COMMENTARY

“Manopause”

Changes do occur in men with age, and these may be amenable to androgen therapy

Stanley G Korenman
Associate Dean and
Professor of Medicine
Reproductive
Endocrinology
UCLA School of
Medicine
Los Angeles, CA 90095

Correspondence to:
Dr Korenman
skorenman@mednet.
ucla.edu

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The authors of this debate describe in detail the physiologic changes that occur in men with age. Although we may disagree with the interpretation of the reported findings, the main results are undisputed. With normal aging, which begins before the 4th decade, men have a progressive reduction in testosterone and bioavailable testosterone levels and an increase in SHBG. A relatively meager, if any, gonadotropin response to these sex hormone changes occurs. Levels of dehydroepiandrosterone, growth hormone, and insulinlike growth factor-1 also decline, which is more marked in the later years. Levels of estradiol remain unchanged, as do those of dihydrotestosterone, although blood levels of the latter are a poor reflection of the biologic activity of this predominantly intracellular hormone.

Starting in the late 20s, men undergo a progressive loss of muscle mass and an increase in fat mass, even those who maintain the same weight. Although cognitive function relating to knowledge and memory remains intact until an advanced age, perceptual speed declines steadily from the 4th decade. No convincing evidence indicates that the prevalence of clinical depression increases with age, but, in my experience, subclinical depression in men is both underdiagnosed and under-researched. Sociologic studies of men in developed countries suggest that a feeling of well-being remains constant until the 8th decade.

Beginning about age 50, the prevalence of erectile dysfunction begins to increase exponentially from 5% of the adult male population to more than 50% by age 80 years. Vascular, neurogenic, and psychogenic risk factors play a more important role than hypogonadism in its cause. This is supported by the fact that androgen therapy rarely reverses the condition in men who have organic risk factors, whereas sildenafil therapy is usually successful.

The semantic question, then, is whether we can attach a name to these changes analogous to the term “menopause” used in women. The term menopause has evolved to mean a brief period during which the ovaries complete their evolution and cease to ovulate. Before that time, there is a variable period termed the “perimenopause,” which some have divided into early and late phases. A few years after the last cycle, women enter the postmenopausal state. Men have no specific analogue to this narrowly defined menopause.

But changes with age in women do not relate solely to estrogen and progesterone levels. Muscle mass declines and fat mass increases from the 4th decade, just as in men. Alterations in cognitive function parallel those in men

exactly, as do changes in mood and sense of well-being. The typical menopause in women, therefore, encompasses sets of changes whose relationship to reproductive hormone concentrations is tenuous. In men, a similar set of changes occurs whose relationship to hypogonadism and somatotropin deficiency remains unknown.

I dislike the term “male menopause” because of its reference to cyclicity, and I have adopted “manopause” as an umbrella term to describe age-related alterations whose exact nature is still to be determined. Perhaps this will cut the Gordian knot.

This, then, leaves the question of how we should define and treat hypogonadism in men. No evidence exists to indicate that older men need less testosterone than younger ones. In fact, studies suggest that because androgens induce their own receptors, tissues receiving inadequate amounts of testosterone will be more resistant to its effects than those more fully supplied. If bioavailable testosterone is what tissues respond to, then hypogonadism can be defined as a bioavailable testosterone level 2 or more SDs below the mean for young men (2.3 nmol/L in our laboratory's assay). Fasting morning values below this level are common in men older than 50 and increase progressively with age.

Many physicians avoid treating men who have mild hypogonadism, fearing the promotion of prostate cancer growth. There is no evidence that this occurs. Because our interventions to treat prostate cancer are aimed at reducing testosterone levels, the fear is that such therapy will boost androgen levels in men who may have subclinical cancer. But if a man has benign findings on a digital rectal examination and normal levels of prostate-specific antigen, these fears are unfounded.

The other problems with androgen therapy are erythrocytosis, possible promulgation of sleep apnea, and a reduction of high-density-lipoprotein (HDL)-cholesterol levels. These can all be easily monitored. In my practice, I usually give a hypogonadal man a 3-month trial of testosterone and then let him and his family tell me whether it was beneficial. If it was, the therapy is continued. To ensure that high enough HDL-cholesterol levels are maintained and that patients get the full benefit of treatment, I insist that they begin a substantial exercise regimen, including strength training. Currently I offer either a skin patch or self-injection therapy. A gel that can be applied to the skin will soon be available. Each treatment brings the plasma testosterone and bioavailable testosterone concentrations to the range of young men. Many men benefit greatly from therapy.