Acta Biomed 2010; 81; Suppl 1: 85-88

Review

Clinical and laboratoristic strategy in late onset hypogonadism

Francesco Lombardo, Cristiana Lupini, Antonella Meola, Francesco Pallotti, Loredana Gandini, Andrea Lenzi

Dipartimento di Fisiopatologia Medica – Università di Roma "Sapienza"

Abstract. Aging in men is associated with a gradual and progressive decline in serum total testosterone concentrations as a result of primary testicular and secondary hypothalamic-pituitary dysfunction. Androgen secretion does not cease, it gradually decreases but usually continues at some level. A diagnosis of hypogonadism should rely on both symptoms and laboratory tests. Declining testosterone levels with age are primarily due to changes in the testes, which show decreases in the number of Leydig cells, the activity of enzymes that contribute to testosterone production, and the ability to increase testosterone production in response to gonadotropin stimulation. Physicians should also take note of symptoms indicatine age-related complaints. Validated questionnaires can be helpful. Administration of androgens appears to improve positive aspects of mood. Hypogonadism is also a risk factors for osteoporosis. Aging is associated with a reduction in sexual activity. T and DHT appear to be essential for development and maintenance of libido or sexual desire, and they probably have a direct effect on penile erections. Testosterone replacement therapy (TRT) affects nocturnal erections and penile rigidity in hypogonadal males. It is not known whether TRT will increase the risk of prostate cancer. The influence of T on prostate carcinogenesis and other prostate outcomes remains poorly defined. The aim of treatment for hypogonadism is to normalize serum testosterone levels and abolish symptoms or pathological states that are due to low testosterone levels. The exact target testosterone level is a matter of debate, but current recommendations advocate levels in the mid-lower normal adult range. (www.actabiomedica.it)

Key words: Aging male, testosterone, Leydig, Osteoporosis, Testosterone replacement therapy (TRT), prostate cancer

Aging in men is associated with a gradual and progressive decline in serum total testosterone concentrations as a result of primary testicular and secondary hypothalamic-pituitary dysfunction. Many symptoms and signs associated with aging in men, including muscle atrophy and weakness, osteoporosis, reduced sexual functioning, and increased fat mass, are similar to changes associated with testosterone deficiency in young men. Unfortunately, symptoms of testosterone deficiency in older population are difficult to distinguish from consequences of aging. Both are associated with decreased muscle tissue mass and strength, increased fatigue, increased body fat mass (particularly intra-abdominal fat), decreased bone mass and an increased incidence of osteoporosis and fractures, loss of libido, erectile dysfunction (ED), impaired cognitive function, and depression. For example, in frail older men in rehabilitation units or living in nursing homes, low testosterone levels are more prevalent than in community-dwelling men of the same age, and average free testosterone levels are usually below the normal range for healthy young men (1-2).

Only in the past few decades has attention turned to 'andropause,' or hormonal changes in aging men.

The term andropause is inaccurate because men do not have menses and because androgen secretion does not cease, it gradually decreases but usually continues at some level.

A diagnosis of hypogonadism should rely on both symptoms and laboratory tests. For initial diagnosis, a morning, non-fasting, serum total testosterone level is often used. Differential diagnosis and exclusion of other disorders requires taking a careful patient history, performing a physical examination and psychiatric evaluation, and conducting laboratory tests.

With increasing age, men experience a gradual decrease in circulating bioavailable testosterone. Some Authors estimate the decrease of about 1% per year, which probably begins at age 30. It does not occur evenly, and it also shows great variation among individuals. As part of the aging process, reduced secretion of testosterone come with a drop in other hormones including melatonin, growth hormone, dehydroepiandrosterone (DHEA), testosterone, and insulin growth factor-1 (IGF-1) (3-5).

Declining testosterone levels with age are primarily due to changes in the testes, which show decreases in the number of Leydig cells, the activity of enzymes that contribute to testosterone production, and the ability to increase testosterone production in response to gonadotropin stimulation

Luteinizing hormone (LH) levels increase slightly with aging (6). However, the majority of hypogonadal men over age 60 have low or inappropriately normal LH levels. Testicular responses to recombinant human chorionic gonadotrophin (hCG) are reduced (23).

Older men with low T levels typically have abnormal LH pulse frequency and reduced pulse amplitude, suggesting hypothalamic dysfunction (7-9). Testosterone production also is influenced by a negative feedback system involving gonadotropin-releasing hormone and luteinizing hormone. Levels of both of these hormones increase with age, but do not increase enough to overcome declining testosterone levels. Serum levels of sex hormone-binding globulin (SHBG) also increase with age (10, 11).

SHBG is the major serum carrier of testosterone, and testosterone bound to SHBG is not bioavailable. The concomitant decrease in testosterone production and increase in SHBG levels result in a more profound decline in bioavailable testosterone than in total testosterone in aging men

SHBG levels are affected by several conditions and are inversely correlated with increased total body fat and with subcutaneous and visceral adiposity.

Levels also vary inversely with hyperinsulinism in non-diabetic subjects. They seem to be an indicator of general adiposity rather than an index of altered insulin/glucose homeostasis in morbidly obese subjects. Estrogen, hyperthyroidism, some anticonvulsants, a high-phytoestrogen diet, hepatic cirrhosis, and aging increase SHBG levels (12-16).

Thus the decrease in testosterone levels with aging seem to be correlated with changes at all levels of the hypothalamic-pituitary-testicular axis. Moreover, with advancing age there is a reduction in androgen receptor concentration in some target tissues and this may contribute to the clinical syndrome.

Physicians should also take note of symptoms indicating age-related complaints. Validated questionnaires can be helpful. Administration of androgens appears to improve positive aspects of mood and reduce negative aspects of mood such as irritability in young, hypogonadal men (17), and improvements in mood are usually observed in clinical trials involving mostly middle-aged men (18). The Aging Male's Symptoms Scale (AMS) is an instrument consisting of 17 items that assess "age-related complaints" on a five-point scale and measures changes as symptom progression or treatment-related improvements (19).

Hypogonadism is also a risk factors for osteoporosis. In fact, Amory et al. (20) observed very significant changes in bone mineral density in men 65 and older with baseline T levels <350 ng/dl when treated for 3 years with T enanthate (150 mg/2 weeks).

It is estimated that skeletal muscle mass decreases 35% between the ages of 20 and 80. This impairment can result in loss of mobility, falls and fractures, loss of independence, and depression. This sarcopenia associated with loss of strength leads to impairment of physical function, such as ability to arise from a chair, climb stairs, maintain balance.

More recent studies have demonstrated that T caused dose-dependent increases in skeletal muscle mass in aging men.

Table 1.

Oral T. undecanoate		40 mg b.i.d./t.i.d.
Transdermal	T. patch	2–5 mg/daily
	T. gel, 25 or 50 mg	50–100 mg/daily
	T. gel, 25 or 50 mg	50–100 mg/daily
	T. gel, 50 mg	50–100 mg/daily
Intramuscular	T. enanthate 250 mg	1 vial every 2–3 weeks
	T. undecenoate	1 vial every 10–14 weeks
Buccal T.	Tablets 30 mg	1 tab. b.i.d.

Aging is associated with a reduction in sexual activity. T and DHT appear to be essential for development and maintenance of libido or sexual desire, and they probably have a direct effect on penile erections. Testosterone replacement therapy (TRT) affects nocturnal erections and penile rigidity in hypogonadal males.

It is not known whether TRT will increase the risk of prostate cancer. The influence of T on prostate carcinogenesis and other prostate outcomes remains poorly defined. Some studies even indicate that T can act as a tumour promoter also at physiological levels (21) Other studies show that TRT is safe when administered only to restore physiological levels of androgen. According to Zitzmann et al (22) absolute contraindications are: Prostate cancer or suspected prostate cancer, cancer or suspected cancer of the male breast, criminal sexual behavior, unexplained polycythemia; untreated sleep apnea, severe urinary passage obstruction, severe heart disease. On the other hand, relative contraindications are: benign prostate hyperplasia, mild polycythemia, acne, competitive sports, unexplained liver and kidney disease, moderate urinary passage obstruction, unexplained gynecomastia.

Androgen action appears to be mostly maintained with aging, though this has not been studied extensively. However, androgen binding sites in the hippocampus, penile tissues, and genital skin are decreased in aging men and animals . It is recognized that shortening of the CAG repeat in the androgen receptor increases androgen action, but it is not likely that this, per se, changes with aging. T is metabolized to dihydrotestosterone (DHT) and to estradiol in tissues that have 5α-reductase activity and/or aromatase activity. DHT is a very potent androgen at the tissue level. It contributes most of the androgenic effects in genital tissues, accessory sex organs and hair follicles. Five-α-Reductase activity also is present in some areas of the brain and in bone.

The aim of treatment for hypogonadism is to normalize serum testosterone levels and abolish symptoms or pathological states that are due to low testosterone levels. The exact target testosterone level is a matter of debate, but current recommendations advocate levels in the mid-lower normal adult range (Nieschlag et al 2005). Truly physiological testosterone replacement would require replication of the diurnal rhythm of serum testosterone levels, but there is no current evidence that this is beneficial.

Monitoring during treatment

Within the first 3 months patients receiving TRT should be seen to evacuate the clinical response first of all to identify both adverse effects and clinical response. Safety monitoring parameters should include measurement of: Haemoglobin, Haematocrit, Serum PSA, Transaminases, Lipid profile, Breast examination, Transrectal prostate ultrasonography at baseline and after 6 months.

References

1. Rudman D, Mattson DE, Nagraj HS, et al. Plasma testosterone in nursing home men. *J Clin Epidemiol* 1988; 41: 231-6.
2. Kosasih JB, Abbasi AA, Rudman D. Serum insulin-like growth factor-I and serum testosterone status of elderly men in an inpatient rehabilitation unit. *Am J Med Sci* 1996; 311: 169-73.
3. Bain J. Epidemiology, evaluation and diagnosis of andropause. *Geriatrics & Aging* 2003; 6 (Suppl 10): 4-8.
4. Matsumoto AM. Andropause: clinical implications of the decline in serum testosterone levels with aging in men. *J Gerontol A Biol Sci Med Sci* 2002; 57: M 76-99.
5. Morales A, Lunenfeld B. International society for study of the aging male. Investigation, treatment and monitoring of late-onset hypogonadism in males. Official recommendations of ISSAM. *Aging Male* 2002; 5: 74-86.
6. Morley JE, Kaiser FE, Perry HM III, et al. 1997. Longitudinal changes in T, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metabolism* 1997; 46: 410-3.
7. Korenman SG, Morley JE, Mooradian AD, et al. Secondary hypogonadism in older men: its relation to impotence. *J Clin Endocrinol Metab* 1190; 71: 963-9
8. Deslypere JP, Kaufman JM, Vermeulen T, et al. Influence of age on pulsatile luteinizing hormone release and responsiveness of the gonadotrophs to sex hormone feedback in men. *J Clin Endocrinol Metab* 1987; 64: 68-73.
9. Tenover JS, Matsumoto AM, Clifton DK, et al. Age-related alterations in the circadian rhythms of pulsatile luteinizing hormone and T secretion in healthy men. *J Gerontol Med Sci* 1988; 43: M 163-9.
10. Gray A, Feldman HA, McKinlay JB, Longcope C. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. *J Clin Endocrinol Metab* 1991; 73: 1016-25.
11. Feldman HA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab* 2002; 87: 589-98.
13. Lovejoy JC, Smith SR, Bray GA, et al. Effects of experimentally induced mild hyperthyroidism on growth hormone and insulin secretion and sex steroid levels in healthy young men. *Metabolism* 1997; 46: 1424-8.
14. Motta E. Epilepsy and hormones. *Neurol Neurochir Pol* 2000; 33 (Suppl. 1): 31-6
15. Adlercreutz H, Hockerstedt K, Bannwart C, et al. Effect of dietary components, including lignans and phytoestrogens, on enterohepatic circulation and liver metabolism of estrogens and on sex hormone binding globulin (SHBG). *J Steroid Biochem* 1987; 27: 1135-44.
16. Selby C. Sex hormone binding globulin: origin, function and clinical significance. *Ann Clin Biochem* 1990; 27: 532-41.
17. Margolese HC. The male menopause and mood: T decline and depression in the aging male - Is there a link? *J Geriatr Psychol Neurol* 2000; 13: 93-101.
18. Wang C, Alexander G, Berman N, et al. T replacement improves mood in hypogonadal men - a clinical research study. *J Clin Endocrinol Metab* 1996; 81: 3578-83.
19. Moore C, Huebler D, Zimmermann T, Heinemann LA, Saad F, Thai DM. The Aging Male's Symptoms scale (AMS) as outcome measure for treatment of androgen deficiency. *Eur Urol* 2004; 46: 80-7.
20. Amory JK, Watts NB, Easley KA, et al. Exogenous T or T with finasteride increases bone mineral density in older men with low serum T. *J Clin Endocrinol Metab* 2004; 89: 503-10.
21. Bosland MC. The role of steroid hormones in prostate carcinogenesis. *J Natl Cancer Inst Monogr* 2000; 27: 39-66.
22. Zitzmann M et al Pharmacogenetics of testosterone replacement therapy. *Pharmacogenomics* 2009; 10 (8): 1341-9.
23. Harman SM, Tsitouras PD. Reproductive hormones in aging men. I. Measurement of sex steroids, basal luteinizing hormone, and Leydig cell response to human chorionic gonadotropin. *J Clin Endocrinol Metab* 1980; 51: 35-40.

Accepted: December 18th, 2009
Correspondence: Dr. Francesco Lombardo
Dipartimento di Fisiopatologia Medica
Università di Roma "Sapienza"
E-mail: francesco.lombardo@uniroma1.it