administration of androgens should be carefully weighted in men with underlying liver diseases.
- Cardiovascular system and lipid profile. The earlier concerns about adverse effects of ART on the lipid profile are rapidly changing. An epidemiological review showed that hypotestorenemia might be a risk factor for cardiovascular disease while normal levels appear to be cardio-protective [14]. More recently Crook [15] has further expanded on the beneficial effect of T on the lipid profile and cardiovascular disease risk factors. ART in aging men results in a decrease in total and low-density lipoprotein-cholesterol levels, with no change or a small decrease in high-density lipoprotein-cholesterol levels. Although these lipoprotein alterations appear to be modest, their clinical significance remains to be elucidated. Interestingly, acute administration of T, at physiological concentrations has been reported to induce coronary artery dilatation and increases in coronary blood flow [16]. Nevertheless, careful monitoring of patients with cardiovascular risk factors is needed if ART is considered.
- Fluid retention is not a relevant problem in otherwise healthy hypogonadal men. In older patients who already have congestive heart failure, severe hypertension or peripheral edema, ART is not necessarily contraindicated but should be used with caution.
- ART in men often produces a significant increase in red blood cell mass and hemoglobin levels. These increases appear to be larger in older hypogonadal men as compared to the young ones. In some cases, particularly older men, when polycythemia develops, it may be necessary to either terminate therapy or decrease the dose of T used for replacement. Sleep apnea (see below) does not appear to be contributing factor in the production of polycythemia. The method of T replacement may affect the magnitude of the change in red blood cell mass [17].
- Sleep apnea and T administration remains a controversial issue. Earlier reports indicated that exogenous T exacerbated the condition [18]. This early view was not supported, in a more recent 36 month transdermal trial of T therapy in older men in whom no effect of treatment was found on apneic or hypoapneic episodes [19].
- Development of gynecomastia may occur in a small number of men on ART. This may be due to the relatively greater increase in serum estradiol levels, as compared to serum T levels. Dose adjustments, normally, resolve the problem. In the rare situation of men with hypogonadism and breast cancer, administration of androgens is contraindicated for their propensity to stimulate growth of this tumor.

4. Testosterone and prostate safety

Current concepts generally agree that T administration in a hypogonadal elderly man may result in modest and usually insignificant volumetric increases in the gland. The same view applies to lower urinary tract obstructive symptoms, urine flow rates, and serum

values of prostatic specific antigen (PSA). It was shown that, when the prostate is of normal size, androgen administration does not stimulate DNA synthesis and, consequently, proliferation of stromal prostate cells [20]. A different story applies to prostatic carcinoma (CaP). To date there is no evidence that exogenous androgens promote development of CaP. On the other hand, an existing CaP may progress vigorously from androgen therapy.

4.1. Benign prostatic hyperplasia (BPH)

The development of benign prostatic hyperplasia (BPH) is believed to be primarily mediated by intraprostatic events due to the action of 5α-dehydrotestosterone [21] most likely with active participation of estrogenic influences [22]. It has long been recognized that the volume of the prostate increases with age in normal men but not in their untreated hypogonadal counterparts. When hormonally deficient men are treated, prostate volume increases but only to the size expected for eugonadal men of the same age [23]. The relationship between symptoms of bladder outlet obstruction (BOO) and their objective correlates (uroflow, residual urine) to androgens levels are being redefined. Earlier studies supported the view that androgen administration resulted in a modest but significant increase in prostate volume and PSA levels which, however, remain within normal limits [24]. Most studies have shown no effect of exogenous androgens on PSA or prostate volume [25]. More recent evidence from placebo-controlled studies of hypogonadal men receiving androgen therapy, indicate that the differences between those men receiving T and those on placebo were insignificant in regards to prostate volume, PSA and BOO [26]. Based on these experiences it is evident that a man with severe BOO secondary to an enlarged, obstructive prostate is not a candidate for androgen administration: even a marginal, although rapid increase in prostate size likely will finally decompensate the detrusor with the ensuing development of urinary retention. The situation is less well defined in men with moderate symptoms of BOO. For them, in the presence of a clear indication for ART, the physician must use good clinical judgment and monitor closely for any possible detrimental effects. However, the benefits of ART should no be denied outright because of the presence of mild stable obstructive symptoms.

4.2. Prostate cancer

It must be stated from the outset that ART is an absolute contraindication in men suspected of harboring cancer of the prostate. This includes those with abnormal DRE or PSA in whom the diagnosis of carcinoma has not ruled out beyond doubt. In addition, those recently treated for prostatic cancer with intent to cure (radical prostatectomy or radiotherapy) in which both the DRE and PSA are normal should be included in the absolute contraindication category. After a prudent period (this remains an uncharted territory) without evidence of recurrence of their cancer, the pros and cons of ART should be carefully considered and the restriction may be lifted. It is necessary to emphasize that the initial monitoring of these men must be particularly close within the first 2 years of the onset of ART, when exacerbation of a sub-clinical cancer is most likely to occur.

4.3. Role of T in the development of prostate cancer

Despite the lack of solid evidence, there exists a deep-rooted suspicion among physicians that ART may have an important causal role in the development of cancer of the prostate. This is based, primarily, on three facts: (1) evidence that in rodents, hypertestosteronemic states result in the appearance of prostatic cancer [27]; (2) the usually dramatic responses of most human prostatic cancers to surgical or medical castration; and (3) the controversial yet widely held impression that there exists a positive relationship between serum androgen levels and prostate cancer in humans [28]. Another contributor to the general concern about the role of T in CaP is the conflicting reports in the literature regarding the association between levels of serum T and the incidence of CaP. A recent review of controlled studies by Slater and Oliver [29] brought into a much needed focus the role of T as a causal factor in the development of CaP. In this review, four studies found a positive association between high serum T levels and risk of CaP, in 15 studies there was no difference, while in the remaining six studies high serum T levels were associated with a reduced risk. Little wonder that there is confusion in this area!

Although a contemporary meta analysis found that men with the highest levels of serum T have a greater incidence of prostate cancer than men with lowest levels [30], currently, the preponderance of the evidence does not support the concept that normal serum levels of T are associated with increased risk of prostate malignancy. Many other factors (environmental, genetic) have been considered, antropomorphic studies suggest that some aspects of body size can be correlated to the risk of prostate cancer [31] and dietary factors either directly or through the action of sex steroids may have an important bearing in the development of CaP [32]. As stated previously, hypogonadal men receiving T supplementation show insignificant

increases in PSA and their prostates only reach sizes that are commensurate to their ages [33]. It is possible that in the presence of hypogonadism a prostatic cancer may not be clinically evident but manifest itself following institution of androgen therapy [34]. Under these circumstances the early discovery of a subclinical cancer may be highly beneficial by allowing prompt, possibly curative therapy. A cautionary note, however, is needed here: longitudinal studies on ART are few, comprise relatively small number of patients with a follow-up period amounting to only a few years. While the results are reassuring only longer periods of observation (>10 years) in large populations will provide reliable answers.

4.4. Testosterone causality and perpetuation of prostate cancer?

Despite the overwhelming evidence supporting a positive relationship between sex hormones and growth of prostate cells (both benign and malignant), there exists a number of perplexing issues, related specifically to CaP that have not been fully elucidated. At the experimental level a prostate cancer cell line (LNCaP), that requires initial stimulation by androgens to grow, eventually is suppressed by androgens. Not all longitudinal human studies have documented the existence of a positive relationship [35,36] between CaP and T levels, some—in fact—documenting that the levels are low rather than high at the time of diagnosis of CaP [37]. A frequently quoted longitudinal study [31] supporting a relationship between T serum levels and CaP indicated that samples were drawn, in many cases, years (up to 10) prior to the clinical detection of the malignancy. Finally, there are a few, early clinical studies showing a variable response of existing prostatic cancers to sex hormone administration: some tumors being stimulated while others were in fact inhibited [38,39]. These conflicting views have led to the radical and highly controversial hypothesis that declining (rather than high) levels of androgens are major contributors to the development of CaP and that when CaP escapes androgen suppression therapy the tumor might be responsive to ART [40]. This hypothesis remains untested and should not be considered for testing outside well designed and rigidly controlled trials.

5. Other hormones and prostate health

5.1. Dehydrotestosterone (DHT)

T, undoubtedly, plays the major role in prostatic function and growth either directly or, more importantly, through conversion into DHT by 5α-reductase. DHT is the most important regulator of prostate cell proliferation. The concerns mentioned previously on the issues of T and prostate safety apply, at least equally, to the use of DHT since the former provides the substrate for the latter [41]. There is, however, a paucity of studies investigating in depth the role of this, obviously, important hormone in prostate cancer. Retrospective studies have been conducted in stored sera from men already harboring CaP to establish a possible correlation with reductase activity [42], or prospectively by surrogate measures (gland size and PSA measurements) in relation to DHT levels [43,44]. Although many discrepancies and contrary findings were reported, the meta analysis of Gann et al. [28] concluded that different levels of androgenic precursors (T levels) rather than differences in 5α-reductase activity ''are responsible for the observed differences in prostate cancer incidence''.

5.2. Dehydroepiandrosterone (DHEA)

DHEA hormone and its sulfate DHEAS are produced in relatively large amounts by the adrenal cortex. They exhibit very limited androgenic activity as compared to T and DHT. However, their function remains to be fully elucidated. It was reported [45] that DHEA inhibits, in vitro the growth of murine prostate cancer cells and a possible correlation between DHEA levels and the presence of CaP has not been established [46,47]. It should be remembered that DHEA is easily converted to DHT and, although, only small amounts result from this metabolism the administration of DHEA should be considered to have the same contraindications that apply to T regarding prostate safety; reports exist of dramatic progression of CaP following DHEA administration [48]. There is, however, a paucity of information on DHEA and its effects on the prostate gland of humans, with only small and short term studies available. This is more surprising since the drug is unregulated and readily available as over the counter ''nutritional supplement'' in some jurisdictions. There is a need for a concerted research effort to establish the relationship between DHEA and prostate health.

5.3. Growth hormone (GH)

The body of literature on growth hormone (GH) and prostate safety is scanty but several hypotheses have been advanced [49] and increased GH levels have been associated with BPH [50]. Since the production of insulin-like growth factor 1 (IGF-1) by the liver depends on the production of GH by the pituitary, for simplicity and accuracy most serum determinations

are on the former. The association for the development of prostate cancer found in the meta analysis of Gann et al. [28] was consistent, strong and significant. The odds ratios being ''similar in magnitude with those between T and prostate cancer''. The difference, of course is that only three studies on IGF-1 were analyzed while there were 28 on androgens and CaP. GH is not as accessible as androgen therapy in most countries and restrictions exist for specific indications for its use. However, GH administration is contraindicated in the presence of any cancer [51], to which prostate is not an exception; but, in addition, is suspected to play a causal role in CaP [47,52]. It is prudent, therefore, to consider that the same concerns and contraindications apply to GH as to androgens in relation to prostate health.

6. Recommendations

The following recommendations on ART and prostate safety are loosely based on the general ones endorsed by the Canadian Andropause Society [53] and those currently under consideration by the International Society for the Study of the Aging Male (ISSAM) [54]. Both sets of recommendations apply primarily to the use of ART in adult men and focus particularly on Leydig cell failure associated with aging. These recommendations remain valid and eminently true in regard to prostate safety. The ones offered here are specifically directed to the issues regarding prostate safety and androgen administration.

1. BPH with moderate or no BOO is a relative contraindication for T administration.
2. Proven or suspected CaP, breast cancer and severe BOO are absolute contraindications for T administration.
3. Men who underwent radical treatment for CaP and who remain clinically and biochemically free of recurrence may be candidates for ART after a prudent period (such period has not been established).
4. Monitoring of men receiving exogenous T is essential and constitutes a serious responsibility for the treating physician. Monitoring should include, in addition to assessment of symptoms, a baseline DRE and PSA. Monitoring should be repeated at 3, 6 and 12 months after onset of therapy. Yearly monitoring may be sufficient afterwards.
5. Androgen supplementation is usually for life. Consequently, monitoring is also a lifetime commitment.
6. Although current views regarding exogenous androgens and prostate health are reassuring, the data has not yet matured. Most longitudinal studies comprise only a few years of observation and the long–long term effects of therapy remain unknown.
7. A well informed clinician using common sense should feel comfortable in prescribing and monitoring elderly men receiving exogenous T.
8. No evidence exists for or against the combination of supplemental T and 5α-reductase inhibitors (i.e. fenasteride).
9. Until further evidence appears, these recommendations generally apply also to the use of DHT, DHEA and GH. Physicians should be particularly concerned about unregulated hormones sold over the counter as ''nutritional supplements'' and that may be not be reported by patients.

7. Conclusions

Aging is unavoidable. However, the judicious administration of androgens in those who need them may make the process of aging healthier. ART requires basic knowledge and good judgment on the part of the clinician and a commitment to careful monitoring by both the clinician and the patient. Monitoring is particularly important in men at risk (genetic and environmental) of harboring prostatic cancer as well as those with BOO secondary to prostatic enlargement. At present there is no evidence linking the appropriate treatment of hypogonadism in the adult male with the development of prostate cancer. Therefore, treatment should not be withdrawn if it is indicated and contraindications are absent. However, until large, longitudinal studies have fully matured, ART must be used following recommendations based on the available evidence.

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