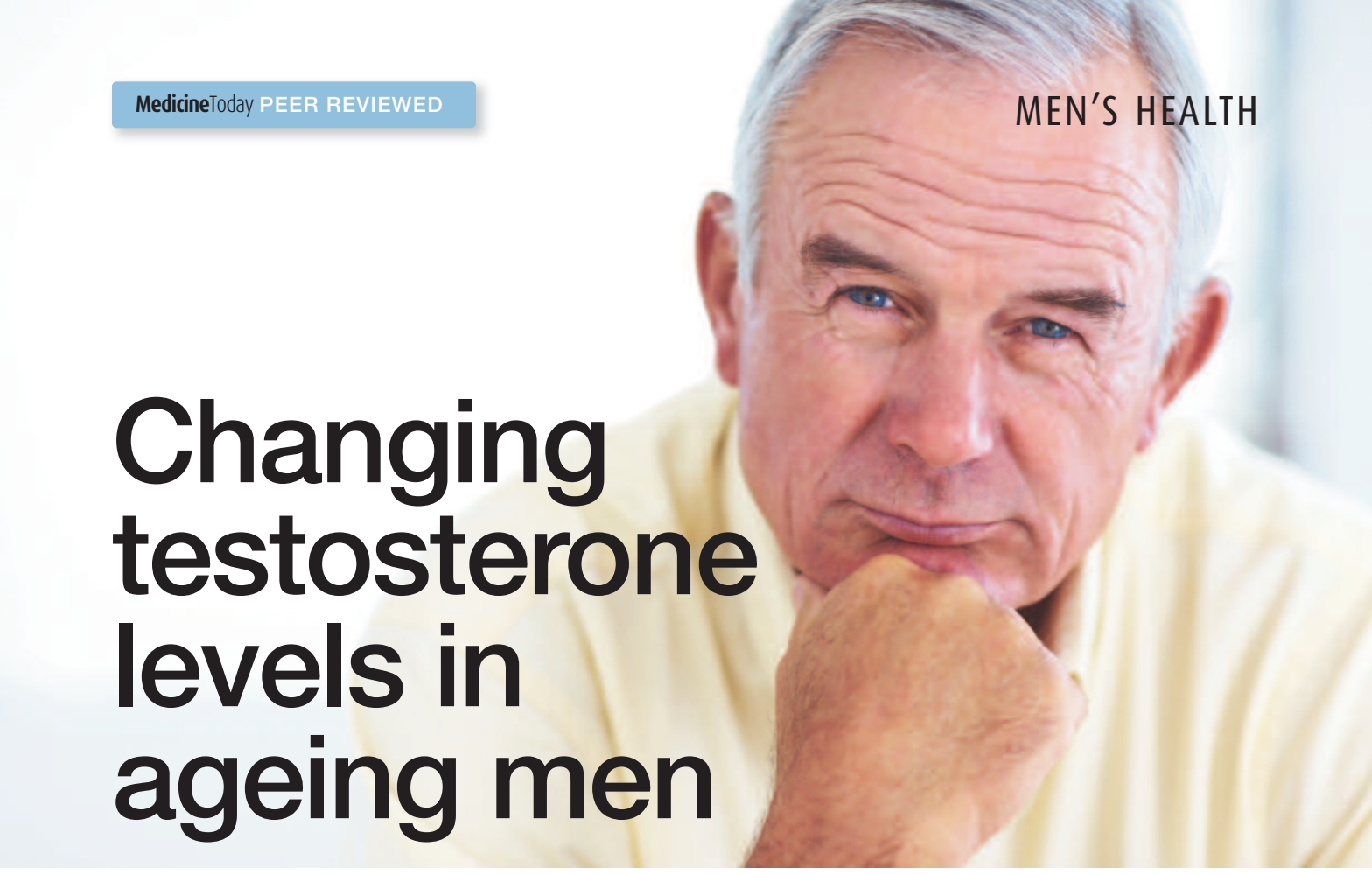

Changing testosterone levels in ageing men

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The role of age in decreasing testosterone levels and their effect on men are not well understood.

MedicineToday 2013; 14(1): 46-48

Recognition and treatment of men with hypoandrogenism or androgen deficiency (established on solid clinical and laboratory evidence of testicular or pituitary disease) is of proven benefit, irrespective of the men's age.[1] However, the entity of age-related hypoandrogenism – so-called 'partial androgen deficiency of the ageing male', 'andropause' or 'late-onset hypogonadism' – is less well understood. As a background to consideration of its diagnosis and treatment, the effects of ageing and related factors on testosterone levels in older men are reviewed in this article.

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ANDROGEN PHYSIOLOGY

Testosterone is the predominant androgen in men, with 95% of testosterone being secreted by testicular Leydig cells under the influence of luteinising hormone from the pituitary gland. Of the 6 mg of testosterone produced by men daily, most is inactivated in the liver and excreted by the kidneys.[2] A small amount of testosterone is converted to bioactive metabolites – 4% is converted to dihydrotestosterone via a 5α-reductase enzyme and 0.2% is converted to oestradiol via the aromatase enzyme. Dihydrotestosterone is a more potent androgen than testosterone and is active in the prostate and hair follicles in adult men. Oestrogen plays an important role in male bone health[3] and is also active in the brain.

LABORATORY MEASUREMENT OF TESTOSTERONE

There is no agreed clinical 'biomarker' of androgen sufficiency in men that equates to, for example, regular menses as a marker of oestrogen effect in women. This means that the diagnosis of testosterone deficiency relies heavily on clinical features (see the box on page 47) supported by laboratory evaluation.

Testosterone circulates predominantly in a bound form – 54% with a low affinity to albumin and other proteins, and 44% with

a high affinity to sex hormone-binding globulin – whereas about 2% remains unbound as free testosterone. The total testosterone level is the sum of these fractions.

It has been suggested that assessment of free testosterone better reflects biologically important 'tissue available' testosterone levels than total testosterone, although there are limited clinical data to support this proposal,[1,4,5] and total testosterone levels remain the key to diagnosis in treatment guidelines.[4,6] Estimates of free testosterone levels may be helpful in men who are obese or have diabetes, in whom the reduction in sex hormone-binding globulin seen with increasing adiposity may account for low-normal total testosterone values.[4,5,7] The 'calculated free testosterone' is derived from mathematical equations that consider total testosterone and sex hormone-binding globulin levels and assumed binding of testosterone to sex hormone-binding globulin and albumin.[8]

Although measurement of total serum testosterone levels remains the mainstay of diagnosing testosterone deficiency, the following points should be kept in mind.

- Reference intervals vary between laboratories because of differences in assay methods and/or the reference population of men (e.g. age and general or reproductive health).[9] Measurement of testosterone levels by mass spectrometry may become the 'gold standard' but this is not currently available in Australian clinical practice. Inconsistency between commercial immunoassays is significant (e.g. the lower reference limit calculated from the same set of young male samples varied from 7.5 to 12.7 nmol/L)[9] and their performance deteriorates rapidly in the zone of clinical interest, testosterone levels less than 11 nmol/L.[9,10]
- There is marked variability between individuals in normal serum testosterone levels (over a fourfold range). In addition, a man's testosterone levels may fluctuate widely within weeks to months necessitating repeated measurements (at least two).[11]
- Testosterone production is circadian with peak serum values occurring in the morning. Although ageing may attenuate this pattern, sampling for serum testosterone should take place in the morning (for practical purposes between 8 am and 10 am).[12]
- The question remains as to whether total testosterone reference ranges for older men should originate from healthy young men or from their healthy nonobese age-matched peers. The latter may be more appropriate but are not currently provided. This in turn would have implications for the prescription of testosterone.

CLINICAL FEATURES OF ANDROGEN DEFICIENCY IN THE ADULT MALE

General
- Reduced facial and body hair
- Gynaecomastia
- Decreased testicular volume*

Mood and cognition
- Low mood, irritability, anxiety
- Poor short-term memory, reduced concentration

Sexual function
- Decreased libido
- Erectile dysfunction†

Body composition
- Decreased skeletal muscle, increased body fat
- Osteopenia, osteoporosis

* Confirmed on clinical examination with reference to orchidometer.
† Erectile dysfunction is more commonly due to neurovascular factors.

CAUSES OF HYPOANDROGENISM

Primary

Congenital
- Klinefelter's syndrome
- Congenital anorchia
- Cryptorchidism
- Myotonic dystrophy

Acquired
- Trauma
- Torsion
- Bilateral orchidectomy
- Orchitis

Secondary

Congenital
- Idiopathic hypogonadotropic hypogonadism
  - Kallman's syndrome
  - Systemic disorders (e.g. Prader–Willi syndrome)

Acquired
- Organic lesions
  - Pituitary adenomas (e.g. prolactinoma, nonfunctioning tumour)
  - Pituitary apoplexy
  - Infiltrative (e.g. sarcoidosis, haemochromatosis, histiocytosis X)
  - Head trauma
  - Central nervous system irradiation
- Systemic disorders
  - Extreme exercise
  - Malnutrition (e.g. anorexia nervosa)
  - Obesity
- Pharmacological agents
  - Anabolic steroid misuse
  - Opiates

AGE-RELATED DECLINE IN SERUM TESTOSTERONE

Unlike oestrogen levels in women, which fall by 90% during the menopause transition, testosterone levels in men decline at a constant rate from their late 30s. A decline of 1 to 2% per year, as a function of age itself, has been well documented in a number of large cross-sectional and longitudinal studies, with the absolute rate of decline in total testosterone levels in longitudinal studies varying from 0.11 nmol/L to 0.38 nmol/L per year.[13-16] This equates to a 20 to 40% fall in serum

testosterone levels as men age from 20 to 80 years.[17]

As sex hormone-binding globulin levels rise with age, by about 1 to 2% per year, the decline in free testosterone level is even greater – about 2% to 3% per year.[13,14]

Ageing is associated with both impaired testicular and pituitary/hypothalamic function. Luteinising hormone levels increase with age in some men, suggesting a degree of primary testicular failure whereas in others low-normal serum luteinising hormone levels despite low serum testosterone levels suggest a degree of hypogonadotropic hypogonadism.[13,15] A careful clinical evaluation for known causes of primary and secondary testicular failure (see the box on page 47) is essential before attributing androgen deficiency to idiopathic or 'age-related' hypothalamo-pituitary failure.

CAUSES OF ANDROGEN DEFICIENCY IN THE AGEING MALE

Many of the causes of androgen deficiency in younger men are seen, and may be present for the first time, when the men reach older age (see the box on page 47). In particular, over half of all men with Klinefelter's syndrome (which affects about one in 550 men) remain undiagnosed[18] but may present in later life with, for example, an osteoporotic fracture. Testicular atrophy of any cause, hypothalamopituitary disease (e.g. tumours, hyperprolactinaemia, haemochromatosis) and drug effects (e.g. from opiates) causing hypoandrogenism require specific evaluation (e.g. anterior pituitary hormone assessment, serum iron studies and medical imaging) and treatment.

Modest, sustained and stable alcohol intake in healthy older men does not influence total testosterone levels but chronic alcoholic liver disease leads to a decrease in total testosterone levels. The effects of smoking on testosterone levels are uncertain, with both increases and decreases noted in current and former smokers.

The Massachusetts Male Aging Study has identified obesity as the most important determinant of total testosterone levels over time, with levels being 25% lower in obese men when compared with their nonobese counterparts.[13] Over nine years of follow up, obesity also predicted a greater decline in total testosterone and sex hormone-binding globulin levels with ageing.[19] In the European Male Ageing Study, overweight and obese men were three and seven times more likely, respectively, to have secondary hypogonadism (defined as a testosterone level of less than 10.5 nmol/L and a low/normal luteinising hormone level) than their healthy weight peers.[20]

Similar effects have been shown in cohorts of otherwise healthy Australian men.[7,21] This has important implications for Australia because 25.5% of men aged 55 to 64 years surveyed in the AusDiab survey were obese (defined as a body mass index of more than 30 kg/m^2).[22]

Men with diabetes and cardiovascular disease are also more likely to have lower serum testosterone levels,[23] as do men with significant depressive illness.[24] Of course, such associations do not indicate causation: low testosterone levels may result from a comorbidity that itself requires treatment.

Data from the Massachusetts Male Aging Study suggest that comorbidities and lifestyle influences are as likely as age to be associated with falling testosterone levels,[25] and it is likely that there is an interaction between these factors and age.[15]

INCIDENCE AND PREVALENCE OF ANDROGEN DEFICIENCY IN AGEING MEN

The incidence and prevalence of androgen deficiency in ageing men is unclear; estimates vary widely because of differing clinical and biochemical criteria and different study populations examined. Prevalence estimates are often based on the assumption that ageing men should be regarded as androgen deficient (synonymous with being deserving of testosterone replacement therapy) when their testosterone levels fall below the lower limit of the healthy young adult male reference range.[4] Small, short-term randomised trials of testosterone supplementation in ageing men have, to date, been inadequate to confirm or refute this hypothesis.[4]

The characteristics of the cohort of older men studied are crucial as many factors common in older men affect testosterone levels. Men recruited from medical clinics have lower testosterone levels than community-dwelling men, consistent with the observation that concomitant ill health, both acute and chronic, depresses testosterone levels by up to 30%.[26] Chronic illness, use of prescription medication, obesity or excessive alcohol intake were associated with a 10 to 15% reduction in serum testosterone level in men aged 40 years or more during seven to 10 years of follow up.[13]

TESTOSTERONE LEVELS IN HEALTHY AGEING MEN

It is important to note that, notwithstanding the small decline in serum testosterone level that occurs as a function of age, older men may maintain testosterone levels comparable with those of healthy young men.[27] In a recent Australian study of 325 men aged 40 years and over with self-reported very good or excellent health who had morning testosterone levels sampled nine times over three months, age per se was not associated with changes in serum testosterone levels. This suggests that comorbidities may be a more important determinant of biochemical androgen status.[21] MT

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References are included in the pdf version of this article available at www.medicinetoday.com.au.

COMPETING INTERESTS: Dr Allan has received educational support from and acted as a consultant to Bayer Australia and Eli Lilly Australia. Professor McLachlan has an equity interest in Monash IVF Pty Ltd.

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