



Editorial – referring to the article published on pp. 935–939 of this issue

Testosterone and Prostate Health: Debunking Myths Demands Evidence, Caution, and Good Clinical Judgment

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The review article by Dr Morgentaler [1] on this highly controversial topic is a timely and well-thought-out challenge to urologists worldwide. I very much admire his refreshing position on this issue and agree with many of his comments. In fact, many years ago, we reported our observation of a dramatic and sustained response to testosterone (T) propionate in 2 of a group of 14 patients with metastatic prostate cancer (pCA) [2].

I said that I share many of his views—but not all of them. From the outset we should recognize that the evidence that T produces pCA simply does not exist. A few anecdotal cases, T levels measured on long-stored serum samples and literature reviews do not make a cause–effect relationship. On this point we agree. I disagree, however, with his statement that T does not cause “enhanced growth of prostate cancer.” There is experimental and clinical evidence showing that administration of T to patients with pCA results in detrimental effects in the majority (although not all) of them [2] (and references 10 and 15 in his paper). This evidence is further supported by the finding that prostate-specific antigen levels may be altered by naturally occurring reductions in serum T levels [3].

It would be naïve to attribute the sole culprit role in the promotion of pCA to T. It is suspected that the most likely culprit, at least in the United States, is the diet rich in animal fats and meats [4]. It is also suspected that factors such as inflammation [5] or the action of other hormones such as leptin [6] may

be significant contributors. The multiple etiology of pCA is far from being clearly defined, but it is recognized that androgens in general play, at the very least, an important facilitator role. The graph in the paper, therefore, makes for good imagery but does not prove the point that T is not one of the mediators involved, since it ignores the fact that a carcinogenic stimulus may precede the clinical finding of the tumor by decades.

The last paragraph of his paper offers an earnest and provocative challenge that we must heed thoughtfully, seriously, and impartially: “The danger of belief trumping evidence is that it impairs our ability to behave logically and consistently, and can cause us to disregard awkward data that may ultimately provide promising avenues of research.” It reminds me of the recent wonderful documentary *An Inconvenient Truth* by the American former vice-president Al Gore. What is needed now is the will to rethink anew the relationship of T and other sex steroids in regard to prostate safety. However, for better or worse, the current wisdom is that it is an absolute contraindication to administer T to men suspected of harbouring pCA. To ignore this almost universal belief leaves not only the patient but also the clinician at great risk and would be a defense lawyer’s nightmare. The studies supporting Morgentaler’s view are but a handful of underpowered studies that have not reached maturity. Hence, the evidence to finally discredit this “myth” is not available, either. And this is the inescapable hard reality.

I am in complete agreement with Morgentaler's position that androgens may not be as deleterious to prostate health as we may have been led to believe by earlier observations. Allow me to paraphrase myself on a commentary [7] I wrote recently about reference 35 in Morgentaler's paper:

Despite the large body of support for a positive relationship between male sex steroids and growth of prostate cells, there are a number of puzzling situations that are under active investigation. At the experimental level, a prostate cancer cell line that requires initial stimulation by androgens to grow is eventually suppressed by them. These and other observations led Prehn to advance a well-thought-out but radical hypothesis that he summarized with these words: "Contrary to prevalent opinion, declining rather than high levels of androgens probably contribute more to human prostate carcinogenesis and that androgen supplementation would probably lower the incidence of the disease. I will also consider the possibility that the growth of androgen independent prostate cancers may be reduced by the administrations of androgens." I then further commented that human research in this area is important but fraught with ethical and clinical difficulties.

Despite the above statements and until convincing evidence to the contrary is presented, I [8] fully subscribe to the recommendation that known or suspected carcinoma of the prostate is a contraindication for T products (reference [3] in Morgentaler's paper). This recommendation has been recently reiterated in the Endocrine Society Guidelines [9]. It is clear that we have to wait for the large studies that are, presently, only at the planning stage but will eventually (10 or more years) shed more light on this very important issue.

Dr Morgentaler is to be congratulated for his thought-provoking, accurate review and courageous interpretation of the data. For too long we have been stuck in the management of pCA because of its frequently impressive but almost universally short-lived response to androgen suppression therapy (AST). Decades of costly, redundant research have been spent debating and investigating ways to improve AST as a means to prevent and control pCA. However, we have lacked the fortitude to truly investigate the effects of T and other sex steroids in prostate carcinogenesis and the progression of established neoplasms (both benign and malignant) of the gland.

We have to accept that there is overwhelming evidence indicating that factors influencing the

development and growth of pCA are much more than simply an excess or shortage of sex steroids: nonsteroidal hormones (insulin, glucocorticoids, leptin, growth hormone), genetic susceptibility, sexually transmitted agents, diet, and environmental carcinogens appear to be significant contributors to the process. We must also accept that there is a growing body of literature presenting the puzzling paradox that T and other androgens are essential for the gland's development, while they may also prevent/inhibit the establishment of prostate cancer. In addition, it is quite clear that novel signalling pathways, with or without participation of the androgen receptor–signalling cascade, can be activated independently of serum androgen levels. Finally, to further complicate the picture, fascinating and convincing evidence has been presented lately demonstrating that "no prostate tissue changes attributable to T supplementation were found (in this study of men with low T receiving T supplementation). Despite marked increases in serum levels, prostate levels of T and DHT were unchanged after 6 months of treatment, gene expression was not altered, cell proliferation was not accelerated, and histologic cancers were not increased" [10]. Thus, it appears that the intraprostatic hormonal environment bears little resemblance to serum levels of androgens. The implications of these findings, once confirmed, are of enormous significance.

Despite the interest and hullabaloo that publications such as this generate, the astute physician must remain extremely cautious, and be well informed and guided by reliable peer-reviewed publications, experience, and good judgment. Administration of T and other steroids to men suspected of harbouring pCA, at this time, should be considered only as part of properly sponsored, well-designed, organized, rigidly controlled, and carefully monitored clinical trials. To do otherwise can easily be construed as reckless behaviour that would potentially endanger the patients' health and the clinician's reputation, and result in further detriment to a field already replete with myths, misinformation, and dubious evidence. I suspect that further critical assessment of the available evidence will not significantly enhance our knowledge on this topic. Only a fresh approach with good studies will lead to the answers that we all yearn for.

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