Late-Onset Male Hypogonadism:

Testosterone in the Aging Male

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Androgen deficiency in the aging male has become a concern. Serum testosterone does fall with age, resulting in an increased number of men > 50-years-of-age with lower serum testosterone than that of healthy 20- to 30-year-old men. The main question is whether it should be replaced and which men may benefit from such an intervention. Like all diagnoses of hypogonadism, it requires the presence of symptoms and biochemical evidence of testosterone deficiency. Late-onset hypogonadism (LOH) is when this occurs with advancing age. Such identified older men have been shown to benefit from testosterone replacement therapy (TRT).

Eldon's case

Eldon is an active 66-year-old man with a several year history of decreasing libido, intermittent spontaneous erectile dysfunction, some depression, abdominal weight gain and noticeable decreasing muscle strength. He and his spouse are questioning if he had andropause and if testosterone therapy would help. He has no chronic health issues and the only medication he takes regularly is low dose ASA. There has not been any loss of height nor fragility fracture. His serum testosterone is 11.2 nmol/L measured in the afternoon and repeated in the morning was 14.9 nmol/L. Testosterone replacement therapy (TRT) was not advised.

LOH

General screening of men for LOH is not recommended. Uncertainty of long-term outcomes would make the early detection and treatment of men without symptoms of questionable value. But it should be looked for in symptomatic men (Table 1). Serum testosterone should then be measured (Figure 1). It should be measured in all men with osteopenia. Transient decreases of serum testosterone may occur with acute illness, flare-up of COPD, an alcoholic binge, or depression, so measuring the serum testosterone should wait until recovery and stable.

Certain medications, such as glucocorticoids and opiates, may lower the serum testosterone. Total serum testosterone should be measured by a reliable assay in the morning (due to diurnal variation). If > 12 nmol/L, it does not require TRT. If < 8 nmol/L, TRT should be considered in the appropriate clinical context. I would still repeat and confirm with a test that compensates for changes in sex hormone-binding globulin (SHBG). If between 8 nmol/L and 12 nmol/L, it should be repeated; ideally, after two to four weeks in the morning and after any ongoing illness has resolved or stabilized. If consistently in that range, a trial of TRT could be considered in the appropriate clinical context. A very low

Table 1

Symptoms and signs associated with androgen deficiency in older men

Symptoms/signs suggesting androgen deficiency	Less specific symptoms and signs associated with androgen deficiency
• Reduced libido	• Decreased energy, motivation
• Decreased ejaculate volume	• Depressed mood, dysthymia
• Fewer spontaneous erections	• Poor concentration/memory
• Gynecomastia	• Sleep disturbance/sleepy
• Loss of androgenic hair	• Mild anemia (normo normo)
• Small or shrinking tests	• Increased body fat (abdomen)
• Height loss, fracture, low BMD	• Decreased physical/work performance
• Lower muscle bulk and strength	• Erectile dysfunction with normal libido
• Hot flushes, sweats	

Table 2

Potential benefits of TRT in men with LOH

Body composition

- Increased muscle with improved physical function
- Decreased body fat, especially abdominal
- Increased BMD

Quality of life

- Improved libido, sexual function
- Improved well-being, sleep
- Improved mood

LOH: Late-onset hypogonadism

serum testosterone and non-elevated serum luteinizing hormone should generate consideration of pituitary disease and its investigation.

Total serum testosterone includes the unbound and bound components and the total is subject to changes in the binding proteins that may alter the total serum testosterone and thus its interpretation. For that reason, a repeat confirmatory test that compensates for changes in SHBG should be used. I prefer to use the free androgen index, especially in obese men. Men with severe obesity may require a true free testosterone measured by equilibrium dialysis to compensate for protein binding changes.

The correct diagnosis is important to select those men most likely to respond to TRT. As high as 50% of men found to have a low serum testosterone will have a normal serum testosterone on repeat testing at a later time. Thus, repeat testing of a low or borderline value should occur in all but obvious cases of hypogonadism. The major reason that TRT is discontinued is the lack of clinical effect. The nonspecific symptoms of testosterone deficiency may occur from comorbid disease or simple lifestyle factors.

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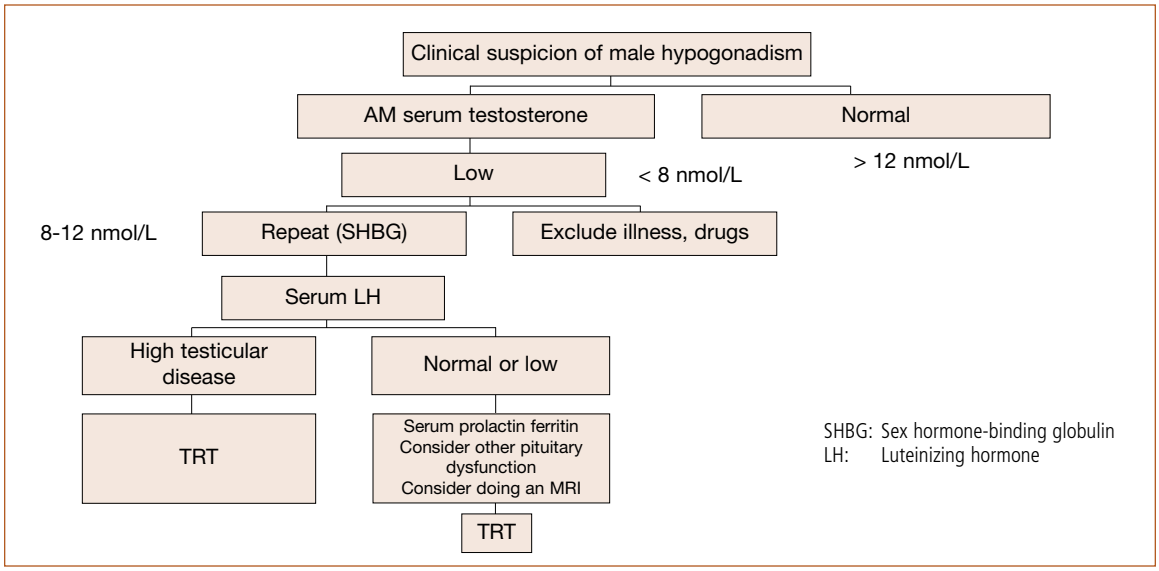

Figure 1. Schematic approach to the diagnosis of male hypogonadism.

Table 3

Contraindications to TRT

- Presence or suspicion of prostate or breast cancer, high risk of prostate cancer
- Erythrocytosis (hematocrit [Hct] > 52)
- Untreated sleep apnea

Table 4

Monitoring

- Hct at 3 and 12 months, then yearly
- PSA, digital rectal exam at 3 months, then yearly

Men with LOH respond to TRT in a manner similar to that of younger men. Men that have low testosterone symptoms but, in reality, have a normal serum testosterone, do not respond to TRT any different than to placebo. In such cases, TRT should not be given and other causes of the symptoms should be considered. Men with true LOH generally show improvement in the somatic and sexual symptoms they have and improvement in body composition (Table 2). Some CV risk factors improve or at least do not worsen. Long-term outcomes such as decreased fractures, decreased CV events, or decreased incidence of frailty are not available. Thus, the indication for TRT is to improve symptoms (quality of life) with a response dictating continued TRT. Because of a placebo effect, any response needs to be maintained. Absence of a response or continued response by three to six months dictates discontinuation of TRT. The presence of a fragility fracture with LOH would suggest continued TRT. A partial response of erectile dysfunction may require the addition of a phosphodiesterase-5 inhibitor.

The non-specific symptoms of testosterone deficiency may occur from comorbid disease or simple lifestyle factors.

To date, there is no evidence that TRT increases the risk of prostate cancer (or increases the grade of prostate cancer) or symptomatic benign prostate hyperplasia. It may increase the hematocrit, which is beneficial in a man with mild anemia, but if too high, may be detrimental. The absolute and relative contraindications for TRT are shown in Table 3. Suggested monitoring for the risks of TRT are in Table 4.

TRT may be used in any of the intramuscular, oral, or transdermal preparations of testosterone; oral 17 α-alkylated androgen preparations should never be used because of the risk of liver toxicity. Dx

Resources
1. Bhasin S, Cunningham GR, Hayes FJ, et al: Testosterone Therapy In Adult Men With Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2006; 91(6):1995-2010.
2. Wang C, Nieschlag E, Swerdloff R, et al: Investigation, Treatment, And Monitoring Of Late-Onset Hypogonadism In Males: ISA, ISSAM, EAU, EAA, and ASA Recommendations. J Androl 2009; 30(1):1-9.
3. Shabsigh R, Crawford ED, Nehra A, et al: Testosterone Therapy In Hypogonadal Men And Potential Prostate Cancer Risk: A Systematic Review. Int J Impot Res 2009; 21(1):9-23.
4. Bhasin S, Woodhouse L, Casaburi R, et al: Older Men Are As Responsive As Young Men To The Anabolic Effects Of Graded Doses Of Testosterone On The Skeletal Muscle. J Clin Endocrinol Metab 2005; 90(2):678-88.

Take-home message

- LOH may be considered in appropriately symptomatic older men and tested with a morning serum testosterone by a reliable assay
- High or low levels of serum testosterone may be useful for the presence or absence of the diagnosis of LOH; all low values, especially borderline ones, require repeat measurement, best done with an assay that compensates for changes in binding proteins
- Be aware of medical and pharmacological causes of a low serum testosterone
- Treatment is for the improvement of symptoms; screening or treating asymptomatic men is not indicated in the absence of valid long-term outcomes
- A trial of TRT of any formulation may be used, continued with a clinical response and discontinued in the absence of a clinical response, except for the ongoing treatment of osteopenia

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