

# Colloquium

## CURRENT PRACTICE IN THE DIAGNOSIS AND TREATMENT OF ANDROPAUSE



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In the sixteenth century, the Spanish explorer Ponce de Leon set out to discover the fountain of youth. He sailed far and wide in search of his dream—a potion that could restore vim and vigour to people with aging bodies and sagging spirits—but never found it.

Fast-forward to the late nineteenth century, when French physiologist Charles Edouard Brown-Sequard concocted what he called a "rejuvenating therapy for the body and mind." A liquid extract made from the testicles of guinea pigs and dogs, Brown-Sequard's potion allegedly increased physical strength and intellectual prowess.

With human longevity at an all-time peak, today's aging men

are as intent as ever to add life to their autumnal years. While researchers no longer grind up animal testicles in search of life-giving elixirs, they do owe a lot to Brown-Sequard's intuition that the testes contained a substance with restorative properties. We now know this substance is testosterone and have come to understand the central role of this hormone in maintaining libido, vitality and

physical prowess. Indeed, given what we know about testosterone, it is very likely that Brown-Sequard's extract had more than a placebo effect.

When testosterone decreases, as it does with increasing age, men may experience a gradual decline in lean body mass, muscle strength, bone density, libido, energy and muscle tone. However, not all men with declining testosterone levels experience these symptoms to the same degree—in the same way that not all women going through menopause experience such "classic" menopausal symptoms as hot flushes and decreased interest in sex. To qualify for a diagnosis of andropause, a man must have both the biochemical insufficiency of testosterone and the biosocial symptoms characteristic of the condition.

### 1. Dr. Tremblay, Laval University: Is andropause for real?

**Dr. Chun:** The term "andropause" may sound like a manufactured counterpart to female menopause, but the phenomenon is certainly real. But up to 30% of men over the age of 50 meet the criteria for andropause (see Table 1 on page 2).

**Dr. Khan, McMaster University:** Andropause occurs with aging and affects a wide segment of the aging male population, but this does not mean that andropausal men should not be treated. Hypertension is also common among aging males, but nobody would suggest that we leave it untreated. With people living longer lives, it is important that they be able to enjoy their final few decades to the best of their potential.

One of the important health conditions affecting men in their later years is osteoporosis. According to current estimates, we are picking up fewer than 25% of osteoporosis cases in men. While it is true that the prevalence of hip fractures in men is only one-third of that seen in women, the mortality associated with hip fractures is much greater in men (40%) than in women (20%). The importance of testosterone in maintaining bone density is well established. As our awareness of skeletal health increases, so does our attention to andropause and its effects on the bones.

### 2. Dr. Tremblay: What causes the decline in testosterone associated with andropause?

**Dr. Bain, University of**

## THE PANEL



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**Toronto:** Under normal conditions, the hypothalamus directs the pituitary to secrete bursts of luteinizing hormone (LH), which acts on the Leydig cells in the testes—the cells that manufacture testosterone in men. Thus, healthy men experience many bursts of testosterone throughout the day.

As men—and their hypothalamus and pituitary glands—age, the number and size of the LH bursts decreases, resulting in a “flatter” testosterone profile. The quantity of circulating testosterone also decreases by about 10% every decade, with the lowest levels seen in men aged 70 and older.

At the same time, the concentration of sex-hormone-binding globulin (SHBG) increases with age. This is significant because about 60% of serum testosterone is bound to SHBG. The rest circulates either freely (about 2%) or weakly bound to albumin. Both the free and albumin-bound testosterone are readily available to tissues when needed, and are thus known as “bioavailable” testosterone. The testosterone bound to SHBG, on the other hand, is not available to the tissues. The net effect of aging, then, is that bioavailable testosterone decreases at a greater rate than total serum testosterone.

**Dr. Chun:** The biochemical imbalance that leads to testosterone deficiency can occur at the pituitary level or at the gonadal level. If testosterone is low but LH is high, this suggests that the testes are not responding normally to LH, which leads the pituitary to produce more LH in compensation. If, on the other hand, both testosterone and LH are lower than normal, a malfunctioning pituitary gland may be the source of the problem.

**Dr. Khan:** Studies have shown that aging can impair the secretion of LH and follicle-stimulating hormone (FSH) from the pituitary gland. Thus, the elderly male may not display pronounced increases in LH secretion in response to declining testosterone levels. Stress, chronic illness, sleep deprivation and poor nutritional intake can also suppress LH secretion and cause testosterone levels to further fall into the hypogonadal range.

### 3. Dr. Tremblay: What does the andropausal male look like?

**Dr. Khan:** The clinical symptoms of andropause can be grouped into four areas of investigation: vasomotor and nervous symptoms,

Men can and do experience a decrease in testosterone that parallels women's decrease in estrogen and progesterone production during and following menopause. The difference is that the pattern of hormonal decrease in men is generally more linear than that found in women, whose production of estrogen drops most significantly over the perimenopausal years. Not all men lose testosterone to the same degree or at the same rate, and not all men experience symptoms that interfere with their lives.

mood disorders, masculinity and physical vigour, and sexuality. More specifically, andropausal men may experience insomnia and nervousness. Mood can take a plunge toward sadness and grumpiness, and formerly stimulating goals and activities may lose their lustre. Concentration may also be impaired. On the physical side, these men often experience a marked drop in muscle mass, strength and endurance, sometimes accompanied by abdominal obesity and loss of body hair. Libido and sexual function can also be affected.

### 4. Dr. Tremblay: Which men should we be screening?

**Dr. Chun:** As a general rule, men can be screened on the basis of symptomatology. If a man presents with all or some symptoms suggestive of andropause, it is appropriate to screen him for testosterone deficiency.

**Dr. Khan:** It is also appropriate to screen older men with low bone density or fractures, even if they do not exhibit many of the symptoms of andropause. Hypogonadism is one of the three most common causes of osteoporosis and should be considered in all men with low-trauma fractures, kyphosis or low bone density. If such a patient turns out to have testosterone insufficiency, treatment with testosterone replacement therapy (TRT) can improve both his bone density (and thus protection against fractures) and his overall sense of well-being.

### 5. Dr. Tremblay: What are the biochemical tests for testosterone and how do they differ?

**Dr. Bain:** The most crude laboratory test for testosterone measures total serum testosterone. This test may not provide a good indication of a man's real testosterone status as it ignores the fact that SHBG increases with age, making a smaller proportion of the circulating testosterone available to the tissues. Studies have found that the total testosterone test misclassifies androgen deficiency in many cases. Free testosterone can be determined through an analog immunoassay or by centrifugation, both inaccurate methods, or by a more accurate but laborious equilibrium dialysis test.

The most reliable methods for evaluating testosterone deficiency are the bioavailable testosterone assay and the “calculated free testosterone,” obtained through a set of equations derived from the mathematical modeling of the law of mass action at equilibrium. The ratio of SHBG to total testosterone yields the so-called free androgen index. Most laboratories in Canada

perform these tests. A bioavailable testosterone level of 2.5 nmol/L or lower, or a calculated free testosterone level of 225 pmol/L or lower, supports a diagnosis of andropause.

### 6. Dr. Tremblay: How is andropause treated?

**Dr. Bain:** The principle behind treatment of andropause is a simple one: replenish the testosterone that is lacking in andropausal men. There is no age limit for receiving testosterone replacement therapy (TRT). Whether 55 or 85 or anything in between, a man can still reap benefits from therapy. TRT is currently available in four different forms in Canada: injectable, oral, patch or gel.

Prior to considering TRT for an andropausal, the clinician should ensure that clinical symptoms are accompanied by low values for bioavailable testosterone or calculated free testosterone. Although the decision to initiate TRT presumes the presence of clinical symptoms, the patient does not have to experience symptoms in all four areas of investigation (vasomotor/nervous, affective, physical and sexual). By the same token, since the blood level of testosterone doesn't always reflect the tissue level, it is appropriate to initiate therapy in patients with low-normal results from the lab.

### 7. Dr. Tremblay: What are the benefits and drawbacks of the different forms of testosterone therapy?

**Dr. Bain:** Available since the 1950s, injectable testosterone is generally administered every two weeks. During the first few days after injection, the patient's

**Table 1**

## Signs & Symptoms of Andropause

- Decreased sex drive
- Weaker erections
- Lack of energy
- Decrease in strength and endurance
- Loss of height
- Decreased enjoyment of life
- Feelings of sadness or irritability
- Deterioration in ability to play familiar sports
- Excessive sleepiness after dinner
- Recent deterioration of work performance

circulating testosterone may reach supraphysiological levels, leading to a noticeable response in terms of energy and sex drive. The downside is that testosterone levels and response taper off after the first week or so, such that the patient may not experience the benefits of therapy in the final days preceding reinjection. Sometimes, adjusting the dose and frequency of injection can produce a better response curve.

Currently, only one form of oral testosterone—testosterone undecanoate (Andriol)—is available in Canada. Since testosterone undecanoate is true testosterone and not a 17-alkylated substitute, it produces no adverse effects on the liver. It is absorbed through the lymphatic system, so it does not make a "first pass" through the liver. In addition, a 10-year safety study has shown that the drug does not appear to induce benign prostatic hypertrophy or gynecomastia. Testosterone undecanoate comes as a 40 mg pill, which delivers about 2.5 mg of testosterone to the bloodstream. Most patients require four daily pills (two pills taken twice a day) to benefit from therapy. The medication is best absorbed with some dietary fat, such as a few nuts, and should be kept at room temperature.

Available since the 1990s, the testosterone patch is applied to specific parts of the body (such as the shoulders or thighs) and kept on for 24 hours, at which point a new patch is applied. It is convenient and easy to apply, but its visibility can cause embarrassment in the gym or during intimate encounters. It can also cause local skin reactions that may require treatment with steroid creams.

Testosterone gel received Canadian approval in June 2002. It comes in a tear-open packet, and is applied to both dry shoulders after a shower. It dries quickly on the skin, so a man can put his shirt on two minutes after applying the gel. Conversely, the man should avoid rubbing his shoulders against a female partner during the first few hours after application, because some testosterone could get transferred into her body. Another disadvantage is that, with the current 5 g formulation, it is not clear that the gel will deliver enough testosterone into the system in the majority of cases.

**Dr. Chun:** In terms of cost, injectable testosterone is the least expensive form of therapy. However, most formulations and drug plans cover oral testosterone

**Table 2**

### Expected Benefit of TRT

- Sense of well-being
- Increase in physical and mental energy
- Increase in sexual desire and performance
- Greater lean muscle mass
- Increase in bone density
- Decrease in total plasma cholesterol

tablets, and some may cover testosterone in patch or gel form.

#### **8. Dr. Tremblay: What can a patient expect from testosterone-replacement therapy?**

**Dr. Chun:** Most patients on TRT report some or all of the following: higher levels of energy, sharper concentration, a more stable mood, less irritability and a more positive attitude toward life. On the sexual front, TRT stands to improve a wide range of sexual feelings and behaviours, including sexual thoughts, dreams and daydreams, sexual desire, spontaneous erections and motivation to engage in sexual activity.

**Dr. Bain:** Sometimes it is only after a man seeks therapy for decreased libido, and only after being on TRT, that he realizes that things were amiss in other departments as well. With the newfound energy and zest for living afforded by therapy, he realizes that he had been living in a subnormal mental and emotional state in previous months or years.

**Dr. Khan:** Suppression of LH into the normal range indicates that androgen replacement therapy is producing the desired physiological effect. In some instances, however, TRT will raise circulating testosterone levels and normalize LH levels as expected but will not improve symptoms. In such a case, the clinician should investigate the possibility of a concomitant disorder such as depression or hypothyroidism. It also bears noting that in men with normal testosterone levels, supplemental testosterone administration does not improve sexual function to any appreciable degree. This suggests the presence of an upper limit to the dose-response relationship between testosterone and sexuality (see Table 2).

#### **9. Dr. Tremblay: What are the health benefits of TRT?**

**Dr. Chun:** Studies in the past decade have shown that testosterone can decrease central body fat, while also increasing lean muscle mass and strength. This has obvious implications to health, as abdominal fat is a strong risk factor for heart disease. Along similar lines, there is evidence that TRT improves insulin sensitivity and exerts a beneficial (though subtle) effect on lipid profile by raising HDL and lowering LDL to some degree.

Another major health benefit of TRT concerns bone health. A recent randomized, placebo-controlled trial showed that a one-year treatment period of TRT increased bone density in the lumbar spine of healthy older men with low testosterone levels. Other studies have found TRT to exert a modest but significant effect on fractures. Considering that one in eight men over 50 has osteoporosis, TRT could represent a significant preventive health measure.

**Dr. Khan:** Androgen administration increases red blood cell mass, thereby correcting anemia in a proportion of treated patients.

#### **10. Dr. Tremblay: Does TRT pose any risks?**

**Dr. Khan:** There is a risk of developing polycythemia while on TRT. Thus, therapy should be discontinued if the patient's hematocrit rises above 50%. In a minority of men, TRT may also induce or exacerbate sleep apnea, as well as cause breast tenderness or enlargement.

**Dr. Bain:** There is a lingering perception that TRT may increase the risk of atherosclerotic heart disease, but the available data do not support this premise. In fact, current evidence supports the idea that testosterone may be cardio-protective.

**Dr. Chun:** There is agreement that short-term testosterone administration is quite safe in

androgen-deficient men. The long-term risks of TRT, if any, are not fully understood. As the recent Women's Health Initiative (WHI) trial of hormone-replacement therapy showed, there is always a chance that previously unknown risks of a well-established therapy will come to light. On the other hand, the concerns stemming from the WHI study cannot be automatically extrapolated to TRT in men. The past few decades of study have revealed no definitive evidence linking TRT to prostate cancer or cardiovascular events. As with all therapies, the known and potential benefits of TRT must be weighed against its known and unknown risks.

#### **11. Dr. Tremblay: How should patients on TRT be monitored?**

**Dr. Bain:** Physicians should monitor the status of their patients in the following domains at three, six, and 12 months after initiation of therapy, and annually thereafter:

- measure hemoglobin and hematocrit, and discontinue treatment temporarily if hemoglobin rises significantly above the upper limit of normal
- enquire about symptoms of sleep apnea
- measure prostate-specific antigen (PSA), perform a digital rectal examination, and evaluate symptoms of benign prostatic hypertrophy; a rise in PSA of more than 1.0 mcg/L between two measurements should be verified by retesting. A persistent increase to this degree or greater warrants a urologic evaluation to rule out prostate cancer. This should include stopping testosterone treatment and performing a transrectal ultrasound and prostate biopsy whether a nodule is present or not.

#### **12. Dr. Tremblay: In which patients is TRT contraindicated?**

**Dr. Chun:** TRT is an absolute contraindication in men with pre-existing prostate cancer or the more rare breast cancer. Men with baseline PSA levels higher than 4 ng/mL should not be put on TRT until urologic evaluation has ruled out prostate cancer. TRT should be administered with caution in men with family histories of prostate cancer and in men with severely symptomatic benign prostatic hypertrophy (BPH). Elevated baseline hematocrit and symptoms of severe sleep apnea warrant a

similarly cautious approach. Men with milder BPH, on the other hand, can be started on TRT with the same confidence as their counterparts with normal prostate glands.

It bears noting that even men with normal digital rectal exams and PSA levels may have occult prostate cancer—about 20%, by some estimates—although it is true that many of these cancers may never progress into a clinically significant range. Still, it is important to inform patients about the potential, if unknown, risks of treatment.

**13. Dr. Tremblay: Andropause and depression seem to have several symptoms in common. How does one avoid confusing the two?**

**Dr. Bain:** Along with its well-publicized effect on libido, androgen deficiency affects other mental/ emotional states, including energy, mood and motivation. In this regard, andropause and depression exert similar effects. Defining symptoms common to the two conditions include dysphoria, fatigue, difficulties concentrating, decreased productivity, decreased motivation, decreased well-being and loss of self-esteem.

On the other hand, one of the hallmark features of depression—a sense of worthlessness often accompanied by suicidal ideation—does not characterize the andropausal man. By the same token, the decreased libido that typifies andropause does not constitute a core symptom of depression, although depressed individuals may certainly lose some interest in sex (as a manifestation of their more generalized loss of interest in formerly pleasurable activities).

A differential diagnosis between andropause and depression can be made on the basis of bioavailable or calculated free testosterone levels, as well as a careful assessment of symptomatology. Clinicians should also remember that depression and andropause may coexist. Thus, treatment of depression does not preclude TRT. In fact, TRT can enhance the effect of antidepressants and result in a more complete response to treatment. Occasionally antidepressant therapy can be discontinued altogether once the hypoandrogenic state is corrected.

**14. Dr. Tremblay: If you had to encapsulate your position about andropause and TRT to family doctors, what would you say?**

Studies in the past decade have shown that testosterone can decrease central body fat, while also increasing lean muscle mass and strength. This has obvious implications to health, as abdominal fat is a strong risk factor for heart disease.

Another major health benefit of TRT concerns bone health. A recent randomized, placebo-controlled trial showed that a one-year treatment period of TRT increased bone density in the lumbar spine of healthy older men with low testosterone levels. Other studies have found TRT to exert a modest but significant effect on fractures. Considering that one in eight men over 50 has osteoporosis, TRT could represent a significant preventive health measure.

**Dr. Bain:** Andropause is a real clinical entity and TRT can bestow increased energy, motivation, self-confidence and libido upon andropausal men. While injected testosterone is the oldest form of delivery, other forms of testosterone may be just as effective and circumvent the need for injections.

**Dr. Chun:** I support the concept of andropause and its treatment with TRT. One of the most promising uses of TRT is in the treatment of incipient or actual osteoporosis. That said, there is still much to be learned about the long-term ramifications of TRT. Proceed with optimistic caution.

**Dr. Khan:** We need to think of andropause as more than a sexual condition. Andropausal men experience a decline in many important aspects of their life. As a corollary, TRT has the potential to boost not only sexual function, but overall quality of life as well.

**15. A 54-year-old college teacher presents to his family doctor with complaints of low energy, impaired concentration and lack of interest in sex. Suspecting depression, the family doctor refers the man to a psychiatrist. The psychiatrist's report indicates the man fulfills only a few of**

**16. A 62-year-old real estate agent presents to his family doctor with the complaint of erectile dysfunction (ED). More detailed questioning by the doctor reveals that the patient does not, in fact, suffer from ED but from decreased libido. He also gives the impression of being apathetic in general, with comments such as "somehow the thrill of closing a sale is gone for me." A laboratory test reveals the patient's bioavailable testosterone to be 1.2 nmol/L, below the normal range of 2.5 to 3.5. Although he has no personal or family history of prostate cancer, his PSA levels are at the high end of the normal range (4 ng/mL). A digital-rectal exam reveals no abnormalities.**

**Dr. Chun:** While there is no evidence that testosterone therapy can cause a prostatic carcinoma to form, men with pre-existing prostate cancer should not receive testosterone supplementation, because of the androgen sensitivity of most clinical prostatic carcinomas. Given this patient's slightly elevated PSA levels, it would be appropriate to order a prostate biopsy to investigate the possibility of early prostate cancer. If no cancer is detectable, the doctor should discuss the benefits and risks of testosterone therapy with the patient, then, if the patient agrees, proceed with supplementation. ■

**the criteria for major depression or dysthymia. The family doctor reviews the patient's chart and notes that her patient has been taking thyroid-hormone supplements (175 µg/day), under the care of his endocrinologist, for the past two years. What is the most logical course of action at this point?**

**Dr. Tremblay:** Thyroid hormone effects an increase in SHGB, leading to a decrease in bioavailable testosterone. In this case, there is good reason to suspect that the patient's symptoms stem from testosterone insufficiency rather than clinical depression. In consultation with the endocrinologist, the family doctor can try the patient on a reduced dose (such as 125 µg/day) of thyroid-hormone supplement. This strategy should lower the patient's SHGB levels and thus raise his levels of bioavailable testosterone. If his symptoms persist, he may be experiencing a testosterone deficiency in excess of that caused by his supplement. A laboratory test can confirm or rule out this possibility. If it turns out the patient's testosterone is subnormal, testosterone supplementation can be initiated (assuming no contraindications exist). If the patient's testosterone is normal, the psychiatrist can be called in to further explore the patient's mental status.

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