

Clinical Impact of Age-related Testosterone Depletion and Therapy

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The march of time brings about many alterations to the endocrine system, including a reduction in hypothalamic-pituitary-testicular function and a variable decrease in testosterone. Both total and bioavailable testosterone levels are affected; the latter exhibits a steeper decline. The effects of decreased testosterone tend to become clinically apparent in the sixth or seventh decades of life but sometimes appear as early as the fourth. The reduction has an impact not just on libido and sexual function but also on multiple body systems in which testosterone has a role in physiologic functioning. Hypogonadism, even that occurring with andropause rather than pathologic deficiency, has been associated with an overall decline in wellness and vigour and has been linked to several age-related diseases.

Impact on Multiple Systems

Decreased testosterone level leads to a reduction in muscle mass, strength and endurance, and an increase in fat mass. Because testosterone helps modulate bone formation (via conversion to dihydrotestosterone by 5- α reductase) and resorption (via aromatase-mediated conversion to estradiol), low testosterone may also increase the risk of osteopenia or osteoporosis. Together, these effects can contribute to an increased risk of falls and fractures. In frail hypogonadal men, treatment with testosterone can increase lean muscle mass, improve physical function and possibly help prevent injuries.

In the brain, testosterone appears to play a role in cell growth and survival and blood flow, notably to regions that direct such executive functions as cognitive behaviour, strategic planning and higher motor activity, as well as emotion, wakefulness and memory. A higher vs. a lower level of bioavailable testosterone has been shown to correlate with better visual and verbal memory and visuospatial function in older men. Preliminary research indicates that adequate testosterone may be important for the prevention and perhaps even the treatment of Alzheimer's disease. Some evidence also supports the notion that reduced testosterone concentrations can be linked to depression in middle-aged and older males and that testosterone therapy can help relieve depressive or dysthymic symptoms.

Among the more intriguing connections between testosterone and disease is the finding that men with coronary artery disease, and conditions that are risk factors for cardiovascular (CV) disease, are more likely to have abnormally low levels of the hormone. For example, low testosterone has been associated with early atherosclerotic disease, changes to insulin and glucose metabolism,

dyslipidemia and anemia. Overall, current evidence in this area suggests testosterone may help protect against the development of CV disease.

Older men with diabetes mellitus tend to have decreased testosterone levels, while treatment of hypogonadism in this population has been shown to have a positive impact on markers of diabetes, total cholesterol and abdominal adiposity. Recent work indicates hypogonadal men, especially those with an elevated body mass index, are also at higher than average risk of developing the metabolic syndrome; and that testosterone administration may constitute a preventive measure in tandem with lifestyle modification.

Additional literature has described a link between decreased testosterone and autoimmune disorders. It has been suggested that testosterone and other androgens have anti-inflammatory properties; some studies have determined that administration of testosterone in patients with rheumatoid arthritis can improve immune response.

Therapeutic Trial in Men with Symptoms

Testosterone therapy in hypogonadal aging men can play a role in retarding or reversing some of these pathologies and contributing to physical and psychological well-being. While the need for treatment of a natural testosterone decline has been somewhat controversial, there is increasing and interesting evidence for a trial of therapy in symptomatic individuals who have no contraindications. The currently accepted philosophy is that testosterone is not an alternative for men with prostate or breast cancer; however, there is little evidence to substantiate the widely expressed concern that testosterone therapy will cause prostate cancer. A six-month trial is generally sufficient to determine if symptoms can be improved.

Questions and Answers

This question-and-answer session is based on an interview with Dr. Jerald Bain, Professor Emeritus, Faculty of Medicine, Division of Endocrinology and Metabolism, University of Toronto, Ontario.

Q: How should the testosterone level be evaluated?

A: The best commercially available test measures bioavailable testosterone. The commercially available test for available free testosterone is not highly reliable.

Q: What guides the decision to administer testosterone therapy?

A: First, the patient must be symptomatic; second, he must have a frankly low or “low-ish” testosterone level. There aren’t strict guidelines that are universally agreed upon as to what “low-ish” means. I rely heavily on the symptoms and will treat if total testosterone is <14 nmol/L or bioavailable testosterone is less than approximately 3.8 nmol/L, regardless of total testosterone. The major arguments for using testosterone therapy are gains in—first—a general sense of well-being; second, energy and strength; and third, sexual dysfunction. If a patient has low testosterone and is lethargic, weak, depressed, and has a depressed libido—that’s a situation in which you can at least give a trial of therapy. And as outlined in the article, there’s growing evidence that it may be useful in mood disorders. It’s not a replacement for an antidepressant in a man whose testosterone level is perfectly satisfactory. But in a man with low testosterone, a trial of therapy is reasonable.

Q: Some physicians have expressed concern about giving testosterone therapy. Why?

A: One of the major areas of anxiety is the prostate gland—that testosterone may encourage cancer development or growth. In fact, there’s no evidence that it causes the development of a new prostate cancer and frankly, there’s very little evidence that it induces further growth of an existing cancer. The other area of concern is the heart. Testosterone therapy has had a bad rap by being associated with the anabolic steroids, which are testosterone-like substances that do have adverse effects

on the heart function, lipid and carbohydrate metabolism and so on. Testosterone—the real thing—doesn’t have those effects.

Q: How do you decide on the appropriate type of administration for a given patient?

A: In Canada, administration may be oral, topical, or by injection. In my practice I use all three types. Not all patients respond as well to one formulation as they do to another—it’s quite variable. Similarly, patient preference is a consideration. Some men find the injections most convenient because they are required only once every two weeks; some prefer to take pills; some don’t want to take pills twice a day and find the topical gel most suitable. Cost and insurance coverage can also be issues; testosterone injections are the least expensive form.

Q: What monitoring is required?

A: The prostate gland must be monitored, both via digital rectal exam and testing of prostate-specific antigen. Hemoglobin and hematocrit are also assessed because in some men, testosterone-mediated stimulation of red blood cells is quite robust. If their hematocrit rises above the upper limit of normal the dose should be reduced.

Q: How do you define treatment success?

A: I rely more on symptomatic response than on blood tests. Testosterone levels vary based on mode of administration and timing of the test relative to timing of administration.

Q: What is known about long-term use and safety of testosterone therapy?

A: Testosterone treatment has been employed for more than 50 years now, primarily via injection, for the long-term treatment of men who have classic hypogonadism. There have been no problems. We still lack long-term data on the more recent use of testosterone in men with hypogonadism associated with aging. However, shorter-term studies have been promising. □

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