POINT: Urologists should take an active role in the diagnosis and treatment of hypogonadism in the aging male

Jeremy P. W. Heaton, MD

Departments of Urology, Pharmacology and Toxicology, Queen's University, Kingston, Ontario, Canada

HEATON JPW. POINT: Urologists should take an active role in the diagnosis and treatment of hypogonadism in the aging male. The Canadian Journal of Urology. 2002;9(6):1677-1680.

Andropause is a problem that can be identified in some men as distinct from the changes associated with aging or chronic disease. These men have mild hypogonadism and a clinical picture that is well within the scope of urologists to identify and manage. Andropause is neither life threatening nor trivial and there are clinical guidelines published that will help to refine the understanding and definition of this condition. The character of andropause is distinct from profound hypogonadism in its relation to age, the scope and degree of contributing symptoms and the marginal reduction in testosterone. Testosterone is the established treatment for some men with andropause and the links between testosterone and cancer of the prostate create an overlap in management that places a premium on urological expertise. Obviously men with cancer of the prostate must not be given testosterone and some men may have clinical andropause and undetected cancer of the prostate. However, current understanding points to the fact that there is no additional risk from re-establishing a normal androgen environment (androgen replacement) in terms of initiating a new cancer of the prostate while testosterone will encourage growth of an established cancer. Therefore, the natural good practice of urology, and only urology, intrinsically encompasses the major issues inherent in the medical collision of cancer of the prostate and testosterone replacement. The good practice of urology includes the use of androgen replacement therapy in men who need it and have been assessed for the presence of cancer of the prostate.

Key Words: testosterone, prostate cancer, andropause, hypogonadism

1. Should urologists be diagnosing and treating ADAM in men who are experiencing some mild symptoms frequently associated with aging with mildly low T levels?
2. Should ADAM be a restrictive diagnosis in patients with very clear cut symptoms and very low levels of T?
3. Which specialty is best suited to manage the condition?

Accepted for publication October 2002

Address correspondence to Dr. Jeremy P.W. Heaton, Kingston General Hospital, 76 Stuart Street, Kingston, Ontario K7L 2V7

The scene for this controversy is the early years of the 21st Century. It is a controversy of our time. It reflects on the one hand the certainty that we have on our hands a great cancer, prostate cancer, that demands our attention, that is devouring billions of dollars ($1,411,687,900 p.a. 1994 total Medicare expenditure for treatment of prostate cancer) in North America alone in management[1] and $438 million for prostate cancer research, that still kills 30,200 men a year in the U.S.[2] and that we are only slowly learning to manage. On the other hand is testosterone to be given for a problem that is dismissed as being a 'life style' problem. The interface between the two is complex, historical (the second Nobel laureate in Urology[3]) and not unemotional (testosterone is so closely related to

male identity). Ironically, by eliminating one we defeat the other – to the greatest extent that we have devised so far. And now we propose to add testosterone to the very patients who are likely to harbor a few cells with malignant intent in their prostates, and for a life-style problem? Anathema! Actually not. There are men who have androgen deficiency syndromes who deserve treatment and this treatment is, at its core, no different from any other in that it requires a balanced understanding of the issues. I propose that this reaction against 'andropause' is thinking from the 1940's. I suggest that if we make such sweeping and prejudiced guesses about health care then we are not fit to utter the words "evidence-based medicine". Differences of opinion are healthy, over-simplification is not.

The third question is easy to deal with. The main treatment for 'andropause' is testosterone. The main risk of testosterone is acceleration of prostate cancer growth. Whoever owns the benefit, urologists certainly own the risk. Therefore there are two solutions that permit a risk-benefit analysis where the balance should be assessed by the same specialist: Urologists either give up prostate cancer to 'andropause' experts; or urologists adopt 'andropause' issues as their own. Only one of these solutions is in the reality domain. Therefore urologists have to accept 'andropause' as an issue for which they are responsible. Q.E.D.

I will admit a problem of nomenclature. Andropause is a poor term.[4] Acronyms such as ADAM, EDAM, SHAME, HAM (hypogonadism in the aging male – from the given title) and so forth do little to disguise the relative imprecision of the diagnosis (no pathological stage, grade or Gleason Score so how can it be real?). To some extent you can say "you know who they are" or "there are criteria" but it has been a problem and the criteria and definition are not well known but have recently been published.[5] Difficulty with definition or diagnosis does not make it go away, however, so this discussion will use the term andropause.

As expressed, question 2 can be reduced to the easy part of the hypogonadal spectrum. If the testosterone is 'very low' and there are hypogonadal symptoms there is no worry whether the measure is total testosterone or bioavailable testosterone or some other fraction of testosterone (that only a few poor souls understand). This is hypogonadism. This is a medical condition with a known treatment that should be used unless there is evidence that the patient will suffer more harm than good. Is there evidence of prostate cancer – and as urologists the reasonable elimination of this diagnosis is routine? If not – treat. If there is prostate cancer – don't. Even this is a little simplistic but the following discussion will tidy up the marginal issues to some extent. There is no excuse for an urologist to be uninformed about androgen supplementation and it is not the role of this debate to review the available compounds and their clinical use.

The real issues in question 1 relate to the issues of degree. Should urologists make the diagnosis and take responsibility for treating ADAM in men who are experiencing some *mild symptoms* frequently *associated with aging* and with *mildly low T levels*? Can the mild symptoms be defined sufficiently? Is the association with aging indicative of a natural event – and should natural events be treated as illnesses? Can the mildly low levels be defined and do they naturally indicate a replacement therapy that risks prostate cancer status?

The symptoms of andropause are well known but do not make a distinct clinical picture either historically or on examination. Table 1 The clinical impression can be enhanced by using one of the formal scales developed for andropause.[6,7] The clinical examination does not usually reveal specific findings (gonadal atrophy, say) but may reveal visceral fat, aging skin and increased hair in ears and nose.

This constellation of symptoms is variable, may be subtle and certainly overlaps many of the changes that are commonly associated with aging. The urologist is often faced with the complaint of erectile difficulties and only a little digging reveals some of the andropause symptoms. They are generally mild and it is the overall clinical context that should trigger a look for biochemical correlates.

For biochemical information relevant to andropause the recommendation is that: In-patients

TABLE 1. **The common changes found in patients with andropause**

Sexual desire and erectile quality	↘
Intellectual capacity (depression, fatigue)	↘
Lean body mass	↘
Bone mineral density	↘
Visceral fat	↗
Body hair and skin alterations	↔
Altered sleep patterns	↔

Note: not all symptoms need be present or of comparable severity to support a diagnosis of andropause.

at risk or suspected of hypogonadism the following biochemical investigations should be done: a. serum sample for testosterone (T) determination between 8:00 AM and 11:00 AM. The most reliable and widely accessible parameter to establish the presence of hypogonadism is the measurement of bioavailable testosterone (BAT) or, alternatively a calculated free testosterone (CFT). 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 follicle stimulating hormone (FSH) luteinizing hormone (LH), and prolactin.[5] In older men measurement of sex hormone binding globulin (SHBG) will add to the understanding of true T availability.

So we have a usually mild condition with similarities to what has previously been accepted as normal aging and a biochemical disturbance characterized by a T value at or below the normal accepted range. Despite the fact that it is accepted that there are more hormonal abnormalities than just the change in androgen milieu (melatonin, growth hormone, IL6, leptin, insulin like growth factor one, dihydroepiandrostenedione, dihydroepiandrostenedione sulfate, antidiuretic hormone and more probably) the only established treatment is testosterone. The goal with androgen replacement therapy (ART) treatment is to bring biochemical T values back to within the normal range – not above – and to improve symptoms.

The molecule itself is not a risk. All preparations of T currently used (excepting the alkylated preparations which should not be used because of their known risks) deliver molecular T. It is the actions of T at serum levels higher than the low levels that precipitated the problem that has become cause for concern. The known issues are: Liver disease (only alkylated forms); cardiovascular system and lipid profile (hypotestorenemia might be a risk factor for cardiovascular disease while normal levels appear to be cardio-protective, but monitoring of patients with significant cardiovascular risk factors is suggested); fluid retention; red blood cell mass and hemoglobin levels (increases appear to be larger in older hypogonadal men, must be monitored); sleep apnea (remains controversial, probably not related); and prostate.

The most significant area where urological expertise is needed, to determine the true risk benefit position, is in prostate health. The prostatic volume increases with age in normal men but not in untreated hypogonadal men. When truly hypogonadal men are treated with T prostate volume increases but only to the size expected for eugonadal men of the same age.[8] Early studies, and intuitive thinking, suggested that androgen administration would result in a small increase in prostate volume and prostate specific antigen (PSA) level within normal limits.[9] Most studies have shown no effect of exogenous T on these parameters.[10] Placebo-controlled studies of hypogonadal men receiving androgen therapy have shown no alterations in prostate volume, PSA and lower urinary tract symptoms (LUTS).[11] These data suggest that severe LUTS might be considered a relative contraindication since even a modest increase in size might not be tolerated.

ART is contraindicated in men with possible cancer of the prostate (CaP). This includes men with an abnormal DRE or PSA where CaP has not been ruled out and men recently treated for CaP with curative intent (radical prostatectomy or radiotherapy) where both the DRE and PSA are normal. After a period of time without evidence of recurrence ART could be considered but there is no clear evidence of what constitutes a reasonable interval.

There is a well established belief among physicians that ART may have an important role in causing CaP – after all, if castration can cause apoptosis, should exogenous T not do the opposite? In reviewing the evidence remember that the goal of ART is replacement to normal levels and not imposition of abnormally high T. Furthermore, early work in artificial hypertestosteronemic states showed the development of prostatic cancer in a rat model.[12] There is also a common, probably incorrect, impression that there is an association between serum androgen levels and prostate cancer in humans.[13] A recent analysis has suggested that in fact higher levels of T are associated with lower risk for CaP.[14] In a review of controlled studies four studies found a positive association between high serum T levels and risk of CaP, 15 found no difference and in the remaining six studies high serum T levels were associated with a reduced risk.[15] A contemporary meta-analysis found that men with the highest levels of serum T have a greater likelihood of CaP than men with lowest levels.[16] The preponderance of evidence does not support the concept that normal serum levels of T are associated with CaP.

In an individual, an untreated hypogonadal state may conceal a CaP that would reveal itself following institution of androgen therapy.[17] This is only an argument for careful urological scrutiny of patients before and during T treatment – the use of T may unmask an otherwise unseen but treatable CaP. There are few patients who have been studied for extended periods of time and such a study, analogous with studies of risks associated with female hormonal replacement therapy, is certainly indicated.

The evidence relating to *de novo* causation of malignant phenotypic change in previously normal prostate cells is lacking. Experimental cellular models may require T for growth but this does not point the finger at T as the trigger for abnormal growth. In fact there is no evidence that T at normal levels will cause changes to the genome. It is also unlikely that men with genetic susceptibility to CaP are at risk from T levels within the normal range unless their personal normal range through youth and young adulthood has been significantly below the societal norms – not a condition that has been recognized.

Conclusion

Andropause is an established and defined if not life-threatening condition. Testosterone is a good treatment for some men with this problem. Men with cancer of the prostate must not be given testosterone. Some men may have clinical andropause and undetected cancer of the prostate. Urologists are uniquely well trained and professionally obliged to make sure that the number of men with undetected cancer of the prostate is as small as possible where cancer of the prostate would represent a significant health threat to the individuals concerned. Therefore, the natural good practice of urology, and only urology, intrinsically encompasses the known issues inherent in the collision of cancer of the prostate and testosterone replacement. And the good practice of urology would easily include the use of androgen replacement therapy in men who need it and have been assessed for the presence of cancer of the prostate. □

References

1. http://www.cancer.med.umich.edu/prostcan/articles/androsupp.htm.
2. American Cancer Society Inc, 2002.
3. CB Huggins, Endocrine-induced regression of cancers, Nobel Lecture, December 13, 1966.
4. Morales A, Heaton JP, Carson CC 3rd. Andropause: a misnomer for a true clinical entity. *J Urol* 2000;163(3):705-712.
5. Morales A, Lunenfeld B. Investigation, treatment and monitoring of late-onset hypogonadism in males. Official recommendations of ISSAM. International Society for the Study of the Aging Male. *Aging Male* 2002;5(2):74-86.
6. Morley JE. Andropause, testosterone treatment and quality of life in aging men. *Cleveland Clin J Med* 2000;67:880-882.
7. Heinemann LAJ, Saad F, Thiele K, Wood-Duphinee S. The aging male's symptom rating scale: cultural and linguistic validation into English. *Aging Male* 2001;4:14-22.
8. Behere, HM. Prostate volume in treated and untreated hypogonadal men in comparison to age-matched controls. *Clin Endocrinol* 1994;40:341- 346.
9. Douglas TH, Connelly RR, McLeod DG, Erickson SJ, Barren III R, Murphy GP. Effect of exogenous testosterone replacement on prostate specific antigen and prostate specific membrane antigen levels in hypogonadal men. *J Surg Oncol* 1995;59:246-250.
10. Tenover JL Androgen administration to aging men. *Endocrinol Metab Clin N A* 1997;23:877-886.
11. Tenover JL. Androgen deficiency in aging men. *Aging Male* 1998;1(Suppl 1):16-21.
12. Nobel R. The development of prostatic adenocarcinoma in Nb rats following prolonged sex hormone administration. *Cancer Res* 1977;37:1929-1934.
13. Gann PH, Hennekens CH, MJ, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst* 1996;88:1118-1135.
14. Aronson KJ, Wilson JWL, Nickel JC, Heaton JPW, MacNeily A, Morales A. Circulating sex hormones and prostate cancer risk. *Can J Urol* 2002;9:3:1515(Abstract).
15. Slater S, Oliver RTD. Testosterone: Its role in the development of prostate cancer and potential risks from use as hormone replacement therapy. *Drugs and Aging* 2000;17: 431-439.
16. Shanayfelt T, Husein R, Bebkey G, Mantzoras C. Hormonal predictors of prostatic cancer: a meta analysis. *J Clin Oncol* 2000;18:847-853.
17. Curran MJ, Bihrle W. Dramatic rise in prostatic specific antigen after androgen replacement in a hypogonadal man with occult adenocarcinoma of the prostate. *Urology* 1999;53:423.