Testosterone Replacement Therapy - why is it so controversial?

It is dangerous to be right when the government is wrong. - Voltaire

For reasons that are not readily apparent, there appears to be a conservative political movement that opposes the use of testosterone in older men. This was clearly demonstrated by the report of the Institute of Medicine, which felt that testosterone is not yet ready for prime time and that there is still a need for studies to prove its efficacy [1]. Along the same lines, the guidelines of the Endocrine Society on testosterone use in older men seem to be ultra-cautious [2]. But fortunately, there are also other, more liberal guidelines and recommendations [3-5].

Probably no other medical issue has been bombarded by the influx of "expert" views from all walks of life; from endocrinologists and psychiatrists to urological surgeons and gerontologists, from the lay press to the regulatory agencies and from the pharmaceutical to the entertainment industries. The dismal result of all this free-for all cacophony of opinions is a great deal of confusion, erroneous information and significant detriment to patients and physicians alike.

Let's take an in-depth look at the reasons for the negative attitudes to male testosterone replacement therapy (I will cover post-menopausal testosterone replacement in an upcoming article), and the hard scientific data that refutes it...

Unsubstantiated Claim 1:
There Is Insufficient Evidence That Testosterone Is Beneficial in Older Men

Data:
Numerous placebo-controlled studies have demonstrated salutary effects testosterone therapy in older men [6-11]. Testosterone therapy clearly improves sexual function (both libido, erectile and ejaculatory function) in older men [12]. In addition, testosterone supplementation in borderline hypo-gonadal men increases muscle mass [13-17], decreases fat mass [14, 15, 17], and improves strength [8, 13, 16, 17]. There are also data showing that testosterone replacement in older men increases bone mineral density [18, 19] (and thereby and counteracts osteoporosis), improves cognition (in both Alzheimer and non-demented elderly) [20-22] and mood [16, 20, 23], and also alleviates depression [24].

Recent studies have also shown that testosterone therapy significantly improves not only symptoms of androgen deficiency (including erectile dysfunction), but also metabolic and control (lowering of blood glucose and glycated hemoglobin (HbA1c) (from 10.4 to 8.6%) [25], while decreasing abdominal obesity [25]. These beneficial effects were seen without any adverse effects on blood pressure or hematological, biochemical and lipid parameters [25]. Testosterone gel also has been shown to reverse the metabolic syndrome and improve glycemic control in men with sub-normal plasma testosterone [26]. The improvements in glycaemic control, insulin resistance, cholesterol and visceral adiposity seen is these studies show that testosterone therapy contributes to an overall reduction in cardiovascular risk.

It is strange that treatment of testosterone deficiency caused by classical diseases affecting the hypothalamus, pituitary, and/or testes has been accepted for decades although there were no large multicenter trials, but that that treatment of testosterone deficiency caused by aging is taboo despite overwhelming scientific data showing significant benefits. It appears that physicians and regulatory agencies are much more comfortable treating older men with questionable drugs that pose more harm

than benefit in terms of both quality of life, cancer and mortality [27-47], than using testosterone, a drug that not only improves important symptoms and risk factors, but also can reverse sarcopenia and frailty [48-54] which has well-documented detrimental effects on well-being, physical independence, morbidity and mortality. This is a poster-child example of "eminence" based medicine trumping evidence-based medicine.

Unsubstantiated Claim 2:
Testosterone Increases Prostate Cancer

Data:
The most prominent concern regarding testosterone treatment is its effect on prostate health. For decades, the concept that testosterone is "bad for the prostate" has gone unchallenged. Even though prostate-specific antigen (PSA) levels increase in response to testosterone supplementation [55, 56], recent research shows that the longstanding fear of stimulating prostate cancer with testosterone supplementation is without scientific basis [57-59].

Mechanistic studies have shown that the development and growth of prostate cancer are much more complex than simply an excess of lack of androgens: nonsteroidal hormones (e.g., insulin, leptin, glucocorticoids and growth hormone), genetic susceptibility, inflammation and environmental factors appear to be significant contributors [60]. Further, there are a number of puzzling situations. For instance, prostate cancer cell lines that requires initial stimulation by androgens to grow is eventually suppressed by them [60]. More evidence for the not so clear-cut relation between testosterone and prostate cancer lies in the fact that prostate cancer occurs in older men at a time when testosterone levels have already declined to low levels [61]. In addition, there is no prospective evidence that testosterone is correlated with the development of prostate cancer [62], and retrospective studies have failed to demonstrate an increase in prostate cancer in men treated with testosterone [63].

Unsubstantiated Claim 3:
Testosterone increases cardiovascular disease risk
Another debate centers on the putative increased cardiovascular risk of testosterone therapy. While it is true that supra-physiological doses of testosterone, such as those administered by athletes, doe increase several risk factors for cardiovascular disease and cardiac events [64-66], this is not the case when testosterone therapy is used to restore low age-related testosterone levels to the normal range [59]. To counter this, the anti-testosterone maffia often points to a study that was stopped before completion because much more adverse cardiovascular events were measured in the treatment group [67]. However, the adverse cardiovascular events in this study could be explained by the pre-study high prevalence of cardiovascular risk factors within the study participants.

The adverse effects of testosterone therapy include an increase in hemoglobin and hematocrit (volume percentage (%) of red blood cells in blood) [59, 68], and a small decrease in HDL (the "good" cholesterol) [59, 69]. However, elderly men with low testosterone tend to have a low hematocrit and also frequently present with anemia (hemoglobin deficiency) [70], so this side-effect can actually be a good thing. And the hematocrit-induced increase in blood viscosity can be alleviated with fish oil [71], while the decrease in HDL can be counteracted by carbohydrate restriction [72] and/or niacin (vitamin B3, the most effective way for increasing HDL) [73, 74], and a moderately increased physical activity [75-78]. It should be noted that the small HDL reduction is primarily observed with intramuscular testosterone injections [69], and not with transdermal gel preparations [79].

To the contrary, it is well documented that low testosterone levels actually increase cardiovascular disease risk [80, 81]. Following the recent reevaluation of the estrogen-protection orthodoxy, empirical research has flourished into the role of androgens in cardiovascular health. Observational studies show that blood testosterone levels are consistently lower among men with cardiovascular disease [80, 81], suggesting a preventive role for testosterone therapy.

In middle-aged and older men, lower testosterone levels are associated with insulin resistance, metabolic syndrome and diabetes, and related conditions that predispose to cardiovascular disease [82]. Lower testosterone levels predict cardiovascular events, such as stroke and transient ischaemic attack, in older men and are associated with higher cardiovascular and overall mortality [82]. Randomized trials have even shown that testosterone supplementation in men with existing coronary artery disease can be protective against heart attack (myocardial ischaemia) [82].

Unsubstantiated Claim 4:
Andropause doesn't exist

Data:
While andropause, the progressive decline in testosterone production in aging men, unquestionably does exist and warrants treatment, whether the term "andropause" per see is a good descriptor for this phenomenon has been debated.

The terms “andropause” or "male menopause” are not completely accurate because androgen secretion does not cease altogether, as the term "pause" indicates [83, 84]. The term menopause is correct in that in women the reproductive cycle invariably ends with ovarian failure and an abrupt cessation of estrogen production and onset of symptoms. In men however, the reduction in testosterone levels is a gradual process and the appearance of its clinical manifestations is more subtle and develop over time. This has unfortunately led to a tendency among many suffering older men to ignore the symptoms and accept it as an unavoidable and untreatable result of aging. In a survey of health care professionals, half reported that their patients rarely or never asked about low testosterone [85]. Several prominent scientists have strongly recommended that awareness of andropause and its consequences be increased [83, 86, 87].

The term “male climacteric” is more appropriate as it suggests a decline and not a precipitous drop in hormones levels [88]. The term “male climacteric” refers to the syndrome of endocrine, somatic, and psychic changes that occur in normal men with aging. This term is good in that it emphasizes the multidimensional nature of age-related changes, including age-related decreases in other important hormones such as growth hormone (GH), insulin-like growth factor-1 (IGF-1), dehydroepiandrosterone (DHEA), and melatonin [89-91], and not only relates aspects of the male aging syndrome specifically with testosterone levels.

Andropause has also been referred to by some medical professionals as “androgen deficiency in the aging male (ADAM),” “partial androgen deficiency in the aging male (PADAM),” or “aging-associated androgen deficiency (AAAD)” [84]. However, andropause is the term that is used commonly by experts in the field and by
lay persons alike because it retains some analogy to the term menopause in women [83]. After all, what's in a name?

Unsubstantiated Claim 5:

Estrogen replacement in post-menopausal women turned out to be bad, and therefore testosterone replacement in men must also be bad.

Data:
This claim is screams irrational logic and an unwarranted extrapolation.

Unsubstantiated Claim 6:

Bad Kharma: It's all about sex

Reality:
Testosterone therapy is a touchy topic because it improves sexual enjoyment. Even in the times of Viagra, attitudes to sex remain embarrassingly silly "imagine if you give an old man testosterone, he may want to have sex!!" The use of testosterone in women is facing a similar issue [92-95].

Unsubstantiated Claim 7:
If testosterone becomes mainstream treatment in elderly it will become abused by younger adults

Reality:
Abuse of testosterone will occur whether or not it is available for older men.

Conclusion
Testosterone deficiency in older men (hypogonadism) is very common [52, 96, 97] (up to 50% of men over the age of 50 are deficient in free testosterone when compared with peak morning concentrations in young men [91]), and yet only a small proportion of hypogonadal men are receiving testosteone replacement therapy [98]. In the end, a particular political viewpoint is in the eye of the beholder. Nevertheless, it is obvious that the political climate is working against testosterone replacement therapy in older men despite overwhelming scientific data supporting this appropriate pursuit as a strategy to prolong healthy longevity.

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