



Review

Testosterone and the aging male: To treat or not to treat?

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ABSTRACT

It is well-established that total testosterone (TT) in men decreases with age and that bioavailable testosterone (bio-T) falls to an even greater extent. The clinical relevance of declining androgens in the aging male and use of testosterone replacement therapy (TRT) in this situation is controversial. Most studies have been short term and there are no large randomized placebo-controlled trials. Testosterone has many physiological actions in: muscles, bones, hematopoietic system, brain, reproductive and sexual organs, adipose tissue. Within these areas it stimulates: muscle growth and maintenance, bone development while inhibiting bone resorption, the production of red blood cells to increase hemoglobin, libido, enhanced mood and cognition, erectile function and lipolysis. Anabolic deficits in aging men can induce: frailty, sarcopenia, poor muscle quality, muscle weakness, hypertrophy of adipose tissue and impaired neurotransmission. The aging male with reduced testosterone availability may present with a wide variety of symptoms which in addition to frailty and weakness include: fatigue, decreased energy, decreased motivation, cognitive impairment, decreased self-confidence, depression, irritability, osteoporotic pain and the lethargy of anemia. In addition, testosterone deficiency is also associated with type-2 diabetes, the metabolic syndrome, coronary artery disease, stroke and transient ischemic attacks, and cardiovascular disease in general. Furthermore, there are early studies to suggest that TRT in men with low testosterone levels may improve metabolic status by: lowering blood sugar and HbA1C in men with type-2 diabetes, reducing abdominal girth, ameliorating features of the metabolic syndrome, all of which may be protective of the cardiovascular system. The major safety issue is prostate cancer but there is no evidence that supports the idea that testosterone causes the development of a de novo cancer. So on balance in a man with symptoms of hypogonadism and low or lowish levels of testosterone with no evidence of prostate cancer such as a normal PSA a therapeutic (4–6 months) trial of TRT is justified. Treatment and monitoring of this duration will determine whether the patient is responsive.

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1. Introduction

It is well-established that total testosterone (TT) in men decreases with age and that bioavailable testosterone (bio-T) falls to an even greater extent [1–3]. Is this decline in testosterone (T) clinically pertinent? Does it produce changes in physiology, in mood, in cognition, in metabolism, that are clinically relevant and, if so, would treatment with testosterone improve or eliminate the pathophysiological state? Are there risks to such treatment and, if so, do the benefits of testosterone replacement therapy (TRT) outweigh the potential risks? Is there evidence for the benefit of TRT, and is there evidence for risk? These questions, and others like them, have occupied the attention of family physicians, specialists concerned with men's health, and researchers from several disciplines who are uncovering an increasing number of associations between T deficiency and pathophysiological states. Associations raise the possibility of a cause-and-effect relationship providing a rationale for TRT. There are, however, skeptics and even antagonists to the concept of testosterone treatment, expressing dissatisfaction with the available evidence [4]. On the other hand, there are many short-term testosterone treatment studies each involving relatively small numbers of subjects. Taken together these studies suggest that the benefits of TRT far outweigh the risks. But what is frustrating both promoters of TRT and their critics, is the absence of a long-term, placebo-controlled double-blind study of a large number of men to definitively demonstrate that TRT is both safe and efficacious.

There is no controversy about TRT for "classical hypogonadism", the very low levels of testosterone seen in hypopituitarism (idiopathic, tumour induced, or post-hypophysectomy for tumour-related disease), or the hypogonadism of primary gonadal failure which may be associated with radiation therapy or chemotherapy for cancer, or with orchidectomy, testicular trauma, Klinefelter's syndrome, etc. The controversy is largely focused on the aging male who has symptoms suggestive of androgen insufficiency but whose TT or bio-T is mildly subnormal or low normal. This large population of symptomatic men may be candidates for at least a trial of TRT. Should they get it?

2. The physiology of testosterone

Testosterone is popularly thought of as a "sex hormone" whose primary role is to turn boys into men and thereafter maintain their libido and ability to have erections for sexual activity. This is an important aspect of testosterone physiology and action, and men (and their sexual partners) are usually happy for it, but sustaining sexual function, as gratifying as that may be, is well down the list of the physiological relevance of testosterone whose activity spectrum and importance extend far beyond sexuality.

2.1. Muscles

Testosterone retains nitrogen, an action essential for the development and maintenance of muscle mass [5]. Testosterone therapy in hypogonadal men restores lean body mass while simultaneously reducing fat mass [6]. TRT in hypogonadal men improves physical strength as well as performance [7].

2.2. Bones

Testosterone has a significant effect in bone health by inhibiting osteoblastic action and resorption after conversion to estradiol through the enzyme, aromatase, and by stimulating osteoblastic activity and bone growth after conversion to dihydrotestosterone via the enzyme, 5- α -reductase [8,9]. Low levels of testosterone can lead to osteopenia and osteoporosis.

2.3. Hematopoiesis

Testosterone is a stimulant of erythropoiesis; anemia is a frequent finding in men with hypogonadism and in men on anti-androgenic therapy [10]. Androgen receptors are found in cultured erythroblasts [11]. Testosterone has a dose-dependent stimulatory effect on erythropoiesis which is more pronounced in older men, an effect which may be independent of erythropoietin and transferrin receptor levels [12].

2.4. Mood

Not only does the brain have androgen receptors as sites for androgen activity, but also the administration of testosterone to hypogonadal men enhances brain perfusion [13]. One of the effects of this action is to improve mood in hypogonadal men who are on TRT [14]. Pope et al. [15], studying men with depression refractory to standard antidepressants, found that TRT lowered the Hamilton Depression scale, a standard scoring system for the assessment of depression (the higher the score, the greater the depression). It has been well-documented that depression tends to increase as testosterone levels become reduced [16].

2.5. Cognition

As noted above, testosterone enhances cerebral perfusion in hypogonadal men, particularly in areas that influence strategic planning, higher motor action, cognitive behaviours, emotional behaviours and memory [13,17]. There are conflicting data about the role of testosterone in cognitive functioning. Moffat et al. [18] found that older men with higher levels of free testosterone index scored better in tests of visual memory, verbal memory, visuospatial functions and visuomotor scanning than men with low testosterone levels. On the other hand, Fonda et al. [19] assessing data from the Massachusetts Male Aging Study could find no correlation between blood levels of hormones and cognition.

3. Metabolic and cardiovascular associations

Over the last several years, the association of testosterone with metabolic and cardiovascular function has become a prominent focus of research and clinical attention. For too long, testosterone has been stigmatized by its undeserved association with the over-used and abused anabolic steroids of the 17-alkylated variety (e.g. methyltestosterone and others). These substances have been associated with insulin resistance and increases in LDL-cholesterol [20,21], adverse cardiac effects [22] and adverse liver effects [23], none of which can be attributed to the mother compound, testosterone [24,25].

It has been known for several years that decreased testosterone levels are associated with increased glucose and insulin concentrations [26], but it has only been in recent years that this association has been studied more seriously, taking into consideration the clinical implications of these findings and the possible benefits of treatment with testosterone.

Men who are obese and who, therefore, are at risk for diabetes, metabolic syndrome and cardiovascular disease, are in a relative state of hypogonadism. The reasons for this are multifactorial [27], but one key factor is increased conversion of testosterone to estradiol catalyzed by the high concentration of the converting enzyme, aromatase, found in adipose tissue [28]. Estradiol, in turn, reduces luteinizing hormone, thus inducing an acquired state of hypogonadotropic hypogonadism [29].

Multiple factors appear to come into play when trying to sort out the relationship between the components of the metabolic syndrome and testosterone availability. Rising body mass index (BMI), for example, is associated with decreasing levels of serum testosterone [30]. One of the actions of testosterone is to inhibit lipoprotein lipase activity which decreases triglyceride uptake by adipocytes thus also decreasing visceral adiposity [31]. Low testosterone, as expected, is conversely associated with increased visceral adiposity and a higher BMI. Dhindsa et al. found that based on either free testosterone or calculated free testosterone levels, 34 of 103 male patients (33%) with type-2 diabetes were hypogonadal [32]. The association between type-2 diabetes and reduced testosterone has now been demonstrated many times; for example, Grossman et al. undertook a cross-sectional survey of 580 men with type-2 diabetes and 69 men with type-1 diabetes [33]. Based on total testosterone alone, 43% of men with type-2 diabetes were hypogonadal, whereas 57% were hypogonadal on the basis of a reduction in free testosterone. Of the men with type-1 diabetes 7.0% had a reduction in total testosterone while 20.3% were hypogonadal when calculated free testosterone was assessed.

The metabolic syndrome (MS) is a cluster of events which together or in part are predictors of cardiovascular events. The main elements (to one degree or another depending on which standard for MS is used) are: hyperinsulinemia or hyperglycemia, increased abdominal girth, increased levels of triglycerides, decreased HDL levels and increased blood pressure. Two widely recognized systems for the criteria necessary to diagnose MS are those from the National Cholesterol Education Program – Adult Treatment Panel III (NCEP ATP III) and the International Diabetes Federation (IDF) [34]. Testosterone levels decrease as the number of criteria for the MS increase [35].

The association of worsening elements of cardiovascular disease with decreasing levels of testosterone is striking and is consistent with the reverse association between testosterone and components of the MS. Contrary to the outmoded view of testosterone's effect on the heart which suggests testosterone is antagonistic to coronary vasculature, intracoronary artery infusion of testosterone actually results in coronary artery dilatation [36]. It had previously been demonstrated that men with coronary artery disease had decreasing levels of testosterone as the degree of coronary artery narrowing increased [37]. On-going studies of testosterone and cardiovascular factors continue to demonstrate the relationship between low testosterone and a number of different cardiovascular phenomena. Lower testosterone, for example, predicts incident stroke and transient ischemic attack (TIA) in older men. Yeap et al. [38] set out to determine whether reduced testosterone levels are independently associated with an increased incidence of stroke and TIA. They prospectively studied 3433 stroke-free men 70 years of age or older with a median follow-up of 3.5 years. During the study period, 119 men had a stroke or TIA. Both total and calculated testosterone levels were significantly reduced in the stroke/TIA group. Several years earlier, Liu et al.

[39] had already demonstrated that men with cardiovascular disease had lower levels of testosterone. The relationship between low testosterone and cardiovascular disease as well as with features of the metabolic syndrome were recently reviewed by Traish et al. [40] They summarized the evidence which indicated that low testosterone:

- (1) predisposes men to an increased risk of cardiovascular disease and mortality,
- (2) can exacerbate cardiovascular risk factors,
- (3) is associated with increased intima media thickness,
- (4) might decrease circulating endothelial progenitor cells and
- (5) decreases flow-mediated vasodilation.

It is one thing to demonstrate an association between adverse metabolic factors or adverse cardiovascular events and low testosterone; but it is quite another to invoke a cause-and-effect relationship. Does low testosterone result in these adverse situations or does hypogonadism occur as a consequence of the onset of cardiovascular disease and the various metabolic abnormalities mentioned above?

There are two ways to explore these questions. The first is to assess the metabolic sequelae of acute loss of testosterone as seen in androgen deprivation therapy (ADT) used in advanced prostate cancer, and the other is to determine what effect testosterone therapy induces on adverse metabolic factors or the sequelae of cardiovascular events. These approaches supply tantalizing, but not necessarily confirmatory, answers.

4. Androgen deprivation therapy

Androgen deprivation therapy (usually in the form of gonadotropin-releasing hormone agonists) is widely used in patients with prostate cancer especially those with advanced and metastatic cancer. ADT improves cancer related symptomatology and quality of life [41]. Clearly established consequences of ADT include sexual dysfunction (both decreased libido and erectile dysfunction), decreased lean body mass, decreased quality of life, and osteoporosis [42]. In addition to these expected and well-known consequences, ADT also brings with it significant detrimental changes in metabolic status. A 48-week study of 40 men treated with ADT for prostate cancer demonstrated an average body mass increase of 2.4%, fat mass increase of 9.4% and lean body mass decrease of 2.7%, all factors increasing the risk for cardiovascular disease [43]. A number of studies have shown that with short-term ADT, insulin levels rise but glucose levels do not; however, with ADT of 12 months or more, not only is there an increase in insulin levels and insulin resistance, but there is also an increased prevalence of fasting hyperglycemia [44]. As expected from these findings ADT with GnRH agonists results in an increased risk for diabetes, coronary artery disease, myocardial infarction, and sudden death [45]. The incidence of metabolic syndrome increases with ADT as do associated components such as abdominal obesity, fasting hyperglycemia and hypertriglyceridemia [46]. Men with prostate cancer being treated by ADT may have as much chance of dying from cardiovascular disease as they do from their cancer [47]. Although not all studies will agree with this high incidence of cardiovascular death as a consequence of ADT it appears that men on ADT for 1 year or more probably have at least a 20% increase in the chance of dying of cardiovascular disease over men with prostate cancer who are not on ADT [48]. Much of this literature has recently been reviewed by Shahani et al. [49].

5. Testosterone replacement therapy

It has long been known that testosterone replacement therapy (TRT) restores partially or completely many of the adverse pathophysiological events which occur in androgen deficiency, including a return of libido and erectile function, an increase in muscle mass, an increase in bone mineral density, an improvement in mood, cognition and general sense of well-being. Brodsky et al. [50], for example, found that TRT in severely hypogonadal men increased body weight by increasing fat free mass due to increased muscle protein synthesis while at the same time fat mass decreased. Normal bone mineral density in men is reliant on an adequate availability of testosterone; hypogonadal men are at risk for the development of osteoporosis [51]. Treatment of hypogonadal men with osteoporosis characteristically improves bone mineral density [52]. Dean et al. [53] administered TRT to 371 hypogonadal men (257 receiving therapy for 9 or more months) and found significant improvements in sexual function (both libido and erectile ability), body composition (increased lean body mass, decreased fat mass), bone mineral density, and mood (with a decrease in negative mood parameters). Testosterone plays a significant role in many of the factors that ultimately lead to erection, a role which has only become apparent with more recent anatomical and biochemical studies [54]. A wide spectrum of the effects of TRT have been reviewed by Bain [55].

The above-described effects of TRT on the major pathophysiological sequelae of testosterone insufficiency have been well-described multiple times. There is little controversy about the positive impact that testosterone has on sexual function, body composition, muscle strength, bone strength, hematopoiesis and mood in hypogonadal men. Where new knowledge and new studies are emerging is in the area of the effect of TRT on the adverse consequences of the metabolic and cardiovascular sequelae of hypogonadism. It is one thing to describe an association between low testosterone with negative metabolic and cardiovascular phenomena; it is another to suggest that TRT may reverse some of those phenomena. That is, however, what the new literature appears to be demonstrating.

In a placebo-controlled double-blind study to assess the effect of TRT on hypogonadal men with type-2 diabetes, Kapoor et al. [56] found that TRT resulted in reductions of glycosylated hemoglobin, insulin resistance, fasting blood sugar, waist circumference, waist/hip ratio and total cholesterol. Saad et al. [57] studied the effect of both testosterone gel and injectable testosterone undecanoate (TU) in hypogonadal men who complained of sexual dysfunction as well as symptoms of the metabolic syndrome. There were 28 men in one group and 27 in the other. Treatment duration was 9 months. Testosterone levels increased in both groups but to a greater degree in the TU group. Although men in both groups demonstrated positive responses, the degree of response was greater in the TU group. Responses included: improved erectile function, decreases in total cholesterol, LDL-cholesterol and triglycerides, a rise in HDL cholesterol, a decrease in waist circumference, a decrease in blood pressure (TU group only).

Heufelder et al. [58] studied 32 hypogonadal men with newly diagnosed type-2 diabetes and metabolic syndrome who were observed for 52 weeks. All men were treated with diet and exercise but 16 of them were treated additionally with transdermal testosterone. In both groups there was improvement in serum testosterone, insulin sensitivity, glycosylated hemoglobin, fasting glucose, HDL cholesterol, triglyceride and waist circumference, but the testosterone treatment group improved to a much greater degree. Criteria for the metabolic syndrome disappeared in 81.3% of the testosterone treated group, whereas only 31.3% of the non-testosterone no longer manifested these criteria.

Forty-six men with chronic stable angina, 22 on a testosterone patch and 24 on placebo underwent a treadmill stress test and time to 1 mm ST segment depression was noted [59]. After 12 weeks of treatment the testosterone group increased this time from 309 to 361 s ($p < 0.01$) compared to the placebo treated group whose time did not change significantly (266–292 s). Testosterone, therefore, appears to enhance coronary artery function.

6. Safety of testosterone replacement therapy

6.1. Prostate

Assuming that the physician is satisfied with the prevailing body of evidence that TRT has positive effects on body composition, metabolic factors, energy, sexual function, cognition, mood, muscle mass, bone strength, and cardiovascular function, the question which most concerns and perturbs him/her is whether or not testosterone replacement therapy (TRT) is safe. The question about safety revolves almost exclusively around effects of TRT on the prostate gland and, in particular, on the possible role that TRT may have to play in either the development of prostate cancer or its further growth. Here is where science, passion, mythology and prejudice come into play and it likely emanates from one lone 1941 publication by Huggins and Hodger in which one patient with cancer demonstrated a regression in the cancer with either estrogen therapy or castration and a growth in cancer with TRT [60]. Despite the subsequent appearance of many papers demonstrating no increase in prostate cancer with TRT and no protection against prostate cancer in men with low T, the 1941 paper still reverberates in the minds of many physicians [61].

The great difficulty in putting the testosterone–prostate cancer apprehension to rest is the fact that in order to do this would require a large scale (5000–10,000 hypogonadal men) placebo-controlled double-blind study (5–10 years) to unequivocally demonstrate that there is no increase in the onset or exacerbation of prostate cancer. Such a study has not yet been done and if started now results would not be available for several years from now. We do, however, have two major pieces of information; the first, is that there is no evidence to support the idea that testosterone causes the development of a *de novo* cancer; the second is that we have little or no evidence that there is enhancement of an existing cancer by TRT.

Although the large placebo-controlled long-term study has not yet been undertaken, we do have an accumulated experience from the published (and anecdotal) reports of TRT in many thousands of men, both in open and placebo-controlled studies. The prostate cancer rate emerging from these studies is approximately 1% [62] which is similar to the cancer detection rate in prostate cancer screening trials. If increasing testosterone availability is to be accused of increasing the incidence of prostate cancer, one would expect low testosterone to confer protection against the development of prostate cancer. This has not been observed [63]. There is even some evidence to suggest that men with reduced testosterone levels are at greater risk of developing aggressive prostate cancer [64,65]. Does blood level of testosterone correlate with the risk of prostate cancer? Slater and Oliver [66] accumulated the results of 25 studies of men with prostate cancer which suggest there is likely no relationship between serum testosterone and the presence of prostate cancer. In 4 studies, serum testosterone was higher than controls without prostate cancer, in 15 studies testosterone levels were equal, and in 6 studies men with prostate cancer had testosterone levels lower than controls. These authors did, however, note that men in the upper quartile of testosterone level were at greater risk for prostate cancer than these in the lowest quar-

tile. The epidemiological evidence suggested that this was not a direct effect of testosterone, but rather indirect, in that men in the upper quartile were more likely to start sex activity at an earlier age and were more likely to have experienced non-specific sexually transmitted diseases more frequently than men in the lower quartile. They also confirmed the observation that prostate cancers are more malignant in men with low serum testosterone. Serum levels of testosterone, or the more active androgen, dihydrotestosterone (DHT), may have no significant relationship to intraprostatic events since increases in serum levels of testosterone or DHT are not reflected in increases in either intraprostatic hormone levels, gene expression or cellular proliferation [67].

6.2. Polycythemia

Testosterone stimulates erythropoiesis, a fact which should alert physicians to thinking about testosterone insufficiency as a possible cause of anemia in male patients, especially in otherwise unexplained anemia [68,69]. Conversely, TRT can result in increases in hemoglobin and hematocrit which may rise about the upper limits of normal and put the patient at risk for an arterial occlusive event. When the hematocrit exceeds 0.50L/L the dose of testosterone should be decreased. If the hematocrit continues to be overstimulated regardless of dose readjustments or if reducing the dose of testosterone re-introduces symptoms of hypogonadism, then it is reasonable to return the patient to physiological (effective) doses of testosterone and institute intermittent phlebotomies to keep the hematocrit below 0.50. Polycythemia can be induced by any form of testosterone administration but is most commonly found with testosterone injections.

6.3. Sleep apnea

One of the concerns about TRT has been its possible association with sleep apnea. The literature has produced inconsistent results. Liu et al. [70] studied 17 community-dwelling healthy men over the age of 60. In a cross-over design they were treated with varying doses of testosterone and placebo. TRT reduced total time slept, increased duration of hypoxemia by approximately 5 min per night and disrupted breathing during sleep. The authors concluded that in their short-term study, TRT shortened sleep and worsened sleep apnea but did not alter physical, mental or metabolic function, nor did it increase daytime sleepiness. On the other hand, Hanafy [71] after an extensive literature search, indicated that there is a lack of consistent findings connecting TRT to obstructive sleep apnea (OSA). In the majority of reports there was little effect of TRT on OSA. In a meta-analysis of 19 randomized controlled trials, Calof et al. [72] found that there was no significant difference in the frequency of cardiovascular events, sleep apnea or death rate between the treated and untreated groups.

7. Summary/conclusions

Testosterone has many physiological actions in: muscles, bones, hematopoietic system, brain, reproductive and sexual organs, adipose tissue. Within these areas it stimulates: muscle growth and maintenance, bone development while inhibiting bone resorption, the production of red blood cells to increase hemoglobin, libido, enhanced mood and cognition, erectile function, lipolysis. Anabolic deficits in aging men can induce: frailty, sarcopenia, poor muscle quality, muscle weakness, hypertrophy of adipose tissue, impaired neurotransmission [73]. The aging male with reduced testosterone availability may present with a wide variety of symptoms which in addition to frailty and weakness include: fatigue, decreased energy, decreased motivation, cognitive impairment, decreased

self-confidence, depression, irritability, osteoporotic pain and the lethargy of anemia.

Added to all of this, we have seen from the foregoing discussion that testosterone deficiency is also associated with type-2 diabetes, the metabolic syndrome, coronary artery disease, stroke and transient ischemic attacks, and cardiovascular disease in general. In addition, there are early studies to suggest that TRT in men with low testosterone levels may improve metabolic status by: lowering blood sugar and HbA1C in men with type-2 diabetes, reducing abdominal girth, ameliorating features of the metabolic syndrome, all of which may be protective of the cardiovascular system.

Discussions dealing with the definition of hypogonadism and what constitutes low or reduced testosterone levels or reduced testosterone availability are continuing. What symptoms are key to the definition? Is one symptom enough? Is any measure of low or "lowish" testosterone adequate enough in a symptomatic patient to consider initiating TRT? Several guidelines have been developed to try to answer these questions but there is not universal agreement on what the best therapeutic strategy is [74].

The stereotypic patient is a man who has one or more symptoms suggestive of hypogonadism. History, physical examination and laboratory investigation do not point to an obvious non-testosterone related etiology for his symptoms, but one or more of the measures of testosterone availability (total testosterone, calculated free testosterone, true or calculated bioavailable testosterone, testosterone by mass spectrometry) suggest a low or lowish level. His PSA is within the normal range (the concept of "normal range" requires more discussion than this paper will allow) and his digital rectal examination does not lead one to suspect the presence of possible prostate cancer. His hemoglobin may be lower than anticipated. He may have type-2 diabetes or features of the metabolic syndrome, but usually he only has one or more symptoms of hypogonadism and a lowish testosterone level. Should he receive a brief (4–6 months) trial of TRT?

Given all the accumulated information, from the thousands of documented patients with no evidence of prostate cancer, the more appropriate question is, why not treat? Four to six months of treatment and monitoring will determine whether the patient is responsive. Why would treatment not be initiated given all the pathophysiological events associated with hypogonadism and the possible benefits of TRT both in terms of metabolic stabilization and improvement in symptoms which may well result?

The evidence suggests that this strategy is efficacious and safe. Perhaps the long-awaited 10 year placebo-controlled double-blind study will tell us otherwise, but until that time the bulk of the evidence informs us that we should feel confident and comfortable in initiating a trial of TRT in appropriately selected men.

Conflict of interest

The author has given lectures sponsored by the former Organon Canada and Solvay Pharma and has served on advisory boards of these companies. He has also given lectures sponsored by Schering-Plough and Paladin Labs Inc.

Provenance and peer review

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