Andropause

Testosterone replacement therapy for aging men

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abstract

OBJECTIVE To review the rationale for treating symptomatic aging men whose testosterone levels are mildly reduced or low-normal with testosterone replacement therapy.

QUALITY OF EVIDENCE Large-scale multicentre prospective studies on the value of treating andropausal men with hormone therapy do not exist because the whole area of hormone therapy is barely 10 years old. Evidence presented is based on physiologic studies, particularly studies in which treatment has been assessed. These were largely uncontrolled open studies. Studies to date report positive responses to testosterone treatment with very few serious side effects.

MAIN MESSAGE Physicians should consider hypoandrogenism if male patients complain of loss of libido, erectile dysfunction, weakness, fatigue, lethargy, loss of motivation, or mood swings. Less obvious associations with reduced levels of testosterone are anemia and osteoporosis. The main cause of reduced testosterone production is primary gonadal insufficiency, but secondary causes, such as hypothalamic-pituitary disease, should be considered. Evidence shows that most men treated with testosterone will feel better about themselves and their lives.

CONCLUSION Andropause is a term of convenience describing a complex of symptoms in aging men who have low testosterone levels. Physicians should be aware of its existence, should consider ordering tests for men who have symptoms, and should treat carefully selected patients whose serum testosterone levels are low.

résumé

OBJECTIF Examiner la raison d'être de l'hormonothérapie de remplacement de la testostérone chez les hommes symptomatiques d'âge mûr dont les taux de testostérone sont légèrement réduits ou sous la normale.

QUALITÉ DES DONNÉES Il n'existe pas d'étude prospective multicentrique de grande envergure sur l'utilité du traitement par hormonothérapie des hommes andropausés parce que tout le domaine de l'hormonothérapie n'existe vraiment que depuis dix ans à peine. Les données probantes présentées se fondent sur des études physiologiques, en particulier là où la thérapie a été évaluée. Il s'agissait principalement d'études ouvertes non contrôlées. Les études jusqu'à présent rapportent des réponses favorables à l'hormonothérapie à la testostérone et très peu d'effets secondaires sérieux.

PRINCIPAL MESSAGE Les médecins devraient envisager l'hypoandrogénisme chez les patients qui se plaignent d'une perte de la libido, d'une dysfonction érectile, de faiblesse, de fatigue, de léthargie, de perte de motivation ou de changements d'humeur. Au nombre des éléments moins évidemment associés avec un taux de testostérone réduit figurent l'anémie et l'ostéoporose. La principale cause de la réduction de la production de la testostérone se situe surtout dans une insuffisance gonadique, mais il faut aussi considérer d'autres causes secondaires, comme une maladie hypotalamo-hypophisaire. Des données probantes font valoir que la plupart des hommes traités à la testostérone se sentent mieux à propos d'eux-mêmes et de leur vie.

CONCLUSION L'andropause est un terme pratique pour décrire un ensemble de symptômes chez les hommes d'âge mûr qui ont de faibles taux de testostérone. Les médecins devraient être au courant de son existence, envisager l'ordonnance d'épreuves chez les hommes qui en présentent les symptômes et traiter attentivement certains patients dont les taux de testostérone sont bas.

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Cet article a fait l'objet d'une évaluation externe.

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The idea of andropause ("male menopause") has received widespread attention in the popular and medical press in the last few years.[1] As men age, total testosterone levels decline gradually[2] and concentrations of free[3] and bioavailable testosterone[4,5] decline sharply with each decade beyond the 30s.

Aging men often begin to experience symptoms such as sexual dysfunction (loss of libido, erectile dysfunction), weakness, fatigue, lethargy, insomnia, mood disorders, flushes, and less motivation.[6] They also tend to lose bone density as they age and might not realize it until they fracture a bone.[7] Are the symptoms and loss of bone related to falling testosterone levels? If so, for carefully selected men, will treatment with testosterone improve bone mineral density and relieve symptoms?

This paper will explore the emerging evidence for a relationship between falling testosterone levels and an increase in symptoms in aging men (an association conveniently called andropause), will urge physicians to look for low-normal or frankly low testosterone levels, and will suggest that many aging men's lives will improve with testosterone treatment.

Quality of evidence

Most articles dealing with testosterone replacement in aging men come from the endocrine and metabolic literature. Geriatric journals were also consulted, but they contained fewer articles on this topic. Biochemical journals provided some physiologic and methodologic background. Selected readings from specialty journals gave information on specific issues (eg, prostate cancer, coronary artery disease).

Peer-reviewed articles with a focus on prospective clinical studies were selected as much as possible. Several articles citing the association of endogenous testosterone levels with various pathophysiologic events were also included. Articles were retrieved through a MEDLINE search using the key words andropause, hypogonadism, testosterone, lipids, osteoporosis, prostate cancer, libido, and sexual dysfunction.

Andropause, assessment of testosterone secretion, and testosterone treatment in aging men are relatively new concepts. Most of the literature on this topic has been published during the last 10 years. As a result, information in this area suffers from the relatively small numbers of men reported in each study and from the short duration of the studies (months to a few years). New evidence continues to emerge.

A new international journal, *The Aging Male*, with a focus on endocrine and metabolic changes, came into existence after formation of the International Society for the Study of the Aging Male in 1997. The First World Congress on the Aging Male was held in 1998 in Geneva, Switzerland; a Second World Congress was held in 2000, also in Geneva.

The accumulated evidence continues to show that declining levels of testosterone could be associated with symptoms and that treatment with testosterone alleviates these symptoms in many men.

What does testosterone do?

Testosterone is a hormone responsible for the secondary sex characteristics that appear at puberty. It has a potent effect on stimulating libido, sexual desire, and arousal.[8] It is also an anabolic hormone that enhances metabolic processes in muscles, bones, bone marrow (erythropoiesis), the immune system, and the brain (cognition and mood).[9] Reduced levels of testosterone, therefore, might be associated with symptoms emanating from these metabolic processes if they function inefficiently.

Since even slightly reduced testosterone levels could be associated with symptoms that can be alleviated by treatment with testosterone, it is inappropriate to accept the idea that older men are not only expected to have hypoandrogenism and hypoandrogenic symptoms but should also learn to live with them. One of our current clinical dilemmas is finding a precise definition of hypoandrogenemia and deciding which assay can best reflect this definition.[10]

Which testosterone to measure? What is low?

Total circulating testosterone is divided into three major fractions[11]: free testosterone (about 2% of the total), testosterone bound to albumin (about 40% to 60%), and testosterone bound to sex hormone–binding globulin (SHBG) (about 40% to 60%). Testosterone binding to albumin is relatively weak, so testosterone can easily dissociate from albumin and be available for biologic activity (passage through the cell membrane and into the nucleus for gene activation). Free testosterone and albumin–bound testosterone together constitute what is called bioavailable testosterone.[4] Testosterone tightly bound to SHBG is thought not to be readily available for biologic activity.

As men age, levels of free and bioavailable testosterone fall as SHBG levels rise, and total production of testosterone falls because both the hypothalamus and

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testes are less active.[12] Total testosterone can be measured accurately with standard radioimmunoassays. Free testosterone assays, however, can be unreliable if done with a kit. True free testosterone can be determined only by separating it from protein-bound testosterone by equilibrium dialysis[13] and measuring total testosterone before and after. This is an expensive, time-consuming procedure that most commercial laboratories are unable to provide. Bioavailable testosterone can be obtained by precipitating out SHBG-bound testosterone and measuring the remainder as total testosterone, but precipitation adds to the cost of the test. Some laboratories provide a free androgen index (total testosterone divided by SHBG), which roughly reflects bioavailable testosterone.

There is no clear consensus on what constitutes low testosterone levels. In one study, 12 nmol/L was arbitrarily chosen as the point below which hypoandrogenism began.[14] Most assays have a normal range of 10 to 35 nmol/L.

Although bioavailable testosterone seems the most logical test to use (offered by some commercial laboratories), it is unclear which measure of testosterone best diagnoses hypogonadism.[10] Until more data are available comparing the three tests, physicians need to use clinical judgment in managing patients who are both hypoandrogenic (as measured by any technique) and symptomatic.

What is the cause of low testosterone?

Testosterone deficiency can be due either to a testicular problem (primary hypogonadism) or to hypothalamic-pituitary disease (secondary hypogonadism). Men with reduced levels of testosterone and increased levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) have primary hypogonadism that could be the result of orchitis, cryptorchidism, trauma, chemotherapy, radiation therapy, vascular insufficiency, or Klinefelter's syndrome. Further investigation (apart from chromosome analysis if Klinefelter's is suspected) is generally not needed for primary hypogonadism.

If LH and FSH are very low (<1 mIU/L), particularly if testosterone is very low, a hypothalamic-pituitary problem, such as a pituitary tumour with or without hyperprolactinemia, should be suspected, and physicians should order magnetic resonance imaging (MRI) of the pituitary gland. In most andropausal men, however, LH and FSH are usually either low-normal or normal[10] as a consequence of reduced gonadotropin-releasing hormone secretion from the hypothalamus, yet another consequence of the aging process.[12]

Despite this, physicians should consider the possibility of hypothalamic–pituitary disease if a patient has symptoms of pituitary enlargement, such as headache or visual field impairment. Serum prolactin levels should be measured, and if they are elevated, physicians should order MRI (or computed tomography scan if MRI is unavailable) of the pituitary gland. Fatigue could be caused by hypothyroidism, and low or low-normal TSH levels with subnormal free thyroxine levels could suggest hypothalamic-pituitary disease. Most cases of hypothyroidism, however, are due to primary thyroid dysfunction (TSH is elevated). Fatigue might also be caused by anemia, which in itself might be due to reduced testosterone production.

Lower hypothalamic-pituitary function could be due to several other less recognized factors. Adipose tissue contains large concentrations of the enzyme, aromatase, which enhances the conversion of androgens to estrogens and causes a reversible form of hypogonadotropic hypogonadism seen in obese men. Weight loss is the main form of treatment, but testosterone therapy can be used on an interim basis for symptoms related to low testosterone. Chronic illness, cancer, chronic renal failure, malnutrition, and anorexia can all result in suppression of gonadotropin-releasing hormone.

Whose testosterone levels should be measured?

Many men 40 years old and older have symptoms. Sometimes patients tell us about them spontaneously; sometimes we have to elicit them by direct questioning. By far the most common symptoms are associated with sexual interest or sexual functioning, but there are others. Heinemann and colleagues[6] devised a 17-item "aging males' symptoms" list that included questions about sense of well-being, sexual concerns, psychological status and mood, strength, energy, and motivation (**Table 1**[6]).

Symptoms can have many causes. Patients who complain of weakness or fatigue could have low testosterone levels, but might also have organic causes such as liver or kidney disease, diabetes mellitus, thyroid dysfunction, cardiac disease, anemia, or malignancy. Sexual symptoms or mood disorders with or without these symptoms could also be related to factors other than reduced testosterone levels, such as depression, anxiety, marital or relationship discord, or stress (eg, money, work, family).

Should all symptomatic men's testosterone levels be measured or only those of men who apparently have no cause for their symptoms? There is no clear answer because hypoandrogenism might be an associated factor if not the prime etiology. Whether medical practice will adopt routine measurement of testosterone in

aging men as it has assessment of thyroid function remains to be seen.

Table 1. Symptoms of aging men: *Symptoms are scored 1—no symptoms, 2—mild, 3—moderate, 4—severe, and 5—very severe.*

Deterioration of well-being
Complaints in joints or muscles
Sweating
Sleep disturbances
Increased need for sleep
Irritability
Nervousness
Anxiety
Exhaustion or decreased energy
Decrease in muscular strength
Depressed mood
Feeling of having passed the zenith in life
Wish to be dead or feeling totally discouraged
Decrease in beard growth
Decrease in potency
Decrease in frequency of morning erections
Decrease in libido or sexual activity

Adapted from Heinemann et al.[6]

Does testosterone therapy actually reduce symptoms?

An increasing number of reports suggest that most patients treated with testosterone have great improvement in symptoms.[10,15,16] Symptom relief falls into two categories: sexual and general sense of well-being.

Low or absent libido might be due to decreased testosterone, but it could also be a consequence of psychogenic factors, substances (eg, antidepressants, alcohol), or chronic illness. When reduced desire is primarily a result of hypogonadism, treatment with testosterone often induces a dramatic increase in sexual arousal.[17] Erections are much less affected by testosterone, but men often claim to have more frequent firm spontaneous erections.

General sense of well-being often improves also when testosterone treatment is initiated. This is due to metabolic changes in various bodily systems.[18] As men age, their proportion of body fat increases (especially intra-abdominal fat) while their lean body mass (mainly muscle) decreases. These changes can impair glucose tolerance or induce hyperlipidemia. As well, muscle strength decreases as muscle mass shrinks. When hypogonadal men are treated with testosterone, their muscle protein synthesis increases.[19]

Many men develop osteoporosis with age. Exact incidence is unknown, but estimates range from 6% to 10% for osteoporosis and 47% for osteopenia.[20,21] Since many cases, both symptomatic and asymptomatic, go unreported, incidence is likely much greater. In 40% to 50% of osteoporotic men, there are three main causes: alcohol abuse, glucocorticoid excess, and hypogonadism.[22] No clear cause is found in the remaining 40% to 50%.[20] This is the group with idiopathic osteoporosis, most of whom have symptoms of fracture or back pain. Are some cases of idiopathic osteoporosis caused by hypoandrogenism? Reducing the incidence of osteopenia and osteoporosis is a worthwhile endeavour, since an Australian study found that a man's lifetime risk of developing an osteoporotic fracture was 29%.[23]

No large studies show that treating men with testosterone reduces the incidence of osteoporosis and also decreases their fracture rate. There is growing evidence, however, to suggest that treating older men with testosterone increases bone mineral density.[24-26] In the most recent study,[26] only men with low-normal or subnormal testosterone levels showed an increase in bone density after treatment with testosterone. Multicentre efficacy studies are needed to determine whether testosterone treatment actually decreases the fracture rate.

Because testosterone stimulates synthesis of erythropoietin, men with unexplained anemia should have their serum testosterone levels measured and be given replacement therapy if levels are low.

Testosterone might also stabilize mood.[27,28] This could happen in one of two ways[29]: a patient's improved anabolic status could increase his general sense of well-being, which would improve his mood, lift depression, and have a calming effect on irritability; or there might be a direct effect on the brain. In addition, men whose enthusiasm for many of their activities has waned might experience a surge of motivation inducing them to take initiatives that they had long forsaken. All of this can result in a new sense of self, in renewed self-confidence.

Hypogonadal men who have symptomatic autoimmune diseases, such as rheumatoid arthritis, might benefit from testosterone treatment.[30] Women are known to have a higher incidence of autoimmune diseases than men; this could be due to the suppressive effect of testosterone on

the immune system. Both laboratory[31,32] and clinical[33] evidence supports this thesis.

Men who have hot flashes or sweats, particularly at night, should have their serum testosterone levels measured. Low levels, whether due to primary or secondary hypogonadism, could induce hot flushes, which are usually relieved by testosterone treatment.

Are there drawbacks to testosterone treatment?

Traditional concern about testosterone treatment has focused on two main areas: lipids and coronary artery disease, and prostate gland disorders. Is this justified?

Lipids and cardiovascular risk. Until quite recently, most of the literature dealing with androgens and cardiovascular risk was based on studies of 17-alkylated steroids (eg, methyltestosterone, fluoxymesterone) particularly in the wake of media attention on athletes who abuse anabolic steroids. Studies demonstrated that these substances, especially if used in pharmacologic doses, could raise low-density lipoprotein (LDL) cholesterol levels, lower high-density lipoprotein (HDL) cholesterol, increase triglycerides, and also induce insulin resistance and carbohydrate intolerance.[34] Testosterone was thought to do the same, but thinking began to change for three main reasons.

- Androgens, such as 17-alkylated steroids, that are not aromatizable (ie, cannot be converted by the enzyme aromatase into estrogens) are much more likely to have a negative effect on lipid metabolism.[35]
- Studies of testosterone itself have generally shown it to decrease triglyceride and both total and LDL cholesterol levels.[36]
- Most studies have shown no change in HDL levels,[18,35,37] a few have shown slight decreases,[24] and some in hypogonadal men have shown that testosterone treatment has induced a rise in HDL levels.[38]

In population studies, men with higher testosterone levels tend to have higher HDL and lower triglyceride levels.[39] Phillips and colleagues[40] showed that men with more advanced coronary artery disease as assessed by angiography tended to have lower testosterone levels than those with less coronary artery narrowing. Lower androgen levels and dyslipidemia have been found in men with type 2 diabetes.[41] Other studies have shown beneficial effects of testosterone treatment on insulin resistance and hypertension and in reducing waist-to-hip ratio. Testosterone has been shown to decrease liposynthesis and increase lipolysis in abdominal fat.[42]

Lipoprotein (a) [Lp(a)] is known to be a risk factor for coronary heart disease. In one report, orchidectomy for prostatic cancer resulted in increased Lp(a) levels, while supraphysiologic doses of testosterone in healthy young men induced a reduction in Lp(a).[43]

Testosterone treatment has not been shown to have a negative effect on cardiac status. On the contrary, accumulated evidence suggests the opposite, that testosterone might well have a cardioprotective benefit. We do not know, however, whether long-term use of testosterone will produce the apparent benefits demonstrated in short-term studies.

Testosterone is not known to affect coagulation of blood adversely. Endogenous testosterone levels correlate positively with the main stimulator of fibrinolysis, tissue plasminogen activator. Endogenous testosterone should, therefore, reduce coronary artery disease by increasing fibrinolytic activity and decreasing fibrinogen.[44]

Prostate gland. Untreated hypogonadal men with very low testosterone levels virtually never get prostate cancer. A mainstay of prostate cancer treatment has been either orchidectomy or antiandrogen medication; however, prostate cancers have both androgen-dependent and androgen-independent components, and despite vigorous antiandrogen therapy, prostate cancer often continues to grow and metastasize. Furthermore, despite the clearly established fall in testosterone levels as men age, these same men have a rising incidence of prostate cancer. This has raised speculation that, if androgens play any role in development of prostate cancer, it must be as a consequence of androgen exposure early in life rather than later.[45] No evidence suggests that testosterone treatment at any dose will initiate development of prostate cancer or exacerbate pre-existing cancer,[46] nor has a link been established between endogenous testosterone levels and benign prostatic hypertrophy.[10]

Will men treated with testosterone have different rates of prostate cancer from men not treated? It will take many years to accumulate these data, but some information about endogenous testosterone levels is available now. In several studies, serum was collected and stored. After several years, the incidence of prostate cancer was determined and the stored blood assayed for a number of factors. No convincing relationship between levels of serum androgens and prostate cancer was seen.[47] It has been shown, however, that higher levels of insulin-like growth factor-1 are a risk factor for development of prostate cancer.[48] In most studies reporting therapeutic trials of testosterone, no increases in prostate-specific antigen (PSA) levels nor clinically significant changes in prostate gland volume have been seen.[49,50] In one study of

13 men, there was no change in prostate size after 3 months of testosterone treatment but PSA increased.[18]

Despite the lack of evidence for a role for testosterone in developing or intensifying prostate cancer, treatment with testosterone is contraindicated for men with known prostate cancer just in case it stimulates cancer growth. It is also contraindicated for men known to have breast cancer because testosterone is converted to the estrogen estradiol, which might promote breast cancer growth.

Other possible side effects. The conversion of testosterone to estradiol could induce mild-to-moderate transient gynecomastia with or without tenderness. Treatment with testosterone might also precipitate (usually mild) acne. Men might gain weight because of both fluid retention and an increase in lean body mass.[51] Testosterone has been reported to worsen sleep apnea.[52]

Because of the erythropoietin-stimulating effects of testosterone, it is not unusual for hemoglobin to rise (a desired effect in men with anemia) with testosterone treatment, but sometimes the rise is too high.[50] If reducing the dose of testosterone does not lower hemoglobin concentration, periodic phlebotomy can be considered.

Testosterone preparations and monitoring

In Canada, two safe forms of testosterone are available: in oil for intramuscular injection (testosterone cypionate [Depo-Testosterone®] at 100 mg/mL and testosterone enanthate [Delatestryl®] at 200 mg/mL) and an oral preparation (testosterone undecanoate [Andriol®] in a 40-mg capsule. The testerosterone patch available in the United States could soon be released in Canada.

Eugonadal men produce about 7 mg of testosterone per day. This can be approximated by intramuscular administration of 200 mg of testosterone in oil every 2 weeks. Patients treated at longer intervals often have symptoms return before the next injection. A dose of orally ingested testosterone undecanoate is much more variable because its efficacy relies on the degree of intestinal absorption. A dose of about 160 mg/d is usually required for a reasonable androgenic response. Unlike 17-alkylated steroids, testosterone undecanoate is not associated with hepatotoxicity.[53]

Physicians must monitor for changes in the prostate gland during testosterone replacement therapy. Benign hypertrophy is not a contraindication, but increasing difficulty in voiding might be related to stimulation of prostatic growth by testosterone. This is managed by adding medication specific for prostatic hypertrophy, reducing the dose, or discontinuing testosterone temporarily.

Editor's key points

- "Andropause" is a convenient term for a complex of symptoms in aging men that are associated with low testosterone levels.
- Consider measuring serum bioavailable testosterone in men who complain of decreased well-being and energy, weakness, fatigue, lower sexual interest and performance, irritability, and anxiety.
- With treatment, men's general sense of well-being and sexual interest (although not necessarily function) improve. Additional benefits seem to include lower likelihood of osteoporosis and anemia.
- To date, treatment with testosterone has not been shown to increase cardiovascular disease or the risk of prostate cancer.

Points de repère du rédacteur

- «L'andropause» est un terme pratique désignant un ensemble de symptômes chez les hommes d'âge mûr, associés à de faibles taux de testostérone.
- Il faudrait envisager mesurer la testostérone sérique biodisponible chez les hommes qui se plaignent d'une réduction du bien-être et de l'énergie, de faiblesse, de fatigue, d'intérêt et de rendement sexuels moins grands, d'irritabilité et d'anxiété.
- Avec une thérapie, le sentiment général de bien-être et l'intérêt sexuel (pas nécessairement la fonction) s'améliorent chez les hommes. Au nombre des autres avantages semblent figurer une moins grande probabilité d'ostéoporose et d'anémie.
- Jusqu'à présent, il n'a pas été démontré que la thérapie à la testostérone augmente le risque de maladie cardiovasculaire ou du cancer de la prostate.

Patients should be checked every 6 to 12 months to see whether they are experiencing new or worsening symptoms of prostatism. A digital rectal examination and tests for hemoglobin and PSA levels are required two or three times during the first year of treatment and thereafter at least annually.[54]

Conclusion

Testosterone levels fall with age, and aging men begin to develop symptoms. Increasing evidence suggests that testosterone replacement therapy can reduce symptoms in some aging men with reduced levels of testosterone. There might even be cardioprotective benefit.[55] We need large multicentre studies looking prospectively for the development of prostate cancer in men who were and were not treated with testosterone, but no evidence yet

suggests that such treatment will induce new cancer development.

Evidence on the merits and efficacy of treating symptomatic men is just beginning to accumulate. Although an increasing number of reports describe positive clinical or biochemical responses to testosterone treatment, the numbers of men studied are relatively small, and the duration of treatment is relatively short (one 10-year study is available[52]). To date, however, the evidence we have suggests that treating symptomatic men who have low testosterone levels will often improve their sexual function, general sense of well-being, and quality of life.

Competing interests

Dr Bain received a grant in the past from Organon Canada for an andropause study.

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