The endocrinology of gonadal involution: menopause and andropause

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Most aging individuals die from atherosclerosis, cancer or dementia. In the oldest old also loss of muscle strength resulting in frailty becomes the limiting factor for an individual’s chances of living an independent life until death. Two hormonal changes mark the aging process in man. In women an acute drop in estrogen production by the ovaries around the age of 50 initiates a symptom complex called menopause. In men a more subtle drop of testosterone bioactivity from 40 yrs onwards might be accompanied by more difficulty to recognize symptoms (andropause). Hormone replacement strategies in elderly women and males with estrogens or androgens, respectively, has some clear advantages, but is currently controversial, because of the occurrence of adverse effects.

There is considerable variation in the effect of aging on healthy individuals, with some people exhibiting extensive alteration in physiological functions with age and others little or none. It has been suggested that it might be useful to distinguish between usual and successful patterns of aging [1]. Genetic factors, lifestyle, and societal investments in a safe and healthy environment are important aspects of successful aging. Traditionally, the aging process, including the development of physical frailty and a gradual loss in cognitive function toward the end of life, has been considered to be physiological and unavoidable. In recent years, however, it has become evident that it might not be necessary to accept the grim stereotype of aging as an unalterable process of decline and loss [1]. As life expectancy increases further in the coming decades, the overarching goal for the coming years should be an increase in years of healthy life with a full range of functional and mental capacity at the last stage of life. Such a compression of morbidity can in principle be achieved in part by healthy lifestyle measures, and these already seem to result in a decline in the prevalence of long-term disability in the elderly population [2].

The endocrine system in man undergoes major changes during the aging process [3]. Three hormonal systems show abrupt or gradual decreases in circulating hormone concentrations: estrogen (in menopause) and testosterone (in andropause), dehydroepiandrosterone (DHEA) and...
its sulfate (DHEAS) (in adrenopause), and the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis (in somatopause) decrease in biologic activity in parallel with the appearance of characteristic changes in aging organs, including the brain. The availability of hormone replacement of all hormones mentioned, as well as the proven clinical effectiveness of such replacement in (young) adults with selective deficiencies in these hormones, has raised hopes that the application of these hormone replacement strategies will prevent or delay some aspects of the aging process in healthy elderly individuals. However, such beneficial effects remain largely unproven and their safety uncertain.

**MENOPAUSE**

In women the acute drop in circulating estrogen levels and the permanent cessation of menstruation around age 50 years is often accompanied by vasomotor reactions, sleep disturbances, changes in skin and body composition, and a depressed mood. The use of hormone replacement therapy (HRT, estrogens or estrogen plus progestogen) rapidly alleviates these symptoms of menopause. In women with these symptoms, HRT also improves verbal memory, vigilance, reasoning, and motor speed, but there is no enhancement of other cognitive functions [4]. Generally, no benefits of HRT were observed in asymptomatic women.

Currently, the long-term use (5-10 years or more) of HRT after menopause is surrounded by controversy; many studies indicate advantages regarding the prevention of the 3 chronic disorders most common in elderly women: cardiovascular diseases, osteoporosis, and dementia. However, these beneficial effects are a double-edged sword because long-term HRT is accompanied by a significant increase in the incidence of breast cancer, thrombosis, and stroke. The controversy has arisen partly because of differences in the selection of the participating menopausal women in the large prospective trials with HRT. For example, the inclusion of nurses, who are probably more aware of the advantages of healthy lifestyle than the “normal” population of menopausal women, might have introduced a “healthy user bias” in several of the best prospective randomized clinical trials [4].

In 2002 the interim results were published of the women’s health initiative trial [5]. This is a randomized trial to assess risks and benefits of intervention strategies in the American postmenopausal population. The trial has shown harm for cardiovascular diseases, including coronary heart disease (the primary outcome) and stroke, although it showed benefits for hip fractures and bowel cancer. The relative risks for invasive breast cancer, coronary heart disease, and stroke were increased, although the absolute risks were very small. One treatment arm of the trial included over 16 000 postmenopausal women who were taking continuous combined estrogen-progestagen hormone replacement therapy, using conjugated equine estrogens 0.625mg plus medroxy-progesterone acetate 2.5 mg daily, tested against placebo [5]. This primary prevention study was due to run for 8.5 years, but was halted at just over 5 years because the number of cases of breast cancer had reached a prespecified safety limit. For 10 000 women taking hormone replacement therapy each year, compared with those not taking it, there would be an additional eight cases of invasive breast cancers, seven heart attacks, eight strokes, and eight pulmonary embolisms. However, there would also be six fewer bowel cancers and five fewer hip fractures. Overall mortality was not increased with therapy.

The decision to stop the trial and to change US recommendations for the use of postmenopausal HRT for primary prevention of chronic conditions might not be automatically applicable to the European countries [6-8]. First, we should realize that the weight and BMI of the US female population is in general considerably higher, making them in itself more prone to breast cancer, stroke, thrombosis and cardiovascular disease. Secondly, more and more evidence is provided that genetic testing, for example for estrogen-receptor polymorphisms, and factor V Leiden, might not only better predict a positive outcome of HRT on cardiovascular disease [9], but the chances of developing thrombosis [10-11] as well. The third, and perhaps in the end most important reason to still consider HRT as an important preventive treatment is its impact on the incidence of dementia [12].

Women seem to be at higher risk for developing Alzheimer disease, and this is in part due to their increased longevity. It has been suggested that the abrupt decline of estrogen production at menopause may be associated with a vulnerability of the female brain. Elderly men have an intrinsic supply of estrogen because they aromatize testosterone into estradiol within the brain. There is strong experimental evidence in the intact brain that estradiol might play a key neuroprotective role by delaying the initiation phase of neurodegenerative disease onset. In a recent study by Dubal et al [13], it was demonstrated that in mice lacking the estrogen-α receptor, estrogen protects the brain from injury by accelerating and amplifying the activity of this receptor. As a consequence, genes that help the brain cells survive are activated, or genes that harm the brain cells are suppressed [13].

Postmenopausal HRT seems to prevent or delay cognitive decline and dementia [14]. In a systematic review
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and meta-analysis [15] of all observational studies conducted thus far, it was concluded that HRT is associated with a decreased risk of dementia (summary odds ratio, 0.66; 95% confidence interval, 0.53-0.82). However, several studies have important methodological limitations, the healthy user bias mentioned earlier being an important one.

Hormone replacement therapy administered for 1 year in women with mild to moderate Alzheimer disease did not slow disease progression, nor did it improve global, cognitive, or functional outcome. Recently, the use of high-dose estrogens to improve cognition in women with dementia was reported in a small study [16]. In a very recent prospective study of incident dementia among 1357 men (mean age 73.2 yrs) and 1889 women (mean age 74.5 yrs) residing in a single county in Utah (USA), it was again demonstrated that prior HRT use is very closely associated with reduced risk of dementia [17]. There was a highly statistical HRT-duration-dependent decrease in incident demented women after the age of 80, with a decrease of incident dementia in those women that had used more than 10 years HRT in the past to those found in men. There was no apparent benefit of current HRT in the older group of women [17].

These considerations on the advantages and risks of HRT in normal post-menopausal women are very sobering. There is no doubt that early HRT, taken immediately at menopause, alleviates most symptomatology and is in principle safe. In women in which cardiovascular disease is symptomatic, other (preventive) medication including  β-blockers, ACE-inhibitors, aspirin and/or statins have been proven to be effective. Also in symptomatic osteoporosis bisphosphonates and SERM’s have similar or even better preventive efficacy than HRT.

In recent studies we investigated the degree and potential cardiovascular determinants of arterial stiffness (assessed by aortic pulse wave velocity (PWV) measurements) in healthy postmenopausal women [18]. PWV has been demonstrated a clear marker of an increased absolute risk of stroke, coronary heart disease, and death within 10-12 years. We observed the classical well-known risks like a positive association between PWV and age, mean arterial pressure, pulse pressure, heart rate, and pack-years of cigarette smoking, and a negative relation with height and HDL-cholesterol [18]. In addition, however, a higher than usual dietary intake of phytoestrogens (isoflavones and lignans) was associated with a lower aortic stiffness in these postmenopausal women, suggesting that phytoestrogens have a protective effect on the risk of atherosclerosis and arterial degeneration through an effect on arterial walls, especially among older women [19]. Interestingly, also alcohol consumption was inversely associated with pulse-wave velocity in the aorta, supporting the concept that moderate alcohol consumption decreases the risk of cardiovascular disease also in postmenopausal women [20].

In a recent study the effects of the combination of GH (20 µg/kg, 3 times per week) and HRT was studied in a 26-week randomized, double-blind, placebo controlled study in healthy women (65 to 88 years old). No significant effects were observed in muscle strength or cardiovascular endurance [21].

In summary, in my opinion, the verdict on the use of HRT in health-conscious women remains out. With the further development of genetic testing to identify those women which might benefit most, and/or are most at risk for thrombotic events and/or breast cancer, the decision to prescribe HRT early after menopause in order to obtain the early beneficial effects on subjective well-being, as well as the late delaying effects on dementia, might remain an attractive option.

ANDROPAUSE

Age-associated hypogonadism develops not as clear in men as it is in women. The key difference from the menopause is the gradual, often subtle change in androgen levels in men compared with the precipitate fall of estrogen production in women. There is now general agreement that as men age, there is a decline in serum total testosterone concentration that begins after the age of 40 years. In cross-sectional studies the annual decline in total and “free” testosterone in 0.4% and 1.2%, respectively. The higher decline in “free” testosterone levels is related to the increase in sex hormone-binding globulin (SHBG) levels with aging [22-23].

It remains unclear today whether the well-known biological changes during ageing in men like the reduction in sexual activity, in muscle mass and strength and in skeletal mineralization are causally related to these changes in testosterone bioactivity (“andropause”) [3].

In a group of over 400 independently living elderly men (mean age 78 years; 73-94 years) a positive association was observed between serum total and free testosterone concentrations and muscle strength as well as an inverse relationship with fat mass. Also low bioavailable testosterone was in a population-based study in 856 men (ages 50-89) associated with a depressed mood [24].

There are many persuasive reports in the literature which demonstrate that treatment of men of all ages (young, adult and old) with clear clinical and biochemical hypogonadism with testosterone replacement in-
stantly reverses vasomotor activity (flushes and sweats), improves libido, sexual activity and mood, increases muscle mass, strength and bone mineralization, prevents fractures, decreases fat mass and decreases fatigue, and poor concentration [22, 25]. Also, the treatment of adult normal men with supraphysiologic doses of testosterone, especially when combined with resistance exercise training, increases fat-free mass and muscle size and strength [26].

A search for studies reporting the results of androgen therapy in older men demonstrates that most studies were small, short-term, non-controlled, and without uniform end-points.

Numerous studies of large populations of healthy men have shown a marked rise in the incidence of impotence to over 50% in men aged 60 to 70 [27]. Although this increase in impotence occurs in the same age group that shows a clear decline in serum (free) testosterone levels, no causal relationships have been demonstrated. Testosterone replacement therapy in elderly men is in most instances not effective for the treatment of loss of libido or impotence in individuals with serum testosterone concentrations within the normal age-matched range: other factors such as atherosclerosis, alcohol consumption, smoking, and the quality of personal relationships seem to be more important denominators [28]. Only in the case of clear hypogonadism does the decrease in libido and testosterone are restored by potency therapy. This suggests that there is a threshold level of testosterone in the low normal range, below which libido and sexual function are impaired and above which there is no further enhancement of response [29].

Summarizing the literature available the indiscriminate (preventive) treatment of healthy elderly men with testosterone at a dose that increases serum testosterone concentrations to those observed in 20-30 year olds, has limited anabolic effects on body composition (a slight decrease in fat mass, and a slight increase in muscle mass). Also minor beneficial effects on muscle strength or physical performance are observed [29, 30].

Detailed analysis of a number of studies in which elderly men were selected on the basis of the presence of “low” pre-treatment serum testosterone concentrations indicates a beneficial effect of testosterone replacement therapy on muscle strength, bone mineral density, mood, as well as (subjective) aspects of the quality of life [22, 28, 31].

In conclusion: testosterone at supraphysiologic doses, when administered to eugonadal men, increases muscle mass and strength. “Replacement” therapy directed at restoring serum testosterone concentrations in healthy elderly males to levels observed between the age of 30 to 50 lowers fat mass and increases lean mass to a limited extent without a beneficial effect on muscle strength and physical performance. At present it remains uncertain whether testosterone replacement produces clinically meaningful improvements in muscle function without significant adverse effects in frail older men or in elderly men with serum testosterone concentrations between 7.0 to 11.4nmol/l (2.0 to 3.3ng/ml) [3].

If one decides to start testosterone replacement, the major goal of therapy is to replace testosterone levels to as close to “physiologic” age-watched level as possible. The dose should then be titrated according to serum levels. At present the duration of administration of testosterone is uncertain. Control of prostate size, prostate-specific antigen levels and hemotocrit levels are mandatory. The identification of elderly men who might benefit most from testosterone treatment remains uncertain, while the risks to the prostate, and possible effects on the process of atherosclerosis remain subjects for study. The concept of developing androgenic compounds with variable biologic action in different organs (selective androgen receptor modulation) is currently pursued [32].

REFERENCES