

# “Could this man have andropause?”

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Population projections from the United Nations have proposed that diseases associated with aging are increasing and will continue to increase. The fragility of the aging man is an important public health problem because it impairs quality of life, overall mobility, and increases the risk of falls and its sequelae.

The International Society of the Study of the Aging Male has defined andropause as “a clinical and biochemical syndrome associated with advancing age and characterized by deficiency in serum androgen levels with or without a decrease in genomic sensitivity to androgens. It may result in significant alternations in quality of life and adversely affect function of multiple organ systems.” There is a characteristic syndrome associated with decreased testosterone production in aging men (Table 1). When the clinical manifestations are associated with decreased testosterone production and improves, in part or in total, with testosterone replacement, it is referred to as the andropause syndrome. The justification here is of subjective improvement.

## George’s change

George, 59, was brought in by his wife. She states that he has developed fatigue and lassitude with decreased performance at work and at home. He has become irritable, unmotivated, and somewhat depressed.



He admits to decreased libido for about 10 years, and decreased strength of his erection. Overall, his health has been excellent, with no doctor visits for 5 years. His weight, mainly abdominal, has slowly increased. His overall muscle strength has decreased.

Physical exam was generally normal, including blood pressure, and cardiovascular exam. He was clinically euthyroid with normal palpable thyroid gland.

- Waist: 102 cm
- No gynecomastia
- Testes: 12-15 cc (3.5 cm in length)
- Digital rectal exam (DRE) of prostate: normal
- Hemoglobin: 120 g/L
- Normal serum thyroid-stimulating hormone (TSH), creatinine, liver function studies, fasting glucose and lipids, and prostate specific antigen.

**Could this man have andropause?**

**How would you further investigate him?**

**If present, how would you treat him?**

**For a followup on George, go to page 110.**

## Andropause

Table 1

### Symptoms of andropause

- Decreased libido
- Decreased motivation/productivity
- Decreased quality of erection
- Decreased mood/irritability
- Fatigue
- Increased body fat
- Lassitude
- Decreased muscle bulk
- Weakness
- Osteoporosis/fracture
- No known chronic disease/drug or alcohol abuse/depressive disorder

### *Does testosterone fall in the aging male?*

There is a general trend to decreased testosterone production with each decade after the age 30. It is related to both decreased central and testicular activity. Thus, unlike younger men, there is no increased serum luteinizing hormone in association with decreased testicular testosterone production. The fall of serum testosterone is not universal in all men, the degree of the fall, if any, is variable, and only affects a proportion of aging men. It is seen in otherwise healthy men without acute or chronic disease, but the fall may be accentuated in men with a chronic disease process.

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Because of the manner in which testosterone is transported in the circulation, and because serum sex hormone binding globulin (SHBG) increases with age, the fall of testosterone with aging is best identified by the measurement of testosterone that compensates for protein binding, as opposed to the total serum testosterone.

### *Are there clinical manifestations related to the fall of serum testosterone?*

Testosterone has anabolic and sexual actions. The changes in organ function and sexuality occur with aging, but this in itself does not prove causality with the fall of testosterone. Not all men with reduced serum testosterone levels have associated symptoms, whereas some men have symptoms associated with decreased testosterone, yet normal serum free testosterone levels. Some men with decreased serum testosterone are given replacement therapy, and realize, in retrospect, they did have symptoms that were otherwise unrecognized because of the slow onset and progression of the andropause syndrome. There is an overall correlation of the fall of serum testosterone with decreased anabolic action, such as decreased muscle mass and strength, bone density, erythropoiesis, decreasing libido, and to a lesser degree, decreased mood. Libido is a central effect and reflects brain function, whereas erectile dysfunction is a local event, usually related to vascular insufficiency, and occasionally from psychological stress. The fall of serum testosterone can be associated with decreased libido, but not with erectile dysfunction.

Table 2

## Testosterone formulations

<u>Formulation</u>	<u>Route of administration</u>	<u>Usual dose (may increase or decrease)</u>
Testosterone depot*	IM injection	150-200 mg every 2 weeks
Testosterone undecanoate	Oral	80 mg bid with food (essential)
Testosterone patch	Transdermal	5 mg a day
Testosterone gel	Transdermal	5 g of 1% gel a day

\* cheapest formulation, the most cost-effective, and the greatest clinical experience  
 IM: Intramuscular  
 BID: twice a day

bioavailable testosterone are not perfect measurements, but do have a satisfactory correlation with androgenicity.

A man with the appropriate symptoms who is found to have a low measurement

of serum testosterone, consistent upon repeat, and not confounded by other clinical conditions, is then diagnosed as having the andropause syn-

### *Do men with decreased serum testosterone have andropause?*

Co-existing disease affecting nutrition and some medications may affect serum testosterone levels. Diseases, like depression, cognitive impairment, thyroid disease, fibromyalgia, diabetes mellitus, and liver disease, can have symptoms similar to the andropause syndrome. So, the serum testosterone measurement requires interpretation. An early morning testosterone is best since normal men may have a fall of serum testosterone throughout the day. The true tissue available testosterone is independent of SHBG, and thus measurement of non-SHBG bound testosterone is a better measurement than total testosterone. Free testosterone is expensive to measure, and thus is usually calculated. Both total testosterone and SHBG are measured, and a calculated free testosterone (free androgen index) is reported, which presumably compensates for any changes in SHBG. Bio-available testosterone measurement is not readily available in all centres, but it represents the active form of testosterone once the testosterone bound to SHBG has been precipitated. Both the free androgen index and the

## Return to George

George was found to have a free androgen index of 21 (normal > 30), serum luteinizing hormone 6, serum follicle-stimulating hormone 9, serum prolactin and TSH were normal. Repeat free androgen index taken at 8 a.m. was 19.

The andropause syndrome was diagnosed. Testosterone replacement therapy was discussed. The advantages and disadvantages of replacement therapy with intramuscular testosterone, oral testosterone, testosterone patch, and testosterone gel were described.

George elected oral therapy, and testosterone undecanoate 80 mg twice a day was prescribed. He was instructed to keep the open bottle at room temperature, and to always take the pills with food.

In three months, he was reassessed, and found to have increased libido, improved sexual performance, and better overall feeling of well being. His wife states that he become less moody, and his background tendency to snore had not worsened. Clinical exam remained unremarkable, including DRE of prostate. Serum prostate-specific antigen was unchanged, and hemoglobin was 127.

He was instructed to continue with the therapy, with plans for followup in three months.

relate, some authors have suggested that symptoms alone, otherwise unexplained, are sufficient for a trial of testosterone. It must be realized that there are other causes of these symptoms, with depression as the most common clinical condition producing decreased libido, so this practice cannot be generally recommended.

## Are testosterone formulations safe?

Testosterone by itself is not orally active as it is unable to bypass the liver. Previous approaches were to use 17-alkylated preparations to allow liver bypass, but these had adverse effects on liver and on lipid metabolism. Only testosterone in the present formulations should be used today (Table 2) if there are no contraindication (Table 3) and a trial of therapy is clinically desirable. Testosterone undecanoate is absorbed through oral administration, and passes through the lymphatic system to the serum. Depo formulations of injectable testosterone in an oil base are administered every two weeks, with peaks after each injection and valleys before each injection. Some patients are sensitive to this fluctuation. Such preparations are the cheapest, and proven to be effective over many years. Testosterone patches are applied and replaced daily, with the biggest problem being skin irritation. Testosterone gel may also be associated with skin irritation, and although it dries rapidly, may be transferred to women or children upon close contact soon after its application.

Despite the variations in these formulations, the positive effects of testosterone replacement may be seen within three months. Measurement of serum testosterone is variable under treatment, is not as reliable as the clinical evaluation, and is usually not needed. Once testosterone has been initiated, the decision may then be made for its continuation.

Table 3

### Contraindications to testosterone replacement therapy

#### Absolute

Prostate cancer  
Severe BPH  
Breast cancer  
Polycythemia

#### Relative

Severe heart failure  
Severe uncontrolled hypertension  
Untreated sleep apnea  
Symptomatic BPH

BPH: Benign prostatic hyperplasia

drome.

Because the andropause symptoms and low levels of serum testosterone may not directly cor-

The clinical response is the guide.

If there is no improvement in symptoms after three months, the dose may be increased or another formulation may be tried. If testosterone is discontinued because of lack of efficacy, often the patient may subsequently recognize that in retrospect there was an improvement in overall symptoms.

At three, six, and 12 months and then yearly after treatment is initiated, patients should have a digital rectal exam of the prostate, serum prostate specific antigen (PSA), and serum hemoglobin. Any suspicious change in the texture of the prostate gland, or an increase of serum PSA dictates that testosterone replacement should be discontinued, and the patient should have a transrectal ultrasound and prostate biopsy. If no prostate malignancy is found, or prostatic intraepithelial neoplasia, a return to testosterone replacement may occur. If there is an increase of hemoglobin above normal, the dose may be decreased, or temporarily halted. Worsening of pre-existing sleep apnea has been anecdotally reported and needs to be evaluated on followup. Acne and gynecomastia may respond to a change in formulation or decrease in dose, and sodium retention may aggravate pre-existing hypertension or cardiac failure. The modern testosterone formulations have, to date, not been shown to be harmful on the cardiovascular system, and some data suggest testosterone may be cardio-protective.

### ***Do clinical outcomes support testosterone replacement therapy?***

Controlled clinical studies have been few in number and short in duration. These results have been variable. In general, they have demonstrated an anabolic effect of testos-

terone replacement in aging men with proven testosterone deficiency. Overall, there is an increase in muscle mass, with inconsistent effects on muscle strength. The latter is of concern since this would relate to improved function. There is generally a reduction in body fat; in association with this improvement in insulin sensitivity and aspects of the metabolic profile, there is especially improvement in lipids. In men with low serum testosterone, there is an improvement in bone mineral density, but a decrease in fractures has yet to be demonstrated. No improvement in bone mineral density is noted in men with low-normal serum testosterone. Libido improves with a threshold in the low-normal range. Erectile function generally does not change, although some studies demon-

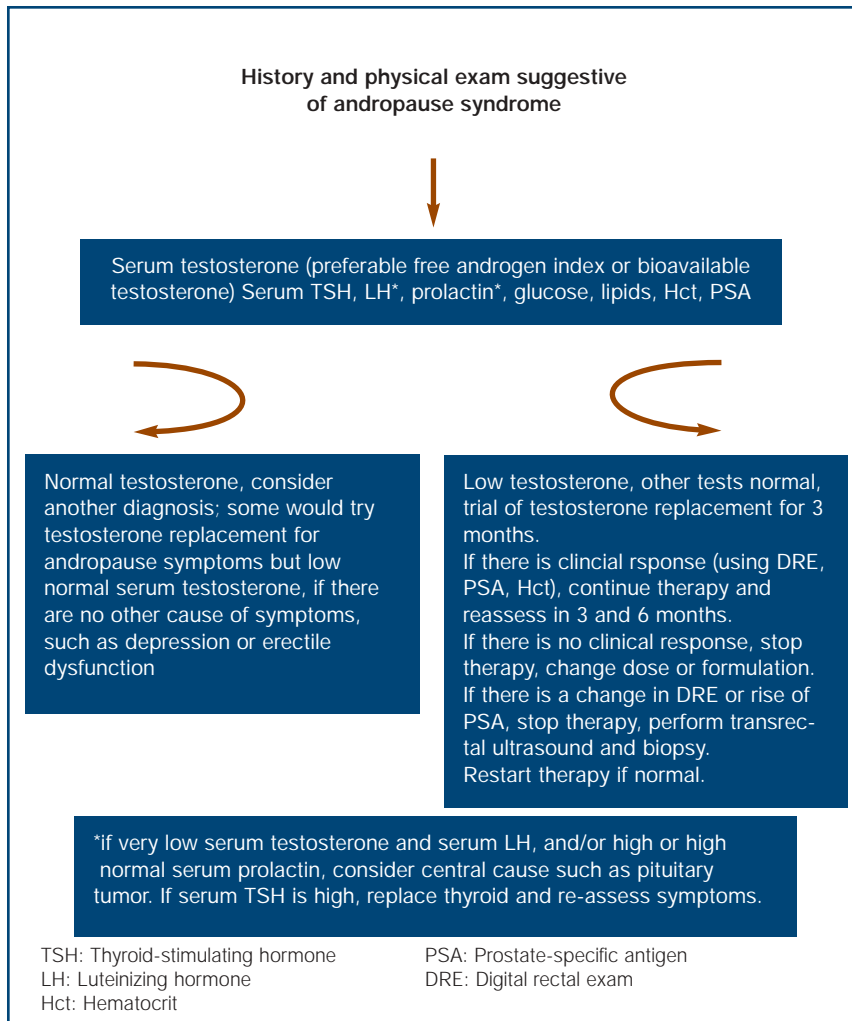


Figure 1. Approach to the andropause syndrome.

## What do the data show?

The long-term risk-benefit data on the safety of testosterone replacement in aging men are unavailable. Hard end points on independent living, fractures, cardiovascular disease, and prostate health remain unknown. Most studies demonstrate a modest increase in prostate size, and very little, if any, change in PSA, not exceeding that of control subjects. These changes must continue to be monitored. Caution should be exercised in men with pre-existing sleep apnea, especially if they are overweight, heavy smokers, or have chronic obstructive airway dis-

ease. An increase in hemoglobin above normal can be associated with an increase in blood viscosity and, in theory, increased thrombotic events, and dictates regular monitoring.

strate that testosterone replacement may have an additive effect to sildenafil. Erectile dysfunction by itself does not respond to testosterone replacement therapy, with an otherwise normal serum testosterone. There is preliminary evidence that testosterone may influence performance on cognitive tasks, such as spatial memory. Testosterone replacement in testosterone deficient men has been associated with a general mood elevating effect, and not associated with an aggravation of negative mood. Its effect on quality of life questionnaires has been variable.

In the aging male with a low measurable testosterone, lowering of the low-density lipoprotein cholesterol or increase in bone density are not by themselves indications for testosterone replacement therapy. The use of statins or bisphosphonates for these indications have proven beneficial outcomes, unlike testosterone replacement therapy.



## Net Reading

Canadian Andropause Society  
<http://www.andropausesociety.ca>

[www.stacommunications.com](http://www.stacommunications.com)



For an electronic version of  
this article, visit:  
*The Canadian Journal of CME* online.

Some otherwise normal aging men do develop symptoms of the andropause syndrome, and have measurable low serum testosterone. Physicians should overcome the natural bias to ascribe these symptoms to the aging process and recognize the beneficial effects of testosterone replacement therapy in symptomatic aging men. Unless an overt contraindication is present, a trial of therapy may be undertaken. While most of the aspects of the aging process are not reversible, any hormonal dysfunction, including testosterone deficiency, is easy to diagnose and to correct by replacement therapy. **CME**

## Take-home message



- Serum testosterone does fall with the aging process, but is variable from one man to another (Figure 1).
- A man with a measurable decrease in testosterone in association with symptoms of the andropause syndrome, not related to other clinical events, can be identified.
- A trial of therapy may be undertaken in selected patients. The goal is to restore or improve anabolic, psychological, and sexual symptoms.
- The testosterone formulation used would be one that best suits the patient's lifestyle.

### Suggested Readings

1. Vermeulen A: Androgen replacement therapy in the aging male: A critical evaluation. *J Clin Endocrinol Metab* 2001; 86(6):2380-90.
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4. Snyder PJ: Effects of age on testicular function and consequences of testosterone treatment. *J Clin Endocrinol Metab* 2001; 86(6):2369-72.
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6. Morley JE, Perry M III: Androgen treatment of male hypogonadism in older males. *J Steroid Biochem Mol Biol* 2003; 85(2-5):367-73.
7. Delhez M, Legrosa H, Legrosa JJ: Andropause and psychopathology: minor symptoms rather than pathological ones. *Psychoneuroendocrinology* 2003; 28(7):863-74.