New diseases

The andropause: fact or fiction?

Nicholas Burns-Cox, Clive Gingell

The menopause is a condition with a proven pathophysiological aetiology, leading in some women to unpleasant symptoms and bone loss over the ensuing years. The relatively sudden onset of ovarian failure causes amenorrhoea, infertility and oestrogen deficiency. There is no analogous process in the male. However, the term andropause is being increasingly used to describe a collection of symptoms including lack of energy, depression, decreased libido and erectile difficulties occurring in middle-aged or elderly men with a testosterone level at the lower end of normal range. The term andropause, like menopause, implies a state of hormone deficiency secondary to gonadal failure and the similarity of the two terms tends to give the andropause some unproved credibility. The incidence of erectile dysfunction increases with age and it is tempting to correlate this with the relative decrease in testosterone seen with age. It is therefore likely that androgen supplementation will be used to try and boost testosterone levels in middle-aged men with erectile difficulties who are not hypogonadal. There is, however, no evidence that the increase in erectile difficulties with age is related to decreasing testosterone levels in these eugonadal men. In this article we review the action of testosterone, the changes that occur with aging and the likely benefits and risks of supplementation.

Androgen production and aging

Testosterone is a C19 steroid and 0.24 µmol/day are secreted by the Leydig cells of the testicle. Its production is regulated by a negative feedback loop involving luteinising hormone and luteinising hormone-releasing hormone (LHRH), and forming the hypothalamic–pituitary–gonadal axis. Androgens are also secreted by the adrenal cortex in men (0.002 µmol/day), mainly as androstenedione but the quantities are of little clinical significance in comparison with the amount secreted by the testes. Testosterone is metabolised by the action of 5-alpha-reductase to to the biologically active androgen dihydrotestosterone and by aromatase activity to oestradiol. Secretion of testosterone begins in the foetus with a peak in the male at 12 weeks. There is another peak after birth and a low level equal to the female remains until puberty. At puberty increased pulsatile secretion of luteinising hormone leads to maturation of the Leydig cells and hence to increased testosterone production.

The action of the testosterone is firstly androgenic leading to the secondary sexual characteristics of the adult male. It also has an anabolic effect on receptive tissue leading to increased muscle bulk. The great majority of testosterone (80%) is bound to sex-hormone-binding globulin (SHBG) and to a lesser degree to albumin and cortisol-binding globulin. Only about 2% of total testosterone remains free, and it is this free portion that is thought to be of biological importance. There is debate as to which fractions are bioavailable but it is generally considered that the non-SHBG bound fraction is biologically active. The other measure of bioavailability is the Androgen Index which is the ratio of total testosterone to SHBG multiplied by 100, and is comparable to the free testosterone concentration. In males, there is a progressive decrease in testosterone levels with age (table 1). However, there is a concurrent increase in SHBG and therefore a greater decrease in the concentration of the free testosterone, which is reported to fall at a rate of 1% per year. The levels of dihydrotestosterone responsible for many of the actions of testosterone at the cellular level do not show a decrease with age. Although the decrease in testosterone is seen in healthy elderly men, a greater decrease in testosterone is seen in people with concomitant illnesses, which are very common in this age group.

There is evidence for some degree of testicular failure with advancing years. There is a decrease in the number of Leydig cells, impaired testicular perfusion, decreased steroid response to stimulation by beta-human chorionic gonadotropin, and a moderate rise in luteinising hormone levels. But there is also evidence that the decrease in testosterone is not all of primary testicular
Table 1  Influence of age on plasma testosterone, free testosterone and SHBG levels in man

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n</th>
<th>Testosterone (nmol)</th>
<th></th>
<th>SHBG (10^8 M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–29</td>
<td>105</td>
<td>23.1 ± 6.8</td>
<td>0.52 ± 0.15</td>
<td>4.2 ± 1.2</td>
</tr>
<tr>
<td>30–49</td>
<td>30</td>
<td>21.4 ± 7.3</td>
<td>0.40 ± 0.12</td>
<td>4.5 ± 1.4</td>
</tr>
<tr>
<td>50–59</td>
<td>24</td>
<td>17.0 ± 8.0</td>
<td>0.3 ± 0.13</td>
<td>5.5 ± 1.3</td>
</tr>
<tr>
<td>60–69</td>
<td>63</td>
<td>16.3 ± 6.6</td>
<td>0.27 ± 0.09</td>
<td>6.0 ± 1.4</td>
</tr>
<tr>
<td>70–79</td>
<td>63</td>
<td>16.5 ± 7.3</td>
<td>0.23 ± 0.08</td>
<td>7.3 ± 1.8</td>
</tr>
<tr>
<td>80–89</td>
<td>60</td>
<td>15.0 ± 5.7</td>
<td>0.17 ± 0.04</td>
<td>7.3 ± 2.0</td>
</tr>
</tbody>
</table>

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origin, the hypothalamic–pituitary–gonadal axis is also implicated. There is loss of the circadian rhythmicity of serum testosterone and increased sensitivity to negative feedback by the sex hormones on gonadotropin secretion. However, although there is a decrease in both total and free testosterone with age, the decrease is gradual and levels do not fall outside the normal range.

The variability between individuals is great and some elderly men have the same levels as young men, indicating that, unlike the ovary after the menopause, the testicle continues to secrete significant quantities of testosterone throughout life. In contrast to the post-menopausal ovary, the testicle continues gamete production and fertility persists life-long. Although a loss of fertility potential is not a typical finding in the elderly, with increasing age the sperm count is reduced due to a decrease in Sertoli cells and some decrease in motility is reported. Nevertheless, it seems that the zona-free hamster egg fertilizing capacity of the spermatozoa of elderly men is similar to that of young men. Although there is no sudden degeneration of the testicle analogous to that of the ovary, there is still a definite progressive decrease in the ability of the testes to produce spermatozoa and testosterone. The reduction of fertility in the elderly male rarely becomes of clinical significance. The decrease in testosterone secretion, however, is thought by some clinicians to be responsible for a group of symptoms ascribed to the andropause. These include nervousness, insomnia, hot flushes, mental and physical tiredness, irritability, reduced libido and erectile dysfunction. There are age-related changes, including decreased muscle mass and body hair, and disturbance of bone density and haemopoiesis have also been described as being due to testosterone deficiency.

Hormone replacement and supplements

The case for hormone replacement in men and children who are truly hypogonadal is generally accepted as beneficial. There is a variety of types and modes of administration of testosterone. The currently available compounds for androgen replacement are shown in table 2. Some of the early oral preparations (e.g., methyltestosterone and Danazol) are alkylated at the 17-

Table 2  Summary of the current available testosterone compounds for androgen replacement

<table>
<thead>
<tr>
<th>Type of testosterone</th>
<th>Name (Trade name)</th>
<th>Route of administration</th>
<th>Dose (mg)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone esters</td>
<td>Testosterone (Restandol)</td>
<td>oral capsules</td>
<td>40-120</td>
<td>once daily</td>
</tr>
<tr>
<td></td>
<td>Mesterolone</td>
<td>oral</td>
<td>25</td>
<td>3–4 times a day, reduced for maintenance every 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Testosterone propionate (Sustanon)</td>
<td>intramuscular injection</td>
<td>40</td>
<td>every 2 weeks</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Testosterone (Testop)</td>
<td>implant transdermal on scrotal skin only</td>
<td>600</td>
<td>6-monthly once daily</td>
</tr>
<tr>
<td>Testosterone</td>
<td>(Andropatch)</td>
<td>transdermal patch placed on any skin which does not cover a bony prominence</td>
<td>2.5</td>
<td>once daily</td>
</tr>
</tbody>
</table>
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hydroxy position, making the androgen more resistant to hepatic metabolism. However, these oral preparations often give unpredictable serum levels of testosterone and are more likely to cause side-effects, including cholestatic jaundice, and can rarely lead to hepatic failure (haemorrhagic liver cysts).26 For these reasons they are no longer available in the UK for androgen replacement. Alternatively, testosterone can be esterified and given as an oral agent daily (eg, mestosterone), a depot injection (eg, testosterone propionate) every two weeks or as a surgically implanted pellet every six months. These result in a sustained level of plasma testosterone. The availability of testosterone patches in the UK will provide a more physiological and ‘user friendly’ delivery system for patients requiring androgen replacement therapy and has been shown to be very effective.27

Support for hormone supplementation comes from trials on men who have moderately low testosterone levels, where low testosterone levels may be associated with increased body fat, decreased muscle mass, and increased age-related factors.5,22 Testosterone replacement therapy has been shown to improve lean muscle mass and improve health and vitality.5,22,23 The availability of depot testosterone formulations allows for the clinician to choose an injection schedule that may suit both the clinician and the patient.5,22,23

It is known that prostatic cancer is androgen-dependent and that the principal therapy of advanced disease is the removal of androgen stimulation.40 This is achieved by medical or surgical castration or the administration of anti-androgen, alone or in combination, so-called maximum androgen blockade.47 It is likely therefore that the administration of androgen to a man with prostate cancer will stimulate activity in what is mainly a hormone-dependent tumour. Certainly in the first 10–12 days after the administration of an LHRH analogue the serum testosterone rises and so-called ‘tumour flare’ results, in which bony metastases become more painful, paraplegia may be precipitated, and ureteric obstruction may occur.48 It is therefore likely that giving testosterone to men with latent cancer within the prostate may promote the development of active clinically evident disease. It is consequently of paramount importance to check the plasma prostate-specific antigen (PSA) level before the administration of testosterone to any man greater than 50 years and to check this regularly on...
Summary points

- Testicular failure analogous to monorchid ovarian failure does not occur
- Testosterone supplementation has no proven role in the treatment of erectile dysfunction in patients with a normal testosterone level
- The risks of subclinical hormone sensitive prostate cancer are unknown but credible
- Men over 60 years starting testosterone supplementation should have a transrectal ultrasound and biopsy and then be followed up with regular serum PSA levels

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Postgrad Med J 1997 73: 553-556
doi: 10.1136/pgmj.73.863.553

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