

## Testosterone prescribing in Australia

*There is yet no convincing evidence that testosterone therapy is safe or effective in counteracting any effects of ageing*

One of the most challenging and time-consuming aspects of medical practice is discussing with patients what they have gleaned from the Internet or popular lay publications. One topic of such discussion is the use of testosterone in male ageing, with public interest fuelled by persuasive publications like *Maximising manhood*,<sup>1</sup> *The testosterone revolution*<sup>2</sup> and *Male menopause*.<sup>3</sup> Much of the information gained from these books may seem to be very convincing, but is, at best, "ahead of the evidence". It is often difficult for doctors not to appear old-fashioned, ignorant or downright contrary when showing scepticism or advising caution in the face of such conviction.

In this issue of the Journal, Handelsman (page 419) has documented temporal and regional trends in testosterone prescribing in Australia.<sup>4</sup> He has shown increases in prescribing corresponding to popular promotion of androgen therapy in ageing. This rise has been particularly marked in Western Australia, coincident with the opening in that state of entrepreneurial clinics aimed at the ageing-male market.

There is no doubt that testosterone therapy benefits patients with documented hypogonadism associated with conditions such as Klinefelter's syndrome and hypopituitarism. Current prescribing guidelines allow for this, regardless of age. However, for the use of testosterone in men of middle age and older with borderline low serum levels of testosterone, the evidence for both efficacy and safety is yet to be established. The original description of the efficacy of testosterone therapy for the vicissitudes of age has been shown to be no more than a powerful placebo effect.<sup>5</sup>

Nevertheless, it would seem that those who espouse testosterone therapy in this setting have identified an expanding market. The Australian population is ageing: 28% of men are over the age of 50 and 12% over the age of 65 years. It is projected that by 2021, 4.0 million Australians will be over the age of 65, an increase of 1.7 million from today's estimate.<sup>6</sup> Together with a documented fall in testosterone level with age, where it is estimated that 20% of men over the age of 60 will have a testosterone level below the reference range, this predicts a large population of men as potential customers for androgen therapy.<sup>7,8</sup>

Although most studies have shown a gradual decline in testosterone level with age, the clinical consequences of this are not known. Conditions such as muscular frailty, loss of bone mass, cognitive decline and erectile dysfunction are also age related, but whether testosterone deficiency has a causal role is not clear. More importantly, it has not yet been established that testosterone therapy has any role in correcting these conditions.

It has been a widely held belief that androgen deficiency is a common and correctable cause of erectile dysfunction. However, in a cohort of 1455 men presenting with erectile dysfunction, we found that testosterone deficiency constituted a correctable cause

in only 3%.<sup>9</sup> All of those who responded to testosterone therapy for erectile dysfunction had a testosterone level < 7 nmol/L, well below the reference range of 11–37 nmol/L. The use of testosterone therapy in patients with normal or slightly depressed androgen levels seems to be of little benefit.<sup>10</sup>

A similar finding has been documented in the response of bone density to testosterone therapy. The largest and longest-term study in this setting examined testosterone treatment in 108 men aged over 65 years with a baseline testosterone level more than 1 standard deviation below the young adult mean (ie, < 16.5 nmol/L).<sup>11</sup> Lumbar spine bone density rose significantly only in those with a baseline testosterone level below the reference range (ie, below 10 nmol/L). Another, smaller study has shown a significant increase in lumbar spine density with androgen therapy in men with a baseline testosterone level < 12.1 nmol/L.<sup>12</sup>

Muscle mass and strength decrease with age, and it is tempting to link this with the decline of testosterone.

In hypogonadal men, testosterone therapy improves muscle strength. In men aged over 65 years, testosterone treatment leads to a fall in fat mass and a rise in lean body mass, together with a perception of increased strength. However, although a perception of

improved muscle function was reported, no objective change in measured physical function, such as walking or stair climbing, knee flexion or in muscle strength as measured by dynamometer, was demonstrated.<sup>13,14</sup>

The safety of sex hormone therapy in menopausal women, used widely for the last 60 years, has recently been scrutinised and reassessed.<sup>15</sup> Knowledge about the safety of sex hormone replacement in men is, by contrast, in its infancy. No studies have been conducted for long enough to identify the long term risks of androgen therapy in ageing. Because of lack of statistical power in studies, it is not known whether testosterone use will increase the incidence of androgen-dependent disease such as prostate cancer, although a sustained rise in prostate-specific antigen level has been observed.<sup>13</sup> Two other side-effects of testosterone treatment have been identified in short term studies, namely an increase in obstructive sleep apnoea and increased haematocrit and polycythaemia, both of which may have implications for cardiovascular risk.<sup>13,16</sup>

Handelsman has documented the effect on testosterone prescribing of entrepreneurial clinics aimed at the ageing-male market.<sup>4</sup> Daily, we see advertisements for similar commercial enterprises which deal in unregistered and/or unproven prescribing, including DHEA (dehydroepiandrosterone) or testosterone to men and women, progesterone cream, and lozenges of variable mixes of oestrogens, progestins and androgens. We should beware when entrepreneurial business ventures overtake evidence-based medicine.

What is needed now regarding testosterone therapy in ageing are large, long-term, prospective, randomised, placebo-control-

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## EDITORIALS

led studies to establish if there is, indeed, benefit for specific symptoms and to identify potential risks.<sup>17</sup>

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