For and against

The male menopause—does it exist?

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Be it "andropause" or "climacteric," do men undergo some kind of hormonal change akin to the female menopause? Adding to the growing debate about men's health, Duncan Gould and Richard Petty argue that some patients need investigation and treatment with testosterone. Howard Jacobs, however, is not convinced.

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FOR The term "male menopause" is inappropriate as it suggests a sudden drop in sex hormones such as occurs in women in the perimenopausal state. It is not an inevitability but may occur mainly in middle aged and elderly men when testosterone production and plasma concentrations fall. There seems to be a threshold plasma concentration below which symptoms may become apparent. Testosterone concentrations found to be critical for sexual functioning in men lie around 10.4 nmol/l (300 ng/dl), though there is variation between individuals.[1] While some have found that differences in plasma testosterone concentrations within the normal range in young healthy men do not correlate with differences in sexual activity and interest, others have shown that differences in the concentrations of the potent metabolite, dihydrotestosterone, do.[2,3]

Earlier this century the term "male climacteric" (from the Greek klimacter—the rung of a ladder) was used and is more appropriate as it suggests a decline and not a precipitous drop in hormones concentrations.[4,5] A landmark paper of 1944 accurately described symptoms, reversed by testosterone replacement but not by placebo, seen in men suffering from an age associated decline in testosterone concentrations.[5] Owing to the similarity between most of the symptoms in men and women the term "menopause" gained popularity and has unfortunately stuck.

An abnormally low concentration of testosterone (hypotestosteronaemia) may occur because of testicular dysfunction (primary hypogonadism) or hypothalamic-pituitary dysfunction (secondary hypogonadism) and may be congenital or acquired.

Endocrinology

In the ageing man reduction in testosterone concentration is due mainly to a decline in Leydig cell mass in the testicles or a dysfunction in hypothalamic-pituitary homeostatic control, or both, leading to abnormally low secretion of luteinising hormone with resultant low testosterone production. It is well recognised that with normal male ageing mean plasma testosterone concentrations decline, albeit with considerable variability between individuals and with a broad range in age related values.

Symptoms encountered in the male climacteric syndrome[5]

Depression, nervousness
Flushes and sweats
Decreased libido
Erectile dysfunction
Easily fatigued
Poor concentration and memory

Cross sectional and prospective studies show a decline that starts in early middle age and then progresses in a linear fashion.[6–11] Mirroring this decline in plasma testosterone concentration is an age associated increase in plasma concentration of sex hormone binding globulin, resulting in a more pronounced decline in the active or bioavailable testosterone moiety.[12–14] Concentrations of bioavailable testosterone decrease by as much as 50% between the ages of 25 and 75 years,[15] and it has been proposed that with respect to bioavailable concentrations as many as 50% of men over the age of 50 are hypotestosteronaemic when compared with peak early morning concentrations in young men.[16] With age there is a loss of hypothalamopituitary circadian rhythm, which may result in exaggerated falls in plasma testosterone concentrations by evening.

Effects of hypotestosteronaemia

A quantitative definition of hypotestosteronaemia has generally been accepted as 11 nmol/l (320 ng/dl) as only 1% of healthy men aged 20-40 will have a concentration below this limit.[17] Development of hypotestosteronaemia may be related to heredity as 60% of the variability of testosterone concentrations and 30% of sex hormone binding globulin may be due to genetic factors.[18] A history of orchitis, testicular trauma, or other pathology may be contributory. The presence of obesity is associated with lower concentrations of bioavailable testosterone,[19] and insulin concentrations have been found to be indirectly correlated with sex hormone binding globulin and testosterone concentrations.[20] With respect to lifestyle, excess intake of alcohol and

physical and psychological stress are all associated with lowered testosterone concentrations.[21 22]

Ageing is usually associated with a decline in sexual interest and potency.[23] This suggests such changes in sexual behaviour are androgen dependent but does not prove the case. Although erectile dysfunction in elderly men is often of non-hormonal aetiology, testosterone deficiency accounts for 6-45% of all cases.[24]

Affective symptoms have long been associated with hypotestosteronaemia: depressed mood is significantly correlated with low concentrations of bioavailable testosterone in older men.[14] Some longitudinal uncontrolled studies of hypotestosteronaemic men have shown that symptoms of depression, anger, irritability, sadness, nervousness, friendliness, sense of wellbeing, and energy levels significantly improved with androgen treatment.[25 26] There is evidence for mood disturbance being linked to hypotestosteronaemia and for testosterone replacement therapy being beneficial, but placebo controlled trials are needed to confirm these issues. Fatigue may occur with hypotestosteronaemia. During one prospective study symptoms significantly improved with supplementation and decreased during androgen withdrawal, another showed significant improvements in energy levels and tiredness.[26]

Male ageing is associated with an increase in central and upper body fat deposition and reduced muscle mass and strength. This could be explained by an age associated decline in growth hormone concentrations, which itself is associated with an increase in sex hormone binding globulin and therefore a reduction in bioavailable testosterone.[27] There is consensus that testosterone supplementation in hypotestosteronaemic men improves fat free mass, muscle bulk, and strength.[28 29] Profound hypotestosteronaemia in younger men results in accelerated bone loss and osteoporosis.[30] In older men bioavailable testosterone concentrations are positively correlated with bone mineral density at the radius, spine, and hip,[31] and men with hypotestosteronaemia have been reported to be at increased risk of hip fracture.[32] Data on the effects of testosterone replacement therapy on bone metabolism in hypotestosteronaemic men are limited but suggest beneficial effects.[33]

Vasomotor disturbance and night sweats occasionally occur, their association with testosterone deficiency and relief by testosterone replacement being noted as far back as the 1930s.[4 5 34] Androgens also have an important role in the development of cognitive functioning, and in men strong correlations exist between testosterone concentrations and visuospatial abilities in certain domains.[35] Testosterone administration to ageing men has been shown to enhance certain visuospatial skills.[36]

Hypogonadism (like hypothyroidism) is a pathological state and is associated with several other comorbid factors such as the presence of cardiovascular risk factors (obesity, higher waist:hip ratio; higher concentrations of glucose, insulin, total cholesterol, low density lipoprotein cholesterol triglycerides, apolipoprotein B, fibrinogen, and plasminogen activator inhibitor I; and lower concentrations of high density lipoprotein cholesterol C and apolipoprotein A I), which are improved by testosterone administration.[37]

Investigations and treatment

Whatever the nomenclature, be it male menopause or climacteric or age related hypotestosteronaemia, men presenting with symptoms outlined in the box should be investigated. Investigations should include assessments of concentrations of plasma gonadotrophin, prolactin, and sex hormone binding globulin and early morning concentrations of testosterone. Men with hypotestosteronaemia with unequivocal signs and symptoms of androgen deficiency, and when reversible causes of testosterone deficiency and contraindications have been excluded, should be offered treatment with testosterone replacement therapy in line with the current WHO guidelines[38]—this is, however, a specialty beyond the scope of this article.

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AGAINST The normal menopause—that is, the final cessation of menstruation—is caused by primary ovarian failure. The oestrogen deficiency that results often causes vasomotor instability (flushing and sweating attacks), genital atrophy (vaginal dryness and discomfort), and bladder irritability, together with difficulties in cognition and loss of a general feeling of wellbeing. This climacteric syndrome, readily reversible by oestrogen treatment,[1] is obviously sex specific. We have to ask whether it really provides a helpful analogy for the features Jaques described as the penultimate age of man[2]:

> The sixth age shifts
> Into the lean and slipper'd pantaloon,
> With spectacles on nose, and pouch on side,
> His youthful hose well sav'd, a world too wide
> For his shrunk shank, and his big manly voice,
> Turning again toward childish treble, pipes
> And whistles in his sound.

In thinking about this we do well to consider how many of the changes in men as they pass from middle to old age should be attributed to the passage of years and how many to a decline in hormone concentrations. It is easy to see the attraction of an endocrine explanation because it raises the possibility of hormone treatment for symptoms that occur at this time of life. Careful review of the literature is at best suggestive. There is, I am afraid, still a way to go.

Firstly, what are the hormonal changes that occur in ageing men? Certainly gonadal function wanes: by the age of 80 years serum total testosterone concentrations have fallen to about 75% and free testosterone concentrations to about 50% of what they were at the age of 20.[3] The fall of free testosterone (that is, of the fraction that is biologically available to the tissues) is amplified by a difficult to explain but regularly observed increase in concentrations of the sex hormone binding globulin.[4] The fall in testosterone production is partly caused by testicular failure and partly by changes in pituitary gonadotrophin secretion (see review by Kaufman and Vermeulen[4]). The key difference from the menopause, however, is the gradual nature of the change in men compared with the precipitate fall of oestrogen concentration in women.[5]

Secondly, what are the biological changes that can be related to these endocrine alterations? The association of a symptom with a particular hormone concentration does not indicate causation. Therefore before attributing to testosterone deficiency the reduction in sexual activity, the decline in muscle bulk to which Jaques referred, and the decline in skeletal mineralisation that may all occur in elderly men, we are obliged to prove that hormone replacement therapy in physiological doses reverses these processes. We must, in other words, shift the argument from epidemiological to interventional studies. The history of this treatment is that it began with a number of persuasive trials of full dose testosterone treatment of both young and older men with hypogonadism.[6–9] When, however, physiologically appropriate doses of testosterone were administered to elderly men the results were less impressive. For example, for three years Snyder and his colleagues treated a group of almost 100 healthy men over the age of 65 years with testosterone patches in doses sufficient to raise their serum testosterone concentrations into the range appropriate for men in their 20s. The overall effects on bone mineral density were no different from those obtained with placebo.[10] While there was a significant increase in lean body mass (1.9 (SD 0.3) kg), principally in the trunk, and a fall in fat mass (−2.9 (0.5) kg), principally in the arms and legs, Snyder and his colleagues were unable to detect a significant increase in muscle strength, as measured in extension and flexion of the knee with a dynamometer.[11]

So far as sexual activity is concerned the role of testosterone in elderly men is still not well defined.[12 13] Circulating concentrations of testosterone in older men are usually well above those needed for a normal sexual response, although the proportion of men complaining of erectile dysfunction rises dramatically with age, such that 50% of men between the ages of 50 and 70 years complain of impotence.[14] As many as 80% of cases of erectile dysfunction are now thought to have a medical cause, such as diabetes mellitus, cardiovascular disease (especially angina and after myocardial infarction), neurological disorders (multiple sclerosis and spinal injury), pelvic surgery (prostatectomy), and trauma. Indeed some have suggested that the development of erectile dysfunction should be regarded as sentinel of disease and constitute an indication for careful medical assessment.

Recent work, reviewed elsewhere,[15] has shown that what ultimately determines potency is the ability of muscles in the walls of the artery supplying the penis to relax and so permit engorgement to occur. Nitric oxide released from parasympathetic nerve endings in response to sexual stimulation causes guanylate cyclase to produce cyclic guanosine monophosphate (cyclic GMP), which relaxes arterial smooth muscle. Cyclic GMP is metabolised by a specific phosphodiesterase. Sildenafil citrate (Viagra) inhibits this enzyme, prolongs arterial relaxation, and so enhances erection. As far as impotence in the older man is concerned, unless

hypogonadism can be clearly shown, treatment with sildenafil citrate (with appropriate warnings about cardiovascular risks and drug interactions with nitrites) is likely to be safer and more efficacious than injections of testosterone esters.

To conclude, I really do not find the analogy of the female menopause helpful in understanding or trying to manage the problems of senescence in men. Moreover, the endocrinology of ageing is much broader than that the term suggests. As Lamberts, van den Beld, and van der Lely have pointed out,[16] while the fragility of elderly people might be related to a gonadopause, an adrenopause (the age related fall of dehydroepiandrosterone sulphate concentrations), or a somatopause (the decline in secretion of growth hormone and insulin like growth factor), actually in old people the commonest endocrine disorders are diabetes mellitus and hypothyroidism. These conditions are definitely treatable.

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Plant sterol and stanol margarines and health

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A new polyunsaturated margarine with added plant stanols, Benecol, was introduced in several European countries last year, and a similar margarine with added plant sterols will be introduced under the Flora label later this year. These products lower serum concentrations of cholesterol, but they are expensive.[1–14] In Great Britain the cost is about £2.50 ($4.00) for a 250 g tub compared with 60p for ordinary polyunsaturated margarine and 90p for butter. This article considers quantitatively the health aspects of adding plant sterols and stanols to margarines and other foods.

Summary points

Plant sterols and stanols reduce the absorption of cholesterol from the gut and so lower serum concentrations of cholesterol

Plant sterols or stanols that have been esterified to increase their lipid solubility can be incorporated into foods

The 2 g of plant sterol or stanol added to an average daily portion of margarine reduces serum concentrations of low density lipoprotein cholesterol by an average of 0.54 mmol/l in people aged 50-59, 0.43 mmol/l in those aged 40-49, and 0.33 mmol/l in those aged 30-39

A reduction in the risk of heart disease of about 25% would be expected for this reduction in low density lipoprotein cholesterol; this is larger than the effect that could be expected to be achieved by people reducing their intake of saturated fat

The added costs of £70 per person per year will limit consumption; however, if stanols and sterols become cheaper, their introduction into the food chain will make them an important innovation in the primary prevention of heart disease

Methods

Randomised trials included in this review were identified by a Medline search using the term "plant sterols." Additional trials were identified from citations in these papers and in review articles. Other trials in children with familial hypercholesterolaemia were not included.

Plant sterols and stanols

Sterols are an essential component of cell membranes, and both animals and plants produce them. The sterol ring is common to all sterols; the differences are in the side chain. Cholesterol is exclusively an animal sterol. Over 40 plant sterols (or phytosterols) have been identified but β-sitosterol (especially), campesterol, and stigmasterol are the most abundant. These three sterols are structurally similar to cholesterol: they are all 4-desmethyl sterols (containing no methyl groups at carbon atom 4).

Stanols are saturated sterols (they have no double bonds in the sterol ring). Stanols are less abundant in nature than sterols. Plant stanols are produced by hydrogenating sterols. The term sterol is sometimes used as a generic term to include unsaturated sterols