Body Shop

ADAM:

Dealing with the Decline

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We now know there is a decline in total and free testosterone with advancing age, which is aggravated by an increase in sex hormone binding globulin. Testosterone deficiency increases in 20% of men by age 60 and 40% by age 80. Multiple factors are responsible (Table 1), but the principle etiologic reason is likely an increase in hypothalamic sensitivity to testosterone feedback, so that the decreasing testosterone levels do not trigger gonadotropin-releasing hormone and, hence, luteinizing hormone (LH) does not increase. Combined with this is an age-related decrease in LH pulse amplitude and frequency.

Terms like "male climacteric," "male menopause" and "andropause" connote an abrupt cessation of function, which is not the case. Thus, a better defining term is "androgen decline in the aging male" (ADAM). Partial ADAM (PADAM), has been used to refer to a decline within, but not below, the normal young male testosterone range.

Terry's Testosterone

Terry, 58, presents with:

- Poor energy
- Decreased libido
- Body mass index: 30
- Total serum testosterone at 3 p.m.: 7 nmol/l (low)

Questions that should be answered include:

- What symptoms are useful in diagnosing hypogonadism?
- What is the best test?
- Is Terry testosterone-deficient?
- What is the cause?
- What other tests are needed?
- Should he be treated and what would this achieve?

For more on Terry, go to page 86.

Does a decline in testosterone cause disease?

True hypogonadism (reduction in testosterone below the young male normal range) definitely results in multiple problems, including reduced sexual function, reduced muscle mass and strength, increased fat mass, decreased bone density, fatigue, negative mood and reduced hematocrit and hemoglobin (Figure 1). All these features can be reversed with testosterone replacement in both younger and older (> 65 years) hypogonadal men and treatment

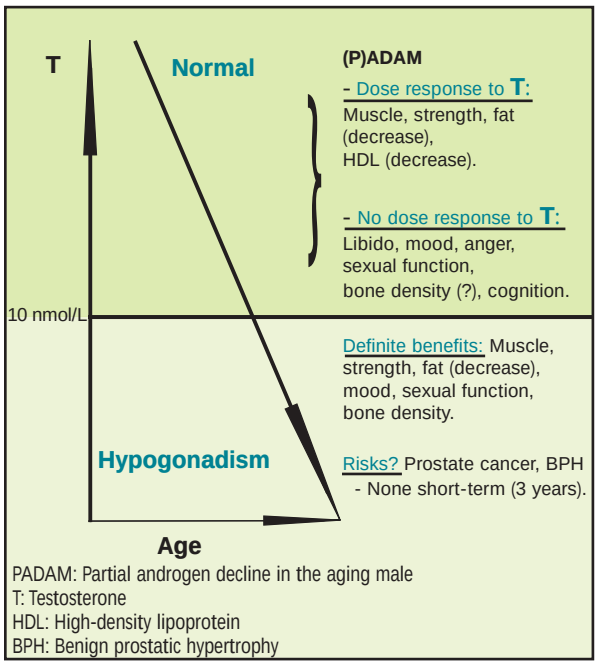

Figure 1. Effects of testosterone in normal and hypogonadal men.

Table 1

Changes in hypothalamic-gonadal function with age

Hypothalamus
- Increased sensitivity to testosterone feedback
- Decreased GnRH pulse size and frequency

Pituitary
- No change with age

Testes
- Decreased Leydig cell (testosterone-producing) number and/or function
- Decreased testicular profusion

End organ tissues
- Decreased receptor responsiveness to testosterone
- Increased hepatic production of SHBG

GnRH: Gonadotropin-releasing hormone
SHBG: Sex hormone binding globulin

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is clearly indicated.

Two issues are important:

1. Does a decline within the normal range produce disease?
2. Does treatment in older males have efficacy and long-term safety?

To answer the second question, current therapy of true hypogonadism has definite short-term benefits and is considered standard medical practice. However, there is no data on long-term safety in the older population. We do not know if there is a "cut off" for minimal levels of testosterone that should be aimed for to produce a biologic effect, or if there is just an increasing effect size with increasing attendant risks.

Recent information indicates that muscle strength and size progressively increase and fat tissue and high-density lipoprotein (HDL) levels progressively decrease as testosterone level increases in a dose-response relationship. However, there appears to be a threshold effect of testosterone on libido, mood, sexual function, cognition and bone density, such that there is no increase in these responses once low-normal testosterone levels are achieved (Figure 1). The quality of evidence for the benefits of testosterone therapy is variable (Table 2).

How does ADAM affect sexual function?

Hypogonadal men clearly improve all aspects of sexual function. Cross-sectional studies show a correlation between declining sexual interest and performance with declining androgen levels. Nocturnal erections correlate with testosterone, but testosterone correlates poorly with erectile dysfunction (ED), as this is usually a multifactoral problem most commonly related to drugs or neural or vascular causes. Less than 10% of men presenting with ED have hypogonadism as a cause.

Testosterone has recently been shown to have vasodilatory effects, similar to estrogen, and combinations of sildenafil plus testosterone are more effective than sildenafil alone, suggesting a direct effect of testosterone on erectile function. The minimum amount of testosterone necessary for normal sexual function is variable, but is approximately at the lower end of the normal range.

One small study shows adjusting the testosterone level to either low-normal or to high-normal levels does not change sexual function, indicating that there is a plateau in response once the normal range is reached. These data indicate that increasing testosterone in men who are not overtly hypogonadal will not progressively improve sexual function.

What about depression and mood?

Hypogonadal men show improved mood with testosterone replacement, but once testosterone levels in the low-normal range are achieved, mood does not show further improvement, suggesting a threshold rather than a dose-response effect. Although testosterone has been implicated in angry behaviour ("roid rage"), placebo-controlled, randomized, controlled trials (RCTs) of even pharmacologic doses of testosterone (600 mg/week for three months) have not resulted in increases in anger.

Testosterone replacement in hypogonadal men also does not result in an increase in anger. The prevalence of major depressive disorder in hypogonadism is not known and the association of testosterone levels and depression has been inconsistent. One small placebo-controlled RCT did not demonstrate any effect of testosterone therapy on depression in hypogonadal depressed men.

Does it affect cognition?

The largest cross-sectional study of endogenous sex hormones and cognitive function found only weak associations of high estradiol and low testosterone with a variety of cognitive measures. No RCTs of the effects of testosterone replacement on cognition have been done.

How is testosterone associated with cardiovascular disease and lipids?

This subject has been exhaustively reviewed recently and is best summarized by Wu *et al.*: "A significant and independent association between endogenous testosterone (T) levels and coronary events in men and women has not been confirmed in large prospective studies, although cross-sectional data have suggested coronary heart disease can be associated with low T in men. Exogenous androgens induce both apparently beneficial and deleterious effects on cardiovascular risk factors by decreasing serum levels of HDL-cholesterol (C), plasminogen activator Type I (apparently deleterious), lipoprotein (a), fibrinogen, insulin, leptin and visceral fat mass (apparently beneficial) in men as well as women. However, androgen-induced declines in circulating HDL-C should not automatically be assumed to be proatherogenic, because these declines may instead reflect accelerated reverse cholesterol transport."

There is no evidence of a significant decrease in HDL-C levels with testosterone replacement *within* the normal range.

Does Terry Really Have Hypogonadism?

Terry's poor energy is of little diagnostic use, but his decreased libido suggests hypogonadism. Better tests would be a morning total testosterone (Terry's was borderline low at 10 nmol/L) or, because of his obesity, a bioavailable testosterone, which corrects for the decrease in sex hormone binding globulin occurring in obesity.

Terry's bioavailable testosterone was low at 2.9 nmol (normal 3.5 nmol to 12 nmol). He had a normal luteinizing hormone (2.3 IU/L) and prolactin (12 g/L), indicating he had hypothalamic hypogonadism, without a pituitary tumour. In a younger man (arbitrarily, < 50) pituitary magnetic resonance imaging could be considered, as an age-related decline in testosterone as a cause becomes progressively less likely. Terry should now be treated with testosterone replacement, and his prostate-specific antigen, digital rectal examination and hematocrit followed.

Table 2

Algorithm for the investigation of hypogonadism

Step 1: Screening

Clinical recognition

- Sexual dysfunction (specific and sensitive)
- Nonspecific symptoms (fatigue, lack of energy)—poor specificity

Biochemical testing

- First choice: Morning serum bioavailable testosterone
- Second choice: Morning total serum testosterone

Step 2: Differential diagnosis

Biochemical testing: Serum luteinizing hormone (LH)

- High LH: Indicates gonadal failure (determine cause); proceed to testosterone replacement therapy
- Normal/low LH: Indicates hypothalamic-pituitary disease; obtain serum prolactin
  - Elevated: Suggests pituitary disease; referral and pituitary magnetic resonance imaging indicated
  - Normal: Assess for symptoms of hypothalamic-pituitary disease; if negative, it is likely hypothalamic hypogonadism from aging and testosterone replacement can be considered

Table 3

Adequacy of RCT evidence for benefits of testosterone replacement in older men

Testosterone effect	RCT evidence
Sexual function	Effective in hypogonadal men; no effect within normal testosterone range (non-RCT)
Depression and mood	No effect on anger even in supraphysiologic doses; improvement in mood if hypogonadal; no RCT within normal testosterone range
Cognition	No RCT data
Cardiovascular disease	No adequate RCT of cardiovascular endpoints
Lipids	Dose-response relationship of HDL-C to testosterone dose; no significant change within physiologic replacement doses
Osteoporosis	Increase in bone mineral density if hypogonadal; no change in bone mineral density within normal testosterone range
Body composition and strength	Dose-response relationship of muscle size and strength from hypogonadal levels to supraphysiologic levels of testosterone; dose-dependent reduction in fat mass
Sleep apnea	No RCT data
Prostate cancer	Short-term studies (three to five years) do not show significant effect on PSA, urine flow or prostate size; no long-term RCTs

RCT: Randomized, controlled trial
HDL-C: High-density lipoprotein-cholesterol
PSA: Prostate-specific antigen

Table 4

Testosterone preparations

Generic name	Route	Dose
Testosterone undecanoate	Oral	160-200 mg/day
Testosterone cypionate IM	150-200 mg IM every two weeks	
Testosterone enanthat IM	150-200 mg IM every two weeks	
Testosterone topical	Patch	5 mg daily
Testosterone	Gel	5 g daily

What about osteoporosis?

Although hypogonadism is the most common secondary cause of osteoporosis in men, testosterone levels do not, in fact, correlate well with decreased bone mass. Rather, current concepts favour estradiol as the major mediator of the sex steroid effect on bone, and bioavailable estradiol correlates best with bone loss.

Since frailty and falls are a significant risk factor for fractures in the elderly, it has been postulated that increased physical activity or muscle strength will reduce fractures. While case-control and prospective studies support this hypothesis, there are no prospective RCTs. Administering testosterone may exert positive effects on bone through conversion to estrogen and, to a lesser extent, by direct effects on bone and will increase muscle strength in PADAM patients, but reduction in fracture events have yet to be demonstrated in RCTs (Table 3).

One RCT of short-term administration of testosterone to men with low-normal testosterone levels demonstrated improved strength and mobility, but not in physical functioning or cognitive function. As noted, hypogonadal men show impressive increases in bone density.

Two studies explore testosterone effects in eugonadal men. In a small, non-randomized trial, Andersen *et al.* (1996) showed a 5% increase in spine bone mineral density by increasing testosterone from mid-normal to the top end of the normal range. In contrast, Snyder *et al.* found no effect of testosterone if the starting testosterone level was within the lowest end of the normal range (10.4 nmol/L), although there was a linear relationship between testosterone level and bone density in overtly hypogonadal men. Larger prospective RCTs would be needed to determine if there is a dose-response relationship of bone density within the normal range and if this translated into reduced fractures.

How does low-dose testosterone affect body composition?

Several placebo-controlled studies now demonstrate a dose-response effect of testosterone in increasing muscle mass and strength and decreasing fat mass. As well, there are no adverse effects on insulin sensitivity, plasma lipids, apolipoproteins or C-reactive protein. This effect extends into the supraphysiologic range and occurs in both young men and men older than 65 years. These studies conclusively demonstrate that testosterone can have positive dose-related effects on body composition and strength within the normal testosterone range. It is unknown whether these effects result in any long-term risks or benefits as all these studies are less than three years in duration.

Does it cause sleep apnea?

Sleep apnea is twice as common in men, implying testosterone may be involved in the etiology. One small series of five hypogonadal patients and isolated case reports suggests testosterone therapy may worsen sleep apnea. Conversely, however, hypoxia, obesity and aging seem to contribute to a suppression of the hypothalamic-gonadal axis in these patients. Blockade of testosterone with flutamide, however, does not improve sleep apnea. There are no RCTs of testosterone therapy and sleep apnea.

What about prostate cancer?

There is no evidence from prospective studies to indicate that endogenous testosterone causes prostate cancer and, indeed, low testosterone seems more related to advanced cancer. Short-term studies of testosterone administration (three to five years) show only minor changes in prostate-specific antigen and no significant effect on urine flow rate or prostate size. Appropriately-powered, long-term RCTs have not been done.

Conclusions…

Whether treating hypogonadism or PADAM, we lack data on the long-term risks and benefits of testosterone replacement. It is clear that large, randomized trials are required to determine if there are positive benefits to the skeleton, cardiovascular system and cognition and what the risks of such therapy may be. Until such studies are done, testosterone replacement is indicated only for true hypogonadism and patients require careful followup.

Diagnosis: Which tests to use?

Total serum testosterone consists of 2% free (non-protein bound), 54% loosely bound to albumin and 44% tightly bound to sex hormone binding globulin (SHBG). Both the free and albumin-bound portions are available to tissues for biological action and hence this combination has been termed "bioavailable testosterone." The gold standard for measurement of testosterone is free testosterone by equilibrium dialysis, but this is not a practical method.

Current studies indicate that bioavailable testosterone or free testosterone done by a calculation using total serum testosterone and SHBG measurements (calculated free testosterone) correlate best with free testosterone by dialysis. Either of these tests is the preferred initial test in screening a patient. Unfortunately, bioavailable testosterone is available only in British Columbia, Ontario, Quebec and New Brunswick with limited or no availability in other provinces, and few labs offer a calculated free testosterone. The second best test is a total testosterone, done in the morning to minimize effects of diurnal variation. So-called "free testosterone" levels by radioimmunoassay are less reliable. A screening symptom questionnaire has been developed by Morley *et al.* (2000), which has 88% sensitivity, but only 60% specificity, and so its usefulness in clinical practice is uncertain. Symptoms of sexual dysfunction (decreased libido or erectile function), however, have high specificity and sensitivity (> 90%).

Once a low testosterone is demonstrated, it is necessary to obtain a serum-luteinizing hormone (LH) to distinguish gonadal failure from pituitary disease and establish the etiology. The largest study of 406 hypogonadal patients (in whom organic lesions were excluded) found that 9% of patients had primary testicular failure and 91% had hypothalamic-pituitary dysfunction (*i.e.*, idiopathic, age-related decline in function) with a low testosterone and normal or low LH. In this latter group, pituitary disease, such as tumours, needs to be considered in the differential diagnosis. If the prolactin level is normal, and there are no clinical findings to suggest pituitary dysfunction, pituitary disease is unlikely.

Therapy and followup…

Table 4 lists recommended testosterone preparations available in Canada. Methylated oral formulations should not be used because of potential liver toxicity. The least physiologic replacement is that of intramuscular injections and should now be considered a secondary choice to other formulations. Recommended followup includes pre-treatment high-density lipoprotein (HDL) and HDL/total cholesterol ratio, liver function tests, prostate-specific antigen (PSA), rectal examination and hematocrit. Followup biochemistry testing is recommended at three, six and 12 months, with yearly PSA and rectal examination. Although these recommendations include liver function tests and HDL, none of the listed preparations are known to cause hepatic dysfunction (associated with the use of methylated preparations) or proven to decrease HDL, so the utility of such measurements is questionable.