Controversial endocrine interventions for the aged

Leow M K S, Loh K C

ABSTRACT

Specific endocrine changes occur with the ageing process. The last decade has witnessed significant progress in the basic and clinical science of ageing, thereby rejuvenating the interest in anti-ageing medicine, especially that of hormone replacement, by medical professionals and the lay public. However, endocrine manipulation as a therapeutic strategy for ageing is still evolving as continuing research attempts to answer the many questions of what it can achieve at the risk of incurring unknown long-term adverse effects. The current day doctor is confronted with a host of options, and will benefit from a synopsis of the latest evidence before making the most appropriate decision for aged patients seeking hormonal replacement therapy as a means to counter the effects of ageing. This review aims to give a rapid overview of the endocrine profile of geriatric population and the studies on the more controversial hormonal replacement therapies for the aged.

Keywords: ageing, androgens, growth hormone, hormone replacement, melatonin

Singapore Med J 2006; 47(7):569-579

Department of Endocrinology
Tan Tock Seng Hospital
11 Jalan Tan Tock Seng
Singapore 308433

Leow M K S, FACE, FACP, FAMS
Consultant

Loh Keh Chuan Diabetes, Thyroid & Hormone Clinic
Mount Elizabeth Medical Centre
3 Mount Elizabeth, #08-08
Singapore 228510

Loh K C, FRCPE, FACP, FAMS
Consultant

Correspondence to:
Dr Melvin K S Leow
Tel: (65) 6256 6011
Fax: (65) 6357 7871
Email: mleowsj@massmed.org

INTRODUCTION

Ageing is an inevitable biological process, and its wide-ranging effects involve a multitude of major organs including the endocrine system. Ageing itself is linked to a host of pathologies that include, but are not limited to, cancer and degenerative disorders like Alzheimer's disease. The decline in various hormones, or "endocrino-senesence", is an important facet of the diverse spectrum of age-related changes. Although clinically, the three most important endocrine effects of ageing are osteoporosis and a decline in the function of the pancreas and thyroid, and that appropriate interventions with medications and hormonal replacement have a positive impact on these three conditions, this review focuses primarily on the current opinions and relevant landmark studies on the clinical utility of growth hormone, testosterone, dehydroepiandrosterone (DHEA) and melatonin replacement in ageing individuals.

SARCOPENIA AND PHYSICAL FRAILTY ASSOCIATED WITH SENESCENCE

A major health impediment confronting many geriatric subjects is the age-related loss of muscle strength resulting in physical frailty. As a serious morbidity of old age, physical frailty has been attributed to the loss of lean body mass. As much of this lean mass comprises predominantly skeletal muscles, this is termed "sarcopenia". In cross-sectional studies, roughly 20%-30% of lean body mass is lost between the third and eighth decade of life[1]. The decline in strength is even more profound, with longitudinal studies demonstrating up to 60% decrease across the same age bracket[2-4]. This accelerates greatly at ages beyond 70 years[5]. Muscle power, defined as work per unit time, may decline by up to double that of loss of strength[6]. The functional correlates of sarcopenia and physical frailty are therefore impaired independence in daily activities and reduced quality of life, both of which are major antecedents to much morbidity and mortality confronting the geriatric population.

AN OVERVIEW OF GERONTOLOGICAL INFLUENCE ON ENDOCRINE PHYSIOLOGY

A substantial number of endocrine axes are affected by ageing. Endocrino-senescence includes ovarian failure or "menopause", involution of the growth hormone-insulin-like growth factor-1 (GH-IGF-1) axis, decline in testosterone and dehydroepiandrosterone (DHEA), also variously termed (though not uniformly accepted) as "somatopause", or "andropause", and "adrenopause", respectively, by some authors. Because each of these separate components is intricately linked together in the body, any major disturbance in a particular endocrine axis can exert an influence on other

endocrine axes in subtle or overt ways. However, for the sake of simplicity, the distinctive alterations in the different hormonal systems due to ageing are considered separately (Table I).

Table I. Age-related changes in endocrine profile.

Endocrine system	Result of ageing and deficiency
Growth hormone/IGF-1 axis	Somatopause
Hypothalamic-pituitary gonadal axis	Hypogonadism
Insulin resistance and carbohydrate metabolism	Glucose intolerance and diabetes mellitus
Calcium and bone metabolism	Osteoporosis
Hypothalamic-pituitary thyroid axis	Thyroid dysfunction
Adrenal DHEA production	Adrenopause
Fat metabolism and body composition	Fat accumulation
Pineal gland and sleep	Insomnia and disordered circadian rhythms
Thymus and immunological sequelae	Tendency to infections

GH/IGF-1 AXIS IN AGEING

The age-related sarcopenia alluded to above is a visible manifestation of a diminished anabolic capacity for cellular protein synthesis. GH and IGF-1 are two important anabolic hormones that regulate metabolic processes including protein synthesis in almost all tissues throughout our lifespan. GH is the most abundant hormone secreted by the anterior pituitary, and its secretion is known to decline with age, paralleled by an age-related decline in IGF-1 beginning from about 30 years of age[7]. By the sixth decade of life, the level of IGF-1 is below the lower normal limit of young adults. As such, the decline of GH and IGF-1 with age has thus been thought to be contributory to sarcopenia.

GH secretion declines by about 14% per decade in normal adults due to age-related neuroendocrine perturbations[8]. In this regard, the mean pulse amplitude, duration and fraction of GH secreted, but not pulse frequency, gradually decline with ageing[9]. Because this reduction in hormone output by pituitary somatotropes is correctable by GHRH and GH secretagogues even in the oldest of old patients, it is speculated that the axis deficiency begins above the pituitary, possibly via alterations in GHRH, somatostatin or ghrelin pulsatility[10,11]. Despite an increase in GH receptor density with age, GH-induced plasma IGF-1 levels decrease with age, implying that tissue resistance to GH may be another manifestation of age. Animal studies reveal that a reduction in GH-induced phosphorylation of intracellular proteins, such as JAK2 kinase and STAT3 crucial in GH signal transduction pathway, account for the GH tissue resistance despite an increase in GH receptor density[12].

Although critical to development and growth in the young, studies on patients with adult GH deficiency (AGHD) suggest that GH remains important in grown adults as these patients have a cluster of abnormalities such as dyslipidaemia, impaired glucose tolerance, protein catabolism with decreased muscle mass, increased visceral fat, decreased bone density and even depression. AGHD patients also appear prone to carotid atherosclerosis[13,14] and possibly cardiovascular risk complications[15]. The potential benefits of GH replacement in the healthy aged are supported by the improvement in muscle strength[16], body composition[16,17], quality of life[16,18], and lipid profile and cardiac performance[19,20] with GH replacement as observed in AGHD patients while those untreated worsened in these aspects[19-21].

CLINICAL TRIALS OF GH/GHRH/GHS

Observations on age-associated attenuation of GH/IGF-1 led to clinical trials attempting to answer the question of how much of such physiological changes as reduced lean muscle mass, reduced strength and aerobic capacity, central adiposity, reduced bone mass and slow wave sleep could be reversed by GH/GHRH supplementation. The increased availability of recombinant human growth hormone (GH) has facilitated research on its use in ageing. It is unclear regarding the benefits of restoration to young levels of the GH/IGF-I axis in ageing. However, the question of whether the "somatopause" observed in ageing is an adaptive mechanism or the verge of growth hormone deficiency that would benefit from exogenous growth hormone replacement is at best only partially answered by clinical studies thus far.

Data on GH replacement in the elderly is summarised in Table II. In one of the pioneering studies, Rudman et al used a dose that brought IGF-1 levels of men over 60 years old to the mid-normal range of men in their twenties. This led to a 14.2% reduction in body fat coupled with an increase of lean body mass by 8.8%[22]. However, this study has its drawbacks. It is not a double-blinded study, and only 12 subjects were studied. The weekly GH dose used was approximately twice as high as those used for AGHD patients, resulting in adverse effects of excessive GH action in the form of hypertension and arthralgia. Furthermore, there was no assessment of muscle strength, exercise endurance or quality of life.

More recently, GH administration over six months to increase serum IGF-1 levels of elderly men and women 65 years and older to levels in young adults

Table II. Summary of major evidence-based studies of GH replacement in the healthy aged.

Study and design	Subjects	Doses of GH	Results	Major end-points
Rudman et al. N Engl J Med 1990[22]. Prospective randomised controlled trial (n=21).	Healthy men aged 61-81 years with plasma IGF-I <350 U/L.	s/c rhGH 0.03 mg/kg BW three times a week for 6 months.	Mean plasma IGF-I level at youthful range of 500 to 1500 U/L in treated group, whereas it is <350 U/L in placebo.	↑ 8.8% in lean body mass, ↓ 14.4% in adipose mass, ↑ 1.6% in lumbar spine BMD ($p<0.05$). ↑ 7.1% in skin thickness ($p=0.07$).
Taafee et al. J Clin Endocrinol Metab 1994[24]. Double-blind, randomised placebo-controlled trial (n=18).	Healthy elderly men aged 65-82 years.	Subjects randomised to either s/c 0.02 mg/kg BW/day rhGH or placebo, while undertaking strength training.	IGF-I levels increased 255 ± 32 ug/L at week 15 and 218 ± 21 ug/L at week 24 in ($p<0.001$). Placebo group: IGF-I increased to 119 ± 6 ug/L at 24 weeks.	Lean body mass increased, fat mass decreased ($p<0.05$) in the rhGH group. Supplementation with rhGH does not the augment the response to strength training in elderly men.
Papadakis et al. Ann Intern Med 1996[25]. Randomised, controlled, double-blind trial (n=52).	Healthy men >69 years old with good functional ability but baseline IGF-1 <161 ng/mL.	s/c rhGH 0.03 mg/kg BW or placebo given three times a week for 6 months.	GH dose adjusted to attain IGF-1 between 190-350 ng/mL (25^{th}-75^{th} percentile of young adults).	Lean mass increased 4.3%, fat mass reduced 13.1% (GH group). No improvement in functional ability.
Munzer et al. J Clin Endocrinol Metab 2001[23]. Randomised, double-blind, placebo controlled trial (n=110).	Healthy men (n=64) and healthy women (n=46), aged 65-88 years.	s/c rhGH 20 ug/kg BW three times per week for 26 weeks.	IGF-1 levels increased higher in men than women (187 ± 10 vs 142 ± 9 ug/L).	Significant reduction in waist circumference but not BMI.

BW: body weight.

of age group 25-40 years, with and without sex steroids (hormone replacement therapy for women and testosterone for men), appears to have a sexually dimorphic response in that while it reduces total and abdominal subcutaneous fat (with no effect on visceral fat) in healthy aged males, it has no impact on fat distribution in females[23].

While several studies demonstrated an increase in lean body mass with GH therapy, its improvement in muscle mass and strength did not increase beyond what could be achieved with exercise. This possibly reflects that exercise itself is already a known physiological trigger of GH secretion. Such were the findings by independent research groups. Taaffe et al found that exercise training improved strength and exercise capacity not increased further by growth hormone therapy[24]. Papadakis et al showed that GH administration in elderly men aged 70 years and older for six months led to a very modest increase in lean body mass. Yet, this was not paralleled by an increase in strength in the upper and lower extremities[25]. Thus, the effects on body composition brought about by GH do not translate clinically into significant improvement in muscular strength or endurance capacity. It remains undetermined if the lack of such anabolic actions of GH to counter physical frailty of the aged is due to inadequate doses of GH or limited by the short duration of the studies.

Adverse effects of GH include dose-dependent sodium and fluid retention associated with clinically significant oedema and hypertension, arthralgia, carpal tunnel syndrome and elevated fasting plasma glucose. These effects respond and improve with dose reduction. In particular, the use of GH in the long-term carries the theoretical concern of propagating the proliferation of tumours that express IGF-1 receptors. However, the mitogenic effects of GH and IGF-1 are still debatable. For instance, certain studies had linked elevated IGF-1 with an increased risk of ovarian, breast, prostate, colorectal and other cancers[26-35]. Yet, not all studies confirm this association[36-39]. So far, there are also no unequivocal data of long-term adminstration of physiological doses of GH in paediatric patients with GH deficiency being linked to an increased incidence of malignancy[40]. But this cannot be extrapolated to the elderly in whom the incidence of cancer is already increased due to the factor of age alone, and the safety of GH in this group thus remains unclear.

Much evidence supports the notion that the pituitary is not primarily defective in the age-related decline of GH, and points to hypothalamic peptides as the main reason for this phenomenon. This implies that the unique situation of sarcopenia secondary to age-related GH deficiency would respond to orally active ghrelin-mimetic GH secretogogues (GHS) in

contrast to patients whose GH deficiency stems from actual loss of somatotropes from various pituitary lesions in whom GHS would have no therapeutic role[41]. Attention is also directed at ghrelin, which possesses orexigenic effects in addition to its metabolic and endocrine function[42]. Interestingly, slow-wave sleep, which correlates with GH secretory peaks in the young, could be restored through GHRH supplementation[43].

Large-scale studies of GHRH or GHS on clinically important endpoints such as body composition, countering sarcopenia and physical frailty and improving functional status at present are awaited, pending favourable results in studies of smaller size focused on intermediate endpoints such as the restoration to young levels of GH/IGF-1 axis activity. All research on GHS published to date have been of this latter type. Randomised double-blind, cross-over placebo-controlled trial using GHS on healthy elderly volunteers showed greater GH secretion rates and plasma GH levels elicited by GHS compared to GHRH[11]. Orally administered GHS in another randomised controlled trial revealed that once daily dosing in elderly subjects enhanced pulsatile GH release, significantly increased serum GH and IGF-I concentrations, and restored serum IGF-I concentrations to young adult levels[44]. In particular, that GHS are far more potent than GHRH itself, and that parenteral administration is not required make them a very attractive therapeutic alternative to GH. While some results are encouraging, they do not yet support the routine use of GHRH or GHS in normal aging. There is still insufficient evidence and consensus as of today that the restoration of GH and IGF-1 of healthy, fit elderly individuals to levels of healthy young adults using r-hGH, r-IGF-1, GHRH, or GHS confer more clinical benefits than harm. As such, we do not recommend using GH or its secretagogues in the healthy aged population on a routine basis, but that any use should be predicated on a research protocol for now.

Further studies are evidently required to define precisely which group of patients in whom the benefits of GH replacement therapy outweigh its undesirable effects. There is much that we have yet to understand, particularly the connection between the molecular level and clinical outcomes. GH and IGF-1 in animal models, for instance, appear to work diametrically opposite to what they are supposed to achieve in humans. Hence, while it is interesting that GH replacement is largely thought to counter the many effects of ageing, it is paradoxical that GH gene receptor knockout mice show significant extension of their life spans[45]. Similarly, attenuated insulin/IGF-1 signaling due to mutation of an important gene that codes for a transcription factor governing the development of pituitary somatotrophs called Pit-1, plays a critical role in extending the longevity of nematodes and GH deficient dwarf mice, another seemingly counter-intuitive outcome[46]. The implications of such findings remain conjectural, and strengthen the case that further research is still necessary to demonstrate the long-term safety of hormonal manipulations as anti-ageing interventions.

TESTOSTERONE

Plasma testosterone steadily declines after the age of 30 years in men[47]. The total serum testosterone declines at a rate of 0.5%-1% per year on average (3-11 ng/dL/year) (0.1-0.38 nmol/L/year) based on longitudinal studies[48]. Yet, due to the simultaneous increase in sex hormone binding globulin (SHBG) by about 1.2% per year, the total plasma testosterone is not a good indicator of bioavailable testosterone[49]. In applying the concept to normal ageing males, the Massachusetts Male Aging Study defined hypogonadism as the presence of at least three symptoms or signs of hypogonadism associated with a total testosterone of less than 200 ng/dL (7 nmol/L) or a free testosterone below 8.9 ng/dL (0.3 nmol/L). Using these criteria, the incidence of hypogonadism is estimated to be about 12 cases per 1,000 patient-years[50]. Assaying bioavailable testosterone, which comprises free testosterone and albumin-bound testosterone, allows this phenomenon of age-associated androgen deficiency, sometimes termed "andropause", to be appreciated better, as bioavailable testosterone declines even more rapidly at a rate of nearly 1% per year[49]. "Andropause" also correlates well with a reduction in leydig cell number and function.

Unlike women who eventually become menopausal, not every man going through this gradual physiological drop in testosterone develops hypogonadism. Data estimates show that between 30%-70% of males will become relatively hypogonadal by the time they approach the 5th decade and older. Harman et al reported the largest longitudinal study done on testosterone in 900 men followed over 30 years, and found that the prevalence of hypogonadism using a total testosterone cutoff of <325 ng/dL (<11.3 nmol/L) was 5% in those 20-29 years of age, but rose significantly to 50% in men older than 80 years of age[47]. This estimate became higher when free testosterone index was utilised. In addition to the fall in absolute levels of testosterone, another crucial feature of testosterone secretion

Table III. Summary of evidence-based studies of testosterone replacement in the aged.

Study and design	Subjects	Treatment	Major end-points	Comments
Tenover. J Clin Endocrinol Metab 1992[54] (n=13).	57-76 years, serum testosterone <400 ng/dL (14 nmol/L).	Testosterone enanthate IM 100 mg weekly or placebo for 3 months.	1.8 kg gain in lean mass, no change in fat mass, no change in grip strength.	Mild increase in PSA and Hct, and decline in total cholesterol and LDL-C.
Urban et al. Am J Physiol 1995[93].	Healthy, >65 years, T <480 ng/dL (16.7 nmol/L).	Testosterone enanthate IM weekly for 4 weeks to increase serum T to young adult range of 500-1,000 ng/dL.	Body composition not reported, increase in hamstring and quadriceps strength.	2-fold increase in muscle protein synthesis.
Sih R et al. J Clin Endocrinol Metab 1997[53]. Randomised placebo-controlled trial (n=32).	Healthy, 51-69 years, Bioavailable T <60 ng/dL (2.1 nmol/L).	Testosterone cypionate IM 200 mg or placebo every 2 weeks for 12 months.	No change in lean body mass or fat mass; 4-5 kg increase in grip strength.	No change in PSA, increase in Hct; may have a role in treatment of physical frailty.
Snyder et al. J Clin Endocrinol Metab 1999[52]. Randomised double-blind placebo-controlled study (n=108).	Healthy, >69 years, serum T <475 ng/dL (16.5 nmol/L).	Scrotal patch (Testoderm) 6 mg daily to increase serum T to mid-normal range of young men, or placebo for 3 years.	1.9 kg increase in lean body mass, 3 kg decrease in fat mass; no change in knee extension and flexion strength.	Improved perception of physical function in men with the lowest serum T.
Kenny et al. J Gerontol A Biol Sci Med Sci. 2002[62]. Randomised placebo-controlled study (n=67).	Men aged 76 ± 4 years with bioavailable testosterone levels <128 ng/dL (4.4 nmol/L).	Testosterone patch 2-2.5 mg daily or placebo for 1 year.	1 kg increase in lean body mass and 2% decrease in fat mass, increase in muscle strength.	Increase in BMD.

affected by ageing is circadian rhythmicity observed in younger males, in which its characteristic morning peaks and evening nadirs become blunted[51].

The target sites of androgen action include the muscle, bone, sexual organ, prostate, haemopoietic system, lipids and carbohydrates. Effects of testosterone at certain end-organs such as the prostate and androgen-dependent pilosebaceous units are mediated through 5-dehydrotestosterone (DHT). Yet, the variation of serum levels of DHT with age is inconsistent, as levels may either be constant or even increased[49]. Clinical features of androgen deficiency include a decline in libido, erectile dysfunction, loss of androgen-dependent hair, reduced muscle mass and endurance capacity, increased adiposity, higher LDL-cholesterol and osteopenia. In tandem with the decline in testosterone is the elevation of LH and FSH, decreased testicular response to hCG and diminished spermatogenesis. Estimates of reciprocal increases in FSH and LH by the Massachusetts Male Aging Study were reported as 1.2% and 1.9% per year, respectively[49]. Low testosterone is also associated with depression, anxiety and decreased energy level.

CLINICAL TRIALS OF TESTOSTERONE REPLACEMENT

Pending evidence from large scale multicentre clinical trials, smaller randomised studies will have to be depended upon for the present to analyse its applicability to physiological hypoandrogenism due to ageing, an intriguing situation considering the expanding range of testosterone replacement products over the past decade. The more notable recent trials relevant to this field are summarised in Table III. The main end-points of clinical interest with respect to testosterone replacement are cardiovascular, mood and cognition, bone health, body composition, sexual function and muscle strength.

Snyder et al showed that with testosterone replacement, fat mass decreased significantly mainly in the extremities while lean body mass increased principally in the trunk[52]. As for testosterone replacement effects on muscle strength of the lower extremities, another clinically meaningful end-point in view of the correlation of lower limb power with ability to ambulate independently by the elderly, this group did not find any significant change in knee flexion and extension strength. Sih et al reported that testosterone significantly increased upper body strength as measured by bilateral hand grip strength compared to baseline strength at three, six, nine and 12 months. The limitations of this study are the small study population and substantial subject drop-out rate and lack of demonstrable increase in bioavailable testosterone throughout the course of the study although there is evidence of suppressed LH that suggested increased testosterone[53]. In yet another

study in elderly men, testosterone therapy led to a rise in lean body mass accompanied by a perception of improved muscle function. However, this study by Tenover et al did not correlate the subjective improvement of muscle function with an objective measure of muscle strength using a dynamometer or an objective assessment of muscle function such as walking or stair climbing[54].

Testosterone replacement studies on bone were largely performed using biochemical markers of bone turnover rather than bone mineral density (BMD). Two studies evaluated effects of testosterone on BMD. In Snyder et al's study using testosterone scrotal patch, he did not find any significant benefit when compared to controls on calcium supplementation, but that the magnitude of any increase in BMD at the lumbar spine was inversely correlated to the serum testosterone level prior to replacement therapy[52]. Tenover however found significant increase in BMD in those on intramuscular testosterone relative to placebo[55]. At least two reasons could account for this discrepancy. The subjects recruited in Snyder et al's study had higher baseline total testosterone (367 ± 80 ng/dL) (12.7 ± 2.8 nmol/L) [compared to those in Tenover's study (<350 ng/dL) (<12 nmol/L)]. Next, while the placebo arm in Snyder's study received calcium and vitamin D, no such supplementation was administered to the control group in Tenover's study. The potential benefits on BMD prompted further research in this important area. One of the most recent studies include a prospective randomised placebo-controlled trial comparing testosterone versus testosterone plus finasteride with placebo over 36 months on BMD in 70 elderly men aged 65 years or older. The results demonstrated that testosterone supplementation increased BMD at the vertebral spine and hip in both treated groups compared to placebo, though the arm on finasteride, a 5-alpha-reductase inhibitor, had less prostate effects and lower PSA[56]. Notwithstanding the above benefits of testosterone on BMD, there are to date no clinical end-point data in terms of fracture rate reduction in the elderly on testosterone therapy.

Healthy aged men receiving testosterone replacement may experience an improvement of sexual function in terms of libido, and it may ameliorate erectile dysfunction given that the physiology of erection is predominantly mediated by generation of nitric oxide and its cyclic GMP messenger and that testosterone functions in this cascade by playing the role of inducing the nitric oxide synthase (iNOS) enzyme[57]. Although libido and sexual function may be restored once a threshold level of testosterone level in the lower normal limit is achieved, there is no definite data suggesting that sexual function can be augmented further by increasing testosterone levels into the upper normal range[58,59].

Important side effects of testosterone, in particular, the cardiovascular system and prostate, are areas of concern. The potential proatherogenic lipid profile, increased blood viscosity from increased erythropoiesis and reduced plasminogen activator inhibitor-1 (PAI-1) induced by exogenous testosterone may theoretically contribute to an increase in cardiovascular morbidity. However, prospective epidemiological studies attempting to clarify this have not confirmed a definite relationship between serum testosterone and the development of ischaemic heart disease in middle-aged and older men[60]. Observational data[61] and short-term studies of testosterone replacement[62] have even suggested that hypogonadism may confer greater cardiovascular risk than testosterone replacement. Although testosterone replacement can suppress HDL-C, it also has advantageous lipid effects by reducing Lp(a)[63]. Moreover, exogenous testosterone can act as a coronary vasodilator in men with established ischaemic heart disease[64]. This vasodilatation effect apparently occurs with supraphysiological concentrations of testosterone, but absent at physiological levels[65]. Recent critical literature reviews[65,66] acknowledge the divided viewpoints of our current knowledge, but advocated that the use of testosterone in androgen-deficient older men should not be limited by fear of increasing cardiovascular risk[67].

As the prostate is an androgen-sensitive organ, its proliferative susceptibility to testosterone is a major concern, especially since ageing males are already at higher risk of prostate hyperplasia and cancer. Studies on rat models of prostate cancer had supported the promotional effects of testosterone on prostate carcinogenesis[68]. This is a valid concern as one clinical study had demonstrated that testosterone replacement led to a significant increase in PSA levels[69]. Yet, the theoretical risk of prostate enlargement and prostate cancer is not borne out by all clinical studies. Sih et al showed no increase in PSA levels after a year of intramuscular testosterone in men aged over 50 years[53]. Those on testosterone in Snyder et al's three-year study had a small but significant increase in PSA that remained within the top normal range. Prostatism symptoms were unchanged in both treated and placebo groups in the entire three-year period[52]. Another reassuring study on the issue of testosterone replacement in hypogonadal men at high risk of prostate cancer in view of background

prostate intraepithelial neoplasia showed that after a year of testosterone replacement, these men had no greater increase in PSA or significantly increased risk of prostate cancer than those without prostate intraepithelial neoplasia, indicating that this high grade prostate precancerous lesion is not an absolute contraindication to testosterone replacement therapy[70]. Statistically significant polycythaemia can also occur with testosterone replacement, but this is dose-dependent and can be controlled by dose reduction[71].

Overall, the studies to date on testosterone replacement in healthy aged men have been limited by the small number of subjects studied over a short duration. Although they have been shown to improve body composition in the healthy aged, the effects on muscle strength and exercise endurance remain uncertain and the effect on clinically relevant end-points, such as fracture reduction, are lacking. Many clinical trials of androgen replacement regimens are ongoing to clarify the risk-benefit ratio in elderly men. Thus, we hold the view that the risks versus benefits of testosterone replacement for aged males must be carefully weighed in each case and properly discussed with the individual patient and documented and monitored.

DHEA AND ADRENAL FUNCTION

Dehydro-3-epiandrosterone (DHEA) is the most abundant steroid hormone. After adrenarche, it rises to attain a peak at the age of roughly 20-30 years, DHEA and its sulfate (DHEAS) then steadily decline in a manner inversely correlated to age at 3.1% and 2.2% per year, respectively, leading to "adrenopause" in the elderly whereby its level is less than a fifth of the peak level[49,72]. Almost 95% of DHEA and its sulfate (DHEAS) are secreted by the adrenal zona reticularis. The adrenals constitute the main source of DHEA/DHEAS in women, unlike men in which 25% of DHEA and 5% of DHEAS are secreted by the testes[73]. Apart from the gonads, the central nervous system is another extra-adrenal source of DHEA where it acts as an excitatory neurosteroid[74]. Given that both testosterone and estrogen are synthesised downstream of DHEA, deficiency of this steroid can itself lead to sex hormone deficiency.

Although the functions of DHEA are still not fully known, a cluster of features associated with DHEA deficiency suggests that DHEA could be involved in libido[75], energy level and mood[76], and insulin sensitivity[77]. Evidence in the medical literature suggests a correlation between a low DHEAS level and psychosomatic symptoms[78]. It should be appreciated that whereas many studies on animals using supraphysiologic doses of DHEA may have shown that it can influence body composition, carbohydrate and lipid metabolism, the studies in man are done on physiological doses. Due to the majority of such studies being done on women more than in men and that most are not randomised, the available data have been controversial and difficult to extrapolate to the normal aged population.

CLINICAL RESULTS OF DHEA SUPPLEMENTATION

Possibly, DHEA could be utilised as an alternative form of androgen supplementation for elderly men with "andropause". As for its salutary effects on ageing, further prospective, randomised clinical trials on large numbers of the aged population will be required to clarify any benefits and risks of long-term replacement for the healthy elderly. Although many other claims have been made for DHEA as an anti-ageing hormone, very few well-designed clinical trials have clearly substantiated the utility and safety of long-term DHEA supplementation.

A study on DHEA found that a dose of 50 mg daily was capable of raising the plasma levels to young adults[79]. However, the androgen levels in women were doubled, associated with a reduction in HDL-C, while there was no demonstrable change in men. This was associated with a subjective improvement of physical and psychological well-being, though there was no improvement in libido. Baulieu et al investigated a group of healthy elderly men and women on DHEA, and found that BMD (especially at trabecular bone areas including the femoral neck and distal radius) and libido increased selectively for elderly women above 70 years old, but this was not observed in either men or younger women[80]. Studies using body composition and muscle strength for end-points yielded inconsistent results, probably due to the lack of statistical power. While the research group of Morales et al observed a decrease in adipose mass and an increase in muscular strength using DHEA of 100 mg daily, its effect on lean body mass either increased or remained unchanged[81].

Intriguingly, Flynn et al, in an independent study using a similar dose of DHEA for three months, failed to demonstrate any changes in the same end-points[82]. The more recent randomised controlled trial on 280 men and women older than 60 years old did not reveal any adverse effect of DHEA 50 mg daily, but neither did it confer significant improvement in muscle strength or muscle cross-sectional areas[83]. In another recent but smaller randomised, double-blinded, cross-over, placebo-controlled study, DHEA did not alter fat distribution, serum insulin, glucose

Table IV. Summary of evidence-based studies of DHEA replacement in the aged.

Study and design	Subjects	Intervention	Major results	Clinical end-points
Morales et al. Clin Endocrinol 1998[81]. Randomised double-blind placebo-controlled cross-over trial (n=19).	Healthy non-obese men 50-65 years (n=9) and women (n=10).	1 year study of 6 months of placebo and 6 months of 100 mg oral DHEA daily.	Serum DHEA restored to levels of young adults and serum DHEAS to levels at or slightly above the young adult range.	In men, fat mass decreased 1.0 ± 0.4 kg and muscle strength increased 15.0 ± 3.3%. In women, increase in body mass of 1.4 ± 0.4 kg occurred.
Percheron et al. Arch Intern Med 2003[83]. Randomized double-blind placebo-controlled cross-over trial (n=280).	Healthy ambulatory and independent men and women aged 60-80 years.	1-year administration of DHEA 50 mg/d, orally administered.	Restored DHEAS serum concentrations to the normal range for young adults.	No significant change in muscle strength or in muscle and fat cross-sectional areas.
Baulieu et al. Proc Natl Acad Sci USA 2000[80]. Randomised double-blind placebo-controlled study (n=280).	Healthy individuals (women and men 60-79 years old).	DHEA, 50 mg, or placebo, orally, daily for a year.	Increase in DHEAS, a small increase of testosterone and oestradiol particularly in women; increase in BMD in women >70years.	No adverse consequences of chronic DHEA supplementation noted; replacement therapy normalised some effects of ageing.
Flynn et al. J Clin Endocrinol Metab 1999[82]. Randomised, double blind, placebo-controlled, cross-over trial (n=39).	Healthy men, aged 60-84 years, from the Longitudinal Aging Study.	Oral DHEA 50 mg twice daily for 3 months, then 3 months of placebo, then another 3 months of washout.	Increase in DHEA, DHEAS, free testosterone and oestradiol, but no significant change in total testosterone or PSA.	Despite surrogate endocrine effects, no improvement well-being or improved sexual function.
Jedrzejuk et al. Aging Male 2003[84]. Randomised, double-blind, placebo-controlled, cross-over trial (n=12).	Healthy males, aged 59 ± 4.8 years, recruited from university employees.	Oral DHEA 50 mg daily or placebo for 3 months, then cross-over for 3 months.	Significant increase in DHEAS level with therapy of active agent.	No change in body fat distribution and indices of insulin sensitivity and resistance.

and lipids and indices of insulin sensitivity and resistance[84]. The available scientific evidence for DHEA supplementation are summarised in Table IV. Despite the optimism generated by animal studies on DHEA, current literature from randomised clinical trials does not support the use of DHEA supplementation in the healthy elderly population, since the benefits predicted were not realised and the theoretical risks of provoking hormonally-sensitive tumours cannot be entirely discounted.

MELATONIN AND THE PINEAL GLAND

The pineal gland, otherwise called the "epiphysis", is a small vestigial endocrine gland located in the midbrain and has a diverse variety of functions, ranging from sleep, immunostimulatory mood, and possibly the ageing process itself. The chief hormone of the pineal gland is N-acetyl-5-methoxytryptamine, or melatonin. Melatonin is secreted in a circadian rhythm according to the dark-light cycle. Maximal secretion occurs in the dark at night, and light exposure of the retina leads to rapid breakdown of melatonin to very low levels. In human plasma, the mean ± SD concentrations in the darkness period were 23.18 ± 7.44 pg/ml for free melatonin and 82.5 ± 36.48 pg/ml for total melatonin, while the lowest concentrations detected during daytime were 2.23 ± 2.22 and 7.40 ± 5.68 pg/ml, respectively[85].

It is likely that the pineal gland regulates neuroendocrine functions to a diurnal rhythm, thereby implying the existence of a potential 'epiphysis-hypophysis' feedback axis[86]. The secretory dynamics of melatonin attenuates gradually with age, resulting in a shorter duration and lower nocturnal amplitude[87]. Deterioration of its secretion may then impair the efficiency of sleep, which in turn can reduce the reparative and anabolic activities of growth hormone maximally secreted during stage 4 delta wave sleep[88]. It remains to be established if ageing is linked to a chaotic pineal gland-dependent neuroendocrine program that causes a desynchronisation of gonadal, thyroid and adrenal functions.

Table V. Summary of major evidence-based studies of melatonin replacement in the aged.

Study and design	Subjects	Intervention	Major results	Conclusions
Peck et al. Am J Geriatr Psychiatry. 2004. Double-blind placebo-controlled randomised clinical trial[94].	26 healthy elderly subjects.	Oral melatonin 1 mg or placebo nightly for 4 weeks.	Improved sleep latency after nocturnal awakening, and improved scores on the California Verbal Learning Test.	Effective in certain aspects of cognition and sleep in the elderly. May benefit age-related cognitive decline.
Pawlikowski et al. Neuro Endocrinol Lett 2002. Open pilot study[95].	14 women (volunteers), aged from 64 to 80 years (mean age 71 ± 4.6 years).	Melatonin (2 mg daily at 19:00 h) was administered for 6 months.	Significant increase in IGF-1 and DHEA, and decrease in oestradiol; no change in cortisol.	Melatonin administration may be beneficial for elderly subjects on the basis of its hormonal effects.
Garfinkel et al. Lancet 1995. Randomised, double-blind, crossover study[96].	12 elderly subjects (aged 76 ± 8 years). with insomnia.	Controlled release melatonin 2 mg per night for 3 weeks.	Greater sleep efficiency after melatonin versus placebo, shorter wake time after sleep onset.	Effectively improves sleep quality in the elderly.

CLINICAL RESULTS OF MELATONIN SUPPLEMENTATION

Melatonin is currently used to treat sleep rhythm disorders, such as those manifested in jet lag, shift work or during spaceflight[89]. Studies are underway in evaluating its beneficial effects on the immune system, its oncostatic properties and its purported actions on longevity, given its ability to extend the lifespan of laboratory mice by up to 25%[90]. As the amplitude of melatonin secretion decreases with age, pharmacological replacement of melatonin may mitigate the ageing process by supplementing the background of the lowered amplitude of melatonin. This could in turn act on the melatonin receptors of the hypothalamic suprachiasmatic nuclei that serve, together with the pineal gland, as the biological clock in mammals[91]. In human studies, melatonin amplified the antitumoural activity of interleukin-2[92]. Some notable randomised clinical trials of melatonin are highlighted in Table V. Other than its more proven beneficial effects on sleep, the present available data do not allow us to recommend the use of melatonin supplementation for the healthy elderly to improve the quality of life until more extensive studies support that view.

CONCLUSIONS

Growing interest in anti-ageing medicine, both among the lay public and medical professionals and scientists, is understandable given the graying population on a global scale, and the desire of nearly every ageing individual and healthy aged to remain youthful. In terms of the use of hormones such as GH, IGF-1, GHRH, GH-releasing peptides, testosterone, DHEA and melatonin in healthy aged individuals, there are relatively few randomised placebo-controlled clinical trials. Also, such studies, if at all available, were largely conducted over a short term, with the longest extending only to a few years. These were also mainly conducted on small numbers of subjects. Hence, the jury is still out on the benefit-risk of endocrine replacement for the elderly. Much of the literature on such hormone studies are gleaned from animal models and on patients with hypopituitarism, as well as on younger patients, and thus may not necessarily extrapolate relevantly to the healthy aged population. Long-term safety data on the chronic use of various hormone replacement therapies in this group are currently still limited. Furthermore, the majority of elderly who might benefit from hormone therapy in reality suffer from at least one or more chronic illnesses that could have an impact on the modality of hormonal replacement chosen. Physicians should exercise caution and prudence in the assessment of patients who seek hormonal replacement carefully, bearing in mind the current limited data of the risk-benefit equation. Any decision for intervention should be made on an individualised basis under a research protocol.

REFERENCES

1. Kyle UG, Genton L, Hans D, et al. Age-related differences in fat-free mass, skeletal muscle, body cell mass and fat mass between 18 and 94 years. Eur J Clin Nutr 2001; 55:663-72.
2. Sinaki M, Nwaogwugwu NC, Philips BE, et al. Effect of gender, age, and anthropometry on axial and appendicular muscle strength. Am J Phys Med Rehabil 2001; 80:330-8.
3. Samson MM, Meeuwsen IB, Crowe A, et al. Relationships between physical performance measures, age, height and body weight in healthy adults. Age Ageing 2000; 29:235-42.
4. Metter EJ, Conwit R, Tobin J, et al. Age-associated loss of power and strength in the upper extremities in women and men. J Gerontol A Biol Sci Med Sci 1997; 52:B267-76.
5. Hughes VA, Frontera WR, Wood M, et al. Longitudinal muscle strength changes in older adults: influence of muscle mass, physical activity, and health. J Gerontol A Biol Sci Med Sci 2001; 56:B209-17.

6. Skelton DA, Greig CA, Davies JM, et al. Strength, power and related functional ability of healthy people aged 65-89 years. Age Ageing 1994; 23:371-7.
7. Lamberts SW, van den Beld AW, van der Lely AJ. The endocrinology of aging. Science 1997; 278:419-24.
8. Toogood AA, O'Neill PA, Shalet SM. Beyond the somatopause: growth hormone deficiency in adults over the age of 60 years. J Clin Endocrinol Metab 1996; 81:460-5.
9. Ho KY, Evans WS, Blizzard RM, et al. Effects of sex and age on the 24-hour profile of growth hormone secretion in man: importance of endogenous estradiol concentrations. J Clin Endocrinol Metab 1987; 64:51-8.
10. Pavlov EP, Harman SM, Merriam GR, et al. Responses of growth hormone (GH) and somatomedin-C to GH-releasing hormone in healthy aging men. J Clin Endocrinol Metab 1986; 62:595-600.
11. Aloi JA, Gertz BJ, Hartman ML, et al. Neuroendocrine responses to a novel growth hormone secretagogue, L-692,429, in healthy older subjects. J Clin Endocrinol Metab 1994; 79:943-9.
12. Xu XW, Bennett SA, Ingram RL, et al. Decreases in growth hormone receptor signal transduction contribute to the decline in insulin-like growth factor I gene expression with age. Endocrinology 1995; 136:4551-7.
13. Leonsson M, Hulthe J, Oscarsson J, et al. Intima-media thickness in cardiovascularly asymptomatic hypopituitary adults with growth hormone deficiency: relation to body mass index, gender, and other cardiovascular risk factors. Clin Endocrinol (Oxf) 2002; 57:751-9.
14. Murata M, Kaji H, Mizuno I, et al. A study of carotid intima-media thickness in GH-deficient Japanese adults during onset among adults and children. Eur J Endocrinol 2003; 148:333-8.
15. Abdu TA, Neary R, Elhadd TA, et al. Coronary risk in growth hormone deficiency hypopituitary adults: increased predicted risk is due largely to lipid profile abnormalities. Clin Endocrinol (Oxf) 2001; 55:209-16.
16. Wallymahmed ME, Foy P, Shaw D, et al. Quality of life, body composition and muscle strength in adult growth hormone deficiency: the influence of growth hormone replacement therapy for up to 3 years. Clin Endocrinol (Oxf) 1997; 47:439-46.
17. Hoffman AR, Kuntze JE, Baptista J, et al. Growth hormone (GH) replacement therapy in adult-onset gh deficiency: effects on body composition in men and women in a double-blind, randomized, placebo-controlled trial. J Clin Endocrinol Metab 2004; 89:2048-56.
18. Ahmad AM, Hopkins MT, Thomas J, et al. Body composition and quality of life in adults with growth hormone deficiency; effects of low-dose growth hormone replacement. Clin Endocrinol (Oxf) 2001; 54:709-17.
19. Elgzyri T, Castenfors J, Hagg E, et al. The effects of GH replacement therapy on cardiac morphology and function, exercise capacity and serum lipids in elderly subjects with GH deficiency. Clin Endocrinol (Oxf) 2004; 61:113-22.
20. Pincelli AI, Bragato R, Scacchi M, et al. Three weekly injections (TWI) of low-dose growth hormone (GH) restore low normal circulating IGF-1 concentrations and reverse cardiac abnormalities associated with adult onset GH deficiency (GHD). J Endocrinol Invest 2003; 26:420-8.
21. Colao A, Di Somma C, Salerno M, et al. The cardiovascular risk of GH-deficienct adolescents. J Clin Endocrinol Metab 2002; 87:3650-5.
22. Rudman D, Feller AG, Nagraj HS, et al. Effects of human growth hormone in men over 60 years old. N Engl J Med 1990; 323:1-6.
23. Munzer T, Harman SM, Hees P, et al. Effects of GH and/or sex steroid administration on abdominal subcutaneous and visceral fat in healthy aged women and men. J Clin Endocrinol Metab 2001; 86:3604-10.
24. Taaffe DR, Pruitt L, Reim J, et al. Effect of recombinant human growth hormone on the muscle strength response to resistance exercise in elderly men. J Clin Endocrinol Metab 1994; 79:1361-6.
25. Papadakis MA, Grady D, Black D, et al. Growth hormone replacement in healthy older men improves body composition but not functional ability. Ann Intern Med 1996; 124:708-16. Comment in: Ann Intern Med 1997; 126:583-4.
26. Shi R, Berkel HJ, Yu H. Insulin-like growth factor-I and prostate cancer: a meta-analysis. Br J Cancer 2001; 85:991-6.
27. Sandhu MS, Dunger DB, Giovannucci EL. Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. J Natl Cancer Inst 2002; 94:972-80.
28. Chan JM, Stampfer MJ, Ma J, et al. Insulin-like growth factor-I (IGF-I) and IGF binding protein-3 as predictors of advanced-stage prostate cancer. J Natl Cancer Inst 2002; 94:1099-106.
29. Lukanova A, Lundin E, Toniolo P, et al. Circulating levels of insulin-like growth factor-I and risk of ovarian cancer. Int J Cancer 2002; 101:549-54.
30. Stattin P, Rinaldi S, Biessy C, et al. High levels of circulating insulin-like growth factor-I increases prostate cancer risk: a prospective study in a population-based nonscreened cohort. J Clin Oncol 2004; 22:3104-12.
31. Oliver SE, Gunnell D, Donovan J, et al. Screen-detected prostate cancer and the insulin-like growth factor axis: results of a population-based case-control study. Int J Cancer 2004; 108:887-92.
32. Renehan AG, Zwahlen M, Minder C, et al. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 2004; 363:1346-53.
33. Terzolo M, Reimondo G, Gasperi M, et al. Colonscopic screening and follow-up in patients with acromegaly: a multicenter study in Italy. J Clin Endocrinol Metab 2005; 90:84-90.
34. Allen NE, Roddam AW, Allen DS, et al. A prospective study of serum insulin-like growth factor-I (IGF-I), IGF-II, IGF-binding protein-3 and breast cancer risk. Br J Cancer 2005; 92:1283-7.
35. Rinaldi S, Kaaks R, Zeleniuch-Jacquotte A, et al. Insulin-like growth factor-I, IGF binding protein-3, and breast cancer in young women: a comparison of risks estimates using different peptide assays. Cancer Epidemiol Biomarkers Prev 2005; 14:48-52.
36. Chen C, Lewis SK, Voigt L, et al. Prostate carcinoma incidence in relation to prediagnostic circulating levels of insulin-like growth factor-I, insulin-like growth factor binding protein-3, and insulin. Cancer 2005; 103:76-84.
37. Augustin LS, Dal Maso L, Franceschi S, et al. Associations between components of the insulin-like growth factor system and endometrial cancer risk. Oncology 2004; 67:54-9.
38. Janssen JA, Wildhagen MF, Ito K, et al. Circulating free insulin-like growth factor (IGF) -I, total IGF-I, and IGF-binding protein-3 levels do not predict the future risk to develop prostate cancer: results of a case-control study involving 201 patients within a population-based screening with a 4-year interval. J Clin Endocrinol Metab 2004; 89:4391-6.
39. Woodson K, Tangrea JA, Pollak M, et al. Serum insulin-like growth factor I: tumor marker or etiologic factor? A prospective study of prostate cancer among Finnish men. Cancer Res 2003; 63:3991-4.
40. Corpas E, Harman SM, Blackman MR. Human growth hormone and human aging. Endocr Rev 1993; 14:20-39.
41. Fuh VL, Bach MA. Growth hormone secretagogues: mechanism of action and use in aging. Growth Horm IGF Res 1998; 8:13-20.
42. Broglio F, Gottero C, Arvat E, et al. Endocrine and non-endocrine actions of ghrelin. Horm Res 2003; 59:109-17.
43. Marshall L, Molle M, Boschen G, et al. Greater efficacy of episodic than continuous growth hormone-releasing hormone (GHRH) administration in promoting slow-wave sleep (SWS). J Clin Endocrinol Metab 1996; 81:1009-13.
44. Chapman IM, Bach MA, Van Cauter E, et al. Stimulation of the growth hormone (GH)-insulin-like growth factor I axis by daily oral administration of a GH secretogogue (MK-677) in healthy elderly subjects. J Clin Endocrinol Metab 1996; 81:4249-57.
45. Coschigano KT, Holland AN, Riders ME, et al. Deletion, but not antagonism, of the mouse growth hormone receptor results in severely decreased body weights, insulin, and insulin-like growth factor I levels and increased life span. Endocrinology 2003; 144:3799-810.
46. Hsieh CC, DeFord JH, Flurkey K, et al. Effects of Pit 1 mutation on the insulin signaling pathway: implications on the longevity of the long-lived Snell dwarf mouse. Mech Ageing Dev 2002; 123:1245-55.
47. Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of ageing on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001; 86:724-31.
48. Anawalt BD, Merriam GR. Neuroendocrine aging in men. Andropause and somatopause. Endocrinol Metab Clin North Am 2001; 30:647-69.
49. Gray A, Feldman HA, McKinlay JB, et al. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. J Clin Endocrinol Metab 1991; 73:1016-25.
50. Araujo AB, O'Donnell AB, Brambilla DJ, et al. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. J Clin Endocrinol Metab 2004; 89:5920-6.

51. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab 1983; 56:1278-81.
52. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab 1999; 84:2647-53.
53. Sih R, Morley JE, Kaiser FE, et al. Testosterone in older hypogonadal men: a 12 months randomized controlled trial. J Clin Endocrinol Metab 1997; 82:1661-7.
54. Tenover JS. Effects of testosterone supplementation in the aging male. J Clin Endocrinol Metab 1992; 75:1092-8.
55. Tenover JL. Testosterone for all? In: Proceedings of the 80th Meeting of the Endocrine Society, New Orleans, 1998.
56. Amory KJ, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab 2004; 89:503-10.
57. Reilly CM, Zamorano P, Stopper VS, et al. Androgenic regulation of NO availability in rat penile erection. J Androl 1997; 18:110-5.
58. Wang C, Swerdloff RS, Iranmanesh A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group. J Clin Endocrinol Metab 2000; 85:2839-53.
59. McNicholas TA, Dean JD, Mulder H, et al. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. BJU Int 2003; 91:69-74.
60. Alexandersen P, Haarbo J, Christiansen C. The relationship of natural androgens to coronary heart disease in males: a review. Atherosclerosis 1996; 125:1-13.
61. Hak AE, Witteman JC, de Jong FH, et al. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. J Clin Endocrinol Metab 2002; 87:3632-9.
62. Kenny AM, Prestwood KM, Gruman CA, et al. Effects of transdermal testosterone on lipids and vascular reactivity in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci 2002; 57:M460-5.
63. Hislop MS, St Clair Gibson A, Lambert MI, Noakes TD, Marais AD. Effects of androgen manipulation on postprandial triglyceridaemia, low-density lipoprotein particle size and lipoprotein (a) in men. Atherosclerosis 2001; 159:425-32.
64. Webb CM, McNeill JG, Hayward CS, et al. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. Circulation 1999; 100:1690-6.
65. Wu FC, von Eckardstein A. Androgens and coronary artery disease. Endocr Rev 2003; 24:183-217.
66. Liu PY, Death AK, Handelsman DJ. Androgens and cardiovascular disease. Endocr Rev 2003; 24:313-40.
67. Eckardstein A, Wu FC. Testosterone and atherosclerosis. Growth Horm IGF Res 2003; 13 Suppl A:S72-84.
68. Pollard M, Luckert PH. Promotional effects of testosterone and dietary fat on prostate carcinogenesis in genetically susceptible rats. Prostate 1985; 6:1-5.
69. Guay AT, Perez JB, Fitaihi WA, et al. Testosterone treatment in hypogonadal men: prostate-specific antigen level and risk of prostate cancer. Endocr Pract 2000; 6:132-8.
70. Rhoden EL, Morgentaler A. Testosterone replacement in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. J Urol 2003; 170:2348-51.
71. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. J Clin Endocrinol Metab 1997; 82:3793-6.
72. Orentreich N, Brind JL, Rizer RL, et al. Age changes and sex differences I serum dehydroepiandrosterone sulfate concentration throughout adulthood. J Clin Endocrinol Metab 1984; 59:551-5.
73. Kroboth PD, Salek FS, Pittenger AL, et al. DHEA and DHEA-S: a review. J Clin Pharmacol 1999; 39:327-48.
74. Legrain S, Girard L. Pharmacology and therapeutic effects of dehydroepiandrosterone in older subjects. Drugs Aging 2003; 20:949-67.
75. Spark RF. Dehydroepiandrosterone: a springboard hormone for female sexuality. Fertil Steril 2002; 77 Suppl 4:S19-25.
76. Genazzani AR, Inglese S, Lombardi I, et al. Long-term, low-dose dehydroepiandrosterone replacement therapy in aging males with partial androgen deficiency. Aging Male 2004; 7:133-43.
77. Kawano H, Yasue H, Kitagawa A, et al. Dehydroepiandrosterone supplementation improves endothelial function and insulin sensitivity in men. J Clin Endorinol Metab 2003; 88:3190-5.
78. Binello E, Gordon CM. Clinical uses and misuses of dehydroepiandrosterone. Curr Opin Pharmacol 2003; 3:635-41.
79. Morales AJ, Nolan JJ, Nelson JC, et al. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. J Clin Endocrinol Metab 1994; 78:1360-7.
80. Baulieu EE, Thomas G, Legrain S, et al. Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge Study to a sociobiomedical issue. Proc Natl Acad Sci USA 2000; 97:4279-84.
81. Morales AJ, Haubrich RH, Hwang JY, et al. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. Clin Endocrinol 1998; 49:421-32.
82. Flynn MA, Weaver-Osterholtz D, Sharpe-Timms KL, et al. Dehydroepiandrosterone replacement in aging humans. J Clin Endocrinol Metab 1999; 84:1527-33.
83. Percheron G, Hogrel JY, Denot-Ledunois S, et al. Effect of 1-year oral administration of dehydroepiandrosterone to 60- to 80-year-old individuals on muscle function and cross-sectional area: a double-blind placebo-controlled trial. Arch Intern Med 2003; 163:720-7.
84. Jedrzejuk D, Medras M, Milewicz A, et al. Dehydroepiandrosterone replacement in healthy men with age-related decline of DHEA-S: effects on fat distribution, insulin sensitivity and lipid metabolism. Aging Male 2003; 6:151-6.
85. Rizzo V, Porta C, Moroni M, et al. Determination of free and total (free plus protein-bound) melatonin in plasma and cerebrospinal fluid by high-performance liquid chromatography with fluorescence detection. J Chromatogr B Analyt Technol Biomed Life Sci 2002; 774: 17-24.
86. Kostoglou-Athanassiou I, Treacher DF, Wheeler MJ, et al. Melatonin administration and pituitary hormone secretion. Clin Endocrinol (Oxf) 1998; 48:31-37.
87. Magri F, Sarra S, Cichetti W, et al. Qualitative and quantitative changes of melatonin levels in physiological and pathological aging and in centenarians. J Pineal Res 2004; 36:256-61.
88. Van Cauter E, Plat L, Leproult R, Copinschi G. Alterations in circadian rhythmicity and sleep in aging: endocrine consequences. Horm Res 1998; 49:147-52.
89. Cardinali DP. The human body circadian: How the biologic clock influences sleep and emotion. Neuro Endocrinol Lett 2000; 21:9-15.
90. Anisimov VN, Mylnikov SV, Khavinson VK. Pineal peptide preparation epithalamin increases the lifespan of fruit flies, mice and rats. Mech Ageing Dev 1998; 103:123-32.
91. Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin. Sleep Med Rev 2005; 9:11-24.
92. Lissoni P. Modulation of anticancer cytokines IL-2 and IL-12 by melatonin and the other pineal indoles 5-methoxytryptamine and 5-methoxytryptophol in the treatment of human neoplasms. Ann NY Acad Sci 2000; 917:560-7.
93. Urban RJ, Bodenburg YH, Gilkison C, et al. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. Am J Physiol 1995; 269(5 Pt1):E820-6.
94. Peck JS, LeGoff DB, Ahmed I, Goebert D. Cognitive effects of exogenous melatonin administration in elderly persons: a pilot study. Am J Geriatr Psychiatry 2004; 12:432-6.
95. Pawlikowski M, Kolomecka M, Wojtczak A, Karasek M. Effects of six months melatonin treatment on sleep quality and serum concentrations of estradiol, cortisol, dehydroepiandrosterone sulfate, and somatomedin C in elderly women. Neuro Endocrinol Lett 2002; 23 Suppl 1:17-9.
96. Garfinkel D, Laudon M, Nof D, Zisapel N. Improvement of sleep quality in elderly people by controlled-release melatonin. Lancet 1995; 346:541-4. Comment in: Lancet 1995; 346:1491.