Ranjan Arianayagam
Mohan Arianayagam
Shaun McGrath
Prem Rashid

Androgen deficiency in the aging man

Background
Androgen deficiency in the aging man is an area of considerable debate because a gradual decline in testosterone may simply be part of the normal aging process. However, there is an alternative view that androgen deficiency in the aging man may constitute a valid and underdiagnosed disorder.

Objective
To discuss the aetiology, clinical features, diagnosis and management of androgen deficiency in the aging man.

Discussion
Late onset hypogonadism has clinical features that overlap with both normal aging and some pathological conditions. It can only be diagnosed on the basis of both suggestive clinical features and clear biochemical evidence of testosterone deficiency. In this group of patients medication may play a role.

Keywords: aging; hypogonadism; androgens; testosterone

The issue of androgen deficiency in the aging man continues to generate considerable discussion because a gradual decline in testosterone may be only a part of the normal aging process and may not represent a true clinical entity.[1–3] However, there is a possibility that androgen deficiency in the aging man constitutes a valid disorder.[4] From data available on diagnostic criteria of symptoms and low testosterone levels, the prevalence of symptomatic androgen deficiency may be up to 12% in males older than 40 years of age.[5]

Various interchangeable descriptions have been used in the literature. These include 'testosterone deficiency', 'andropause' and 'late onset hypogonadism' (LOH). The latter is in accordance with the 2008 European guidelines[6] and will be the term used in this article. Late onset hypogonadism may be defined as 'a clinical and biochemical syndrome associated with advancing age and characterised by typical symptoms and a deficiency in serum testosterone levels'.[6] Throughout this article 'total testosterone' is referred to as 'testosterone', any other forms (eg. free, bound) will be specified.

Androgen physiology

Ninety-five percent of androgen production occurs in the testes. Testosterone is synthesised and secreted by testicular Leydig cells under the influence of pituitary luteinising hormone (LH) and local paracrine factors.[7] Two percent of testosterone circulates freely, 44% is bound to sex hormone binding globulin (SHBG) with high affinity, and 54% to albumin with lower affinity.[7] It has multiple physiological effects including involvement in spermatogenesis, testicular function, hair growth, bone density, muscle mass and distribution, libido and secondary sexual characteristics.[7] Testosterone is converted through 5-alpha reduction, mainly at the target organ level, to its biologically active form of dihydrotestosterone (DHT).[7] The hypothalamic-pituitary-gonadal axis is illustrated in *Figure 1*.

Aetiology of late onset hypogonadism

Androgen levels decrease by approximately 1% per year after the age of 40[8] and the levels of SHBG increase with age, resulting in reduced bioavailable (free) testosterone.[9] Low testosterone levels in the aging male can be associated with chronic conditions such as obstructive sleep apnoea, depression, obesity, chronic obstructive pulmonary disease, type 2 diabetes mellitus, rheumatoid arthritis, haemochromatosis, and renal or liver disease.[10–12]

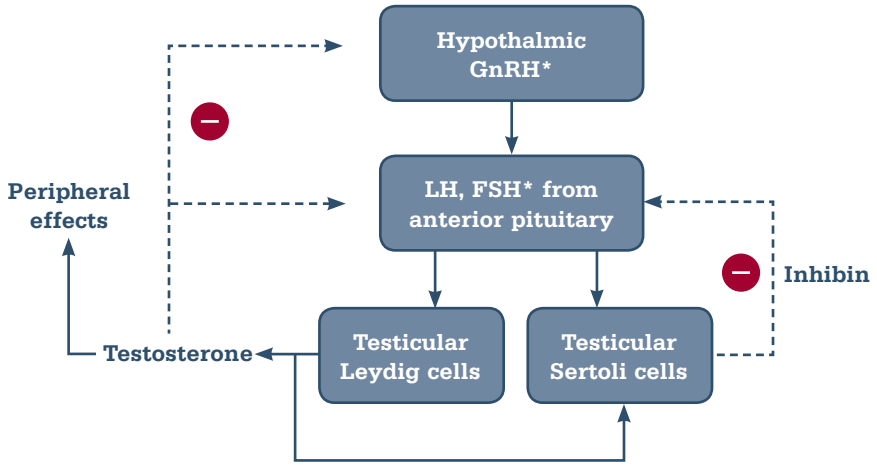

Figure 1. Testosterone production – the hypothalamic-pituitary-gonadal axis. Testosterone undergoes 5-alpha reduction into dihydrotestosterone in the peripheral tissues

* GnRH: gonadotropin releasing hormone; FSH: follicle stimulating hormone

Furthermore, several commonly used drugs (eg. opiates, glucocorticoids, and gonadotropin-releasing hormone agonists such as finasteride, oestrogen, spironolactone and ketoconazole) will reduce testosterone secretion and/or its effects.[13] There may also be variations in the sensitivity of the testosterone receptor itself which may explain why, at the same testosterone level, some men can be asymptomatic while others have symptomatic LOH.[14]

Diagnosis and presentation

Many features of aging parallel the features of hypogonadism in younger males.[15] In addition, among aging male patients, there is considerable overlap between the symptoms and clinical examination findings of testosterone deficiency and the features of normal aging.[13] Common features of LOH, taken from international guidelines, are summarised in *Table 1*. General practitioners will notice that this list includes clinical features that are also present in other common conditions such as depression. The clinical picture varies according to factors that include age, androgen sensitivity and medical comorbidities.[10] Decreased libido is the most common symptom of LOH and findings of physical examination are usually unremarkable.[4]

Diagnosis of LOH requires two elements: the presence of at least one clinical symptom (*Table 1*) and biochemical confirmation of low total testosterone levels.[6] The available evidence does not support the use of population based screening for testosterone deficiency or the testing of testosterone levels in asymptomatic individuals presenting with unrelated health complaints.[10] Accordingly, biochemical testing should only be used if suggestive symptoms are present. Various validated symptom scale questionnaires exist but have limited clinical use.[6,9,16]

Diagnostic difficulties also arise from uncertainty about the correct reference range to apply to various age groups, and there are reliability issues with various testosterone assays.[15] The reference range generally used for the diagnosis of LOH is the healthy young adult male range.[17] The Endocrine Society of Australia defines hypogonadism as a morning testosterone level of <8 nmol/L in the presence of any LH level, or a level of 8–15 nmol/L with a high LH level, which indicates Leydig cell failure.[18] Prolactin should be measured if the total testosterone is <5.2 nmol/L. Australian clinical guidelines dictate that testosterone replacement for LOH is only indicated when levels are below this range.[18] Timing of assays is important, as acute illness may result in a transient decrease in testosterone levels, which may necessitate repeat measurement.[6] An abnormal result requires the morning blood sample to be repeated to account for circadian variation. A normal result does not need to be repeated.

Luteinising hormone should also be measured to distinguish between primary and secondary hypogonadism.[6] Measurement of free testosterone is too inaccurate in commercially available assays to be helpful in clinical practice. Measurement of SHBG is sometimes helpful in determining who should be treated when the total testosterone is mildly reduced and the LH normal. However, correct identification of all men who are truly testosterone deficient (and who should respond to treatment) remains impossible without empirical validation of these measures against independent biological markers of androgen action.[19] Bone density should be measured when testosterone deficiency has been confirmed.[19] Rebate is available under Medicare in the hypogonadal patient.

Therapy risks and efficacy

Testosterone replacement has benefits in patients with proven androgen deficiency – men with both suggestive clinical symptoms and biochemical testosterone deficiency.[6]

Studies that have considered the risks and efficacy of long term testosterone replacement therapy in LOH have produced inconsistent results. A recent systematic review[10] found inconsistent evidence of the benefits of testosterone therapy on bone mineral density, sexual function, depression and cognition. However, it found that therapy did confer significant benefits through increased lean body mass, reduction in fat mass and improved grip strength. Other research suggests an improvement in lower urinary tract symptoms (LUTS) in men with LOH.[20] Evidence on improved physical function is inconsistent.[10]

In terms of adverse events, therapy was associated with a significant increase in obstructive LUTS and increased haematocrit.[10] Therefore, bladder outflow obstruction secondary to benign prostatic enlargement should be treated before testosterone supplementation.[17]

Table 1. Clinical features of LOH[6]
Decreased libido
Decreased muscle mass and strength
Decreased bone mineral density and osteoporosis
Decreased vitality
Depressed mood
Increased body fat

Table 2. Testosterone replacement in Australia (MIMS)

Formulation	Dosing	Advantages	Disadvantages
Testosterone undecanoate – oral (Andriol™, Andriol Testocaps™)	• 120–160 mg/day for 2–3 weeks, then 40–120 mg/day in 2 divided doses; needs to be taken with food as the testosterone is esterified to lipids and enters the circulation via the lymphatics	• Oral administration	• Testosterone levels vary
Testosterone patch (Androderm™)	• 5 mg patch/24 hours – titrate to serum testosterone, dose varies from 2.5–7.5 mg/24 hours	• Easy to apply • Diurnal variation	• Skin irritation
Testosterone enanthate – depot (Testosterone enanthate injection™)	• Intramuscular injection – 250 mg every 2–3 weeks	• Flexible dosing	• Significant variation in testosterone levels • Painful injection
Testosterone propionate (30 mg) Testosterone phenylpropionate (60 mg) Testosterone isocaproate (60 mg) Testosterone decanoate (100 mg) (Sustanon™)	• Intramuscular injection – 100 mg every 2 weeks, or 250 mg every 3 weeks	• Flexible dosing	• Significant variation in testosterone levels • Painful injection
Testosterone gel (Testogel™)	• 50 mg/day – titrate to serum testosterone	• Easy application	• Potential for transfer to others
Testosterone pellets	• Subcutaneous insertion – titrate 1–6 pellets (each pellet 100 mg)	• Infrequent application	• Pellet extrusion • Wound infection.
Long acting testosterone undecanoate injection (Reandron 1000™)	• 1000 mg at week 1 and week 6 then every 12 weeks	• Infrequent application	• Large volume to inject • Cannot be removed if complication occurs

Note: Trade names in parentheses

Although there is some doubt about its impact on prostate cancer recurrence and progression,[18] and its role in the progression of subclinical prostate cancer, the prevailing view is that testosterone replacement is contraindicated in patients with locally advanced and metastatic prostate cancer,[17,22] and is relatively contraindicated in men who are at high risk of developing prostate cancer (eg. strong family history).[6]

There is also concern that testosterone therapy may increase the risk of, or worsen, erythrocytosis, sleep apnoea, cardiovascular disease and thromboembolic events.[13,17] In particular, the potential to cause disordered sleep and breathing, and polycythaemia, is dose responsive.[19] Accordingly, European recommendations preclude treatment in patients with untreated sleep apnoea, significant polycythaemia or severe heart failure.[6,17]

Some patients with LOH may be using or have used alternative treatments such as growth hormone, dehydroepiandrosterone and testosterone cream or troches. There is currently no evidence of the safety or efficacy of these treatments in LOH.

The aim of testosterone replacement is to normalise testosterone levels. Testosterone replacement can be delivered in several ways (*Table 2*) and must be tailored to the individual patient. Concomitant lifestyle modifications may also be useful in improving overall wellbeing and may assist some symptoms (eg. mood and vitality) and can include weight loss, regular exercise, moderating alcohol intake and smoking cessation. An endocrinology opinion is required before treatment when the diagnosis is uncertain, in all cases of hypogonadotrophic hypogonadism (low testosterone and low LH), hypopituitarism, and in cases when there are relative contraindications to treatment.

Follow up

It is difficult to quantitatively monitor treatment effect as checking testosterone levels after short acting testosterone ester preparations is not valuable in determining efficacy or safety. Absorption of transdermal preparations is variable and checking a level after the introduction of treatment (in the morning after a testosterone patch placed at night or late morning after testosterone gel application in the morning) ensures adequate absorption in the individual is documented. A trough testosterone level after the fourth dose of long acting injectable testosterone undecanoate (Reandron 1000™) should be in the low-normal adult male reference range (10–15 nmol/L) or interval adjustment is necessary.

An improvement in nonspecific symptoms is not an accurate marker. Clinical improvement in libido, muscle function and body fat should be evident within 3–6 months, although bone density may take longer to improve. Failure to improve in specific symptoms may require cessation of treatment and further investigation into alternative pathologies.[6]

There may be local reactions depending on the testosterone delivery method. It is also essential to monitor erythrocytosis and testosterone dependent disease.[6] In particular, men must be monitored for prostate cancer. No

clear guidelines exist for men on testosterone replacement with regard to prostate cancer risk. It would be reasonable to follow current policies from the Urological Society of Australia and New Zealand and screen men over the age of 50 (or over 40 if they have a first degree relative with prostate cancer) with annual serum prostate specific antigen and digital rectal examination.[23]

Conclusion

While controversial, LOH may be present in up to 12.3% of the male population and there may be benefits to identifying and treating this group of men. Population based screening is not indicated. In the general practice setting it is useful to consider LOH in men with suggestive symptoms and investigate their androgen status. Careful consideration and counselling is required before commencing androgen replacement and, in particular, lower urinary tract symptoms and risk factors for prostate cancer need to be considered.

Summary of key points

- Diagnosis of LOH requires both the presence of at least one clinical symptom and biochemical confirmation of low total testosterone levels.
- Testosterone replacement confers benefits through increased lean body mass, reduction in fat mass and improved grip strength.
- Treatment is precluded in patients with untreated sleep apnoea, significant polycythaemia, severe heart failure, or significant lower urinary tract symptoms or obstruction.
- Testosterone replacement is contraindicated in patients with prostate cancer, and is relatively contraindicated in men who are at high risk of developing prostate cancer.
- An endocrinology opinion is required before treatment when the diagnosis is uncertain, in all cases of hypogonadotrophic hypogonadism, and in cases when there are relative contraindications to treatment.

Resources

- Additional information regarding the Urological Society of Australia and New Zealand's policy on PSA testing can be obtained at www.usanz.org.au/usanz-2009-psa-testing-policy
- The Andrology Australia website provides useful information on LOH: www.andrologyaustralia.org/pageContent.asp?pageCode=LOWTESTOSTERONE
- The European Association of Urology guidelines on LOH: www.uroweb.org/guidelines/online-guidelines.

Authors

Ranjan Arianayagam BA, LLB, MBBS(Hons), is an intern, Royal North Shore Hospital, Sydney, New South Wales. rari6999@uni.sydney.edu.au

Mohan Arianayagam BSc, MBBS, is Urology Fellow, Department of Urology, Jackson Memorial Hospital and The University of Miami, Florida, United States of America

Shaun McGrath MBBS(Hons), FRACP, is Consultant Endocrinologist, Department of Endocrinology, John Hunter Hospital, Newcastle, New South Wales

Prem Rashid MBBS, FRACGP, FRACS(Urol), PhD, is a urological surgeon and Conjoint Associate Professor, Department of Urology, Port Macquarie Base Hospital and University of New South Wales Rural Clinical School, New South Wales.

Conflict of interest: Prem Rashid has been a visitor to the American Medical Systems (AMS) US manufacturing facility undertaking a cadaveric dissection clinic and observed operative procedures by high volume implant urologists affiliated with AMS during that time. He also has acted as a consultant for Coloplast, Astra Zeneca, Hospira and Abbott pharmaceuticals. No commercial organisation initiated or contributed to the writing of the article.

References

1. Handelsman DJ. Testosterone: use, misuse and abuse. Med J Aust 2006;185:436–9.
2. Finucane TE. Men, androgen deficiency, and pharmaceutical promotion. Arch Intern Med 2009;169:88–9.
3. Page ST, Matsumoto AM, Bremner WJ. DHEA and testosterone in the elderly. N Engl J Med 2007;356:635–7.
4. Tostain JL, Blanc F. Testosterone deficiency: a common, unrecognized syndrome. Nat Clin Pract Urol 2008;5:388–96.
5. Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab 2007;92:4241–7.
6. 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. Eur Urol 2009;55:121–30.
7. Nieschlag E. Andrology: male reproductive health and dysfunction. Berlin: Springer, 2001.
8. Jones R. Human Reproductive Biology. 3rd edn. London: Academic press, 2006.
9. Morales A, Buvat J, Gooren LJ, et al. Endocrine aspects of sexual dysfunction in men. J Sex Med 2004;1:69–81.
10. 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;91:1995–2010.
11. Dhindsa S, Prabhakar S, Sethi M, et al. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab 2004;89:5462–8.
12. Zarrouf FA, Artz S, Griffith J, et al. Testosterone and depression: systematic review and meta-analysis. J Psychiatr Pract 2009;15:289–305.
13. Cunningham GR. Testosterone replacement therapy for late-onset hypogonadism. Nat Clin Pract Urol 2006;3:260–7.
14. Harkonen K, Huhtaniemi I, Makinen J, et al. The polymorphic androgen receptor gene CAG repeat, pituitary-testicular function and andropausal symptoms in ageing men. Int J Androl 2003;26:187–94.
15. Handelsman DJ, Liu PY. Andropause: invention, prevention, rejuvenation. Trends Endocrinol Metab 2005;16:39–45.
16. Martinez-Jabaloyas JM, Queipo-Zaragoza A, et al. Relationship between the Saint Louis University ADAM questionnaire and sexual hormonal levels in a male outpatient population over 50 years of age. Eur Urol 2007;52:1760–7.
17. Wang C, Nieschlag E, Swerdloff RS, et al. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. Aging Male 2009;12:5–12.
18. The Endocrine Society of Australia. Use and misuse of androgens. Available at www.endocrinesociety.org.au/posstat2.htm.
19. Liu PY, Swerdloff RS, Veldhuis JD. Clinical review 171: the rationale, efficacy and safety of androgen therapy in older men: future research and current practice recommendations. J Clin Endocrinol Metab 2004;89:4789–96.
20. Kalinchenko S, Vishnevskiy EL, Koval AN, et al. Beneficial effects of testosterone administration on symptoms of the lower urinary tract in men with late-onset hypogonadism: a pilot study. Aging Male 2008;11:57–61.
21. UBM Medica. MIMS. St Leonards: UBM Medica, Issue 1, 2010.
22. Morgentaler A. Testosterone therapy in men with prostate cancer: scientific and ethical considerations. J Urol 2009;181:972–9.
23. Urological Society of Australia and New Zealand. PSA testing guidelines, 2009. Available at www.usanz.org.au/usanz-2009-psa-testing-policy.

correspondence **afp@racgp.org.au**