ECRONICON OPEN ACCESS

EC ENDOCRINOLOGY AND METABOLIC RESEARCH
Guest Editorial

Aging-Related Gonadal Hormonal Deficiency and (Sex)-Hormone Replacement Therapy

Vinod Nikhra*

Senior Chief Medical Officer and Consultant, Department of Medicine, Hindu Rao Hospital and NDMC Medical College, New Delhi, India

***Corresponding Author**: Vinod Nikhra, Senior Chief Medical Officer and Consultant, Department of Medicine, Hindu Rao Hospital and NDMC Medical College, New Delhi, India.

Received: May 28, 2019; **Published:** June 26, 2019

Aging process and humoral alterations

The aging is a temporal process involving a general decline in various physiological functions and a reduced capacity to maintain efficient homeostasis and reparative mechanisms, resulting in loss of function and senescence. In addition, the aging is associated with significant changes in the regulation of hormonal axes and the downstream availability of their active components [1]. The alterations occur in the functional interface between somatic physiology and endocrine systems with the aging and result in a greater prevalence of endocrine malfunction-related disorders in the elderly population. In this context, a major proportion of morbidity afflicting the older adults, may be attributed to potentially amenable hormonal imbalances by judicious hormonal supplementation.

The complex changes occurring in the endocrine system with aging, have impact on the hormone production and secretion, hormone metabolism, hormone levels circulating in blood and the target tissue response to hormones. Yet, despite age-related changes, the endocrine system functions well in most older adults. However, some changes occur because of either damage to cells and tissues during the aging process or because of the genetically programmed cellular alterations. In general, the clinically identifiable changes are seen during later years of life because the physiological circadian rhythms are lost and secretion of various hormones decreases, the impact of which is augmented by the reduced sensitivity of tissues to their action.

Gonadal steroids are produced by the gonads and include estradiol and progesterone from the ovaries and testosterone from the testes. The aging process affects the gonadal endocrine function, as well. There occurs reduced protein synthesis, a decrease in lean body mass and bone mass; increased fat mass, insulin resistance and higher cardiovascular disease risk; and fatigue, depression, anaemia, poor libido, erectile deficiency and a decline in immune function. The contribution of sex steroids to the development and progression of the CVD is related to the clustering of interrelated risk factors that promote the development of atherosclerosis and insulin resistance [2].

The testosterone story

The testosterone has favourable direct vasodilatory effects on coronary vasculature and peripheral system vascular resistance and positive effects on cardiac and skeletal muscle function. There is testosterone-mediated control of the musculoskeletal system and age-related testosterone deficiency may result in loss of muscle mass and muscle strength, and sarcopenia. The relationship between testosterone and heart disease in both males and females is less clear. Further, the testosterone might provide metabolic benefits including improved insulin sensitivity and favourable changes in body composition. The testosterone deficiency as indicated by low serum testosterone concentrations or hypotestosteronemia, is a common hormonal alteration strongly associated with male aging.

Testosterone is essential for the maintenance of libido and fertility, and its deficiency has been correlated to depressive symptoms with a syndrome called partial androgen deficiency of the aging male (PADAM). The andropause is a relatively ill-defined process characterised by a progressive age-dependent loss of the anabolic androgen testosterone in males [3]. The decline in testosterone levels with age, is gradual and much less dramatic than the decline of estrogens in women, and rarely affects sperm production until very old age. Over the

past two decades, there has been an increase in testing of testosterone levels and therapeutic use of testosterone [4]. The testosterone supplementation has been proved to be effective, for improving quality of life of aged patients with PADAM.

The decline in ovarian hormones

The Oestrogens act in target tissues through oestrogen receptors and G protein-coupled oestrogen receptor 1. With increasing age, the ovaries decrease in both size and weight and become progressively less sensitive to gonadotropins. There occurs a decline in the peripheral levels of oestrogen and progesterone, with an increase in luteinizing hormone (LH), follicle-stimulating hormone (FSH) and sex hormone-binding globulin. Premenopausal women have a reduced risk of CVD compared with age-matched men, but mortality as a result of CVD is higher in premenopausal women than in age-matched men. The protective role of oestrogens as relates to CVD is not fully established.

The low levels of estrogens and progesterone associated with menopause have been linked to some disease states, such as osteoporosis, atherosclerosis and dyslipidemia. This is accompanied by diverse sequelae, including an increased risk of osteoporosis, cardiovascular and cerebrovascular disease and psychogenic disturbances [5]. The measures to attempt to ameliorate losses in oestrogen through hormone replacement therapy (HRT) is, however, controversial as it has been related to increased risks of malignancy and vascular events [6].

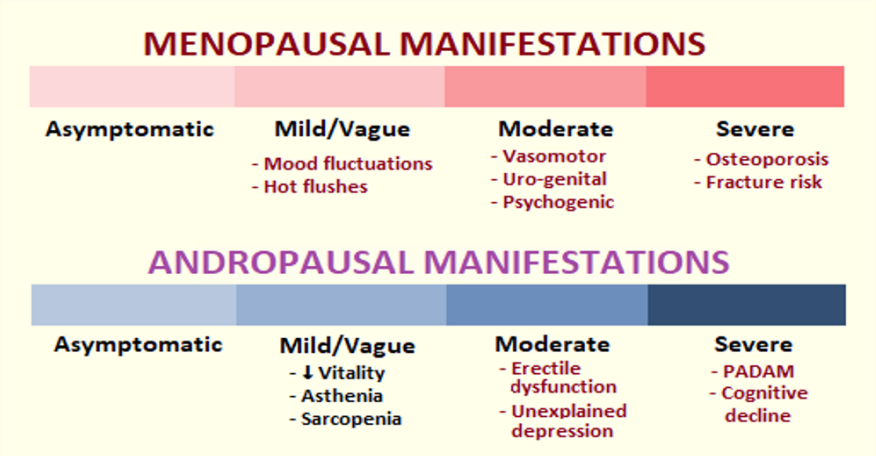

Figure 1: *The clinical manifestations of menopause and andropause. Extent of the severity guides the initiation, maintenance and monitoring (Sex)-Hormone Replacement Therapy.*

(Sex)-hormone replacement therapy

Following menopause, approximately 90% of circulating oestrogen is lost during the fourth and fifth decade of life and the extra-glandular production of oestrogens by aromatase expression within adipose and skin becomes the predominant source of sex steroids, with additional contribution from the adrenals. As compared to the, sudden and dramatic changes seen in women, testosterone loss seen during the andropause is insidious and variable, there being no specific age at which the process starts. The global reduction in activity across the hypothalamic-pituitary-gonadal axis and reduced GnRH is the principal factor leading to gradual testicular failure. Sex hormone-binding globulin (SHBG) levels increase with aging, manifesting the andropause as there occurs relative decrease in free testosterone than the SHBG-bound hormone [7].

In both men and women, the loss of sex hormones with aging leads to alterations in body mass, musculoskeletal changes, sexual dysfunction and long-term affectations to health and certain disease-risks (Figure 1). There occurs decreased libido in post-menopausal women due to loss in testosterone, which in men may manifest as erectile dysfunction [8]. The most important alteration following the menopause is osteoporosis, which is driven by reductions in metabolically active trabecular bone due to uncoupling of the bone remodelling cycle secondary to oestrogen loss and leads to an increased fracture risk in older women [9]. While men are generally protected

from the effects of pathologically decreased bone mineral density by virtue of having a higher peak bone mass, though the prevalence of osteoporosis is known to increase in the aging males.

There have been reported both positive and negative health outcomes associated with gonadal HRTs. The current evidence is contentious as to whether the testosterone replacement therapy provides a significant advantage to men with testosterone within normal parameters for their age. The loss of sex hormones may modulate cardiovascular risk through adverse alterations in lipid profile. Additionally, the falling sex hormone concentrations may lead to increased insulin resistance. The menopause is attended by urogenital symptoms such as urinary frequency, dysuria, incontinence and vaginal atrophy. In addition, there result symptoms due to from alterations in the set point of the hypothalamus, including recurrent hot flushes following luteinizing hormone (LH) surges, and changes in serotonin levels. Despite the incapacitating symptoms affecting health and QOL in menopausal women, the HRT has met with considerable controversy during recent years [10]. Analysing thirteen trials incorporating a total of 38,171 women, a recent Cochrane review identified an increased risk of stroke, venous thromboembolic events and pulmonary embolism in patients treated with HRT.

Yet, the HRT is useful for treating vasomotor, urogenital and some psychogenic symptoms related to the menopause. In addition, it decreases osteoporosis and fracture risk. But, its role in the prevention or treatment of CVD is contentious. Though, the significant increase in the risk of heart disease in women undergoing the menopause, indicates a cardioprotective role for oestrogen which is lost in later age. Also, the claims about a significantly reduced risk of colorectal cancer have not been established. On the flipside, there is an increased risk for breast cancer, coronary events, venous thromboembolism, gallbladder disease and ovarian cancer in women taking HRT. Further, the clinical studies favour that when indicated, HRT should be given as short-term therapy.

Various previous and present pharmaco-epidemiological studies do not support any causal role between testosterone replacement therapy (TRT) and adverse CV events. Yet, TRT may represent an important new strategy for improving cholesterol and insulin resistance and reducing body fat and increasing lean muscle mass. There are potential cardiovascular risks of TRT. Some retrospective studies and randomized trials have suggested that TRT may increase the CVD risk. Still, the population studies suggest that low serum levels of endogenous testosterone are a risk factor for cardiovascular events and cognitive decline. There are no large, long term randomized controlled TRT studies that include cardiovascular outcomes [11]. In general, it appears that TRT does not cause marked increases in risk of cardiovascular events [12]. There might be differential effects on cardiovascular and cerebrovascular risk related to endogenous and exogenous testosterone on cardiovascular risk. The low endogenous serum testosterone appears to be associated with higher risk of cardiovascular disease and overall mortality in older men [13]. There might be a U-shaped curve like effect for circulating endogenous androgen concentrations such that lower and higher concentrations might confer greater risk of cardiovascular events and all-cause mortality than midrange concentrations [14]. A review of testosterone prescription database studies demonstrated that TRT was not associated with overall mortality, myocardial infarction, stroke, or deep venous thrombosis events [15]. But, as inferred by a recent study, there is a potentially higher risk of cardiovascular events in men receiving testosterone, with the risk increasing early after treatment initiation and the TRT should be individualised [16]. Another major undergoing study, The TRAVERSE trial, which began in 2018, is the first detailed trial of TRT that is adequately powered to assess cardiovascular events. The findings from the TRAVERSE study may become available about a decade later.

The aggressive marketing strategy of pharmaceutical companies has resulted in this marked increase in testosterone use. There are promises for being more alert, energetic, mentally sharp and sexually functional; to combat fatigue, low sex drive, and weight gain, with the goal of regaining the vitality of their youth [17]. The number of testosterone prescriptions issued for middle-aged or older men with either age-related or obesity-related decline in serum testosterone levels has increased even though these conditions are not approved indications for TRT [18].

Bibliography

1. Chahal HS and Drake WM. "The endocrine system and ageing". *Journal of Pathology* 211.2 (2007): 173-180.

2. Morselli E., *et al*. "The effects of oestrogens and their receptors on cardiometabolic health". *Nature Reviews Endocrinology* 13.6 (2017): 352-364.

3. Somboonporn W., *et al*. "Testosterone for peri- and postmenopausal women". *Cochrane Database of Systematic Reviews* 4 (2005): CD004509.

4. Lee OD and Tillman K. "An Overview of Testosterone Therapy". *American Journal of Men's Health* 10.1 (2016): 68-72.

5. El Khoudary SR., *et al*. "Longitudinal assessment of the menopausal transition, endogenous sex hormones, and perception of physical functioning: The Study of Women's Health Across the Nation". *Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* 69.8 (2014): 1011-1017.

6. Marioribanks J., *et al*. "Long term hormone therapy for perimenopausal and postmenopausal women". *Cochrane Database of Systematic Reviews* 7 (2012): CD004143.

7. Batrinos ML. "The aging of the endocrine hypothalamus and its dependent endocrine glands". *Hormones* 11.3 (2012): 241-253.

8. El-Sakka AI and Hassoba HM. "Age related testosterone depletion in patients with erectile dysfunction". *Journal of Urology* 176 (2006): 2589-2593.

9. Wells G., *et al*. "Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group: Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women". *Endocrine Reviews* 23.4 (2002): 529-539.

10. Panay N., *et al*. "British Menopause Society and Women's Health Concern: The 2013 British Menopause Society and Women's Health Concern recommendations on hormone replacement therapy". *Menopause International* 19.2 (2013): 59-68.

11. Gagliano-Juca T and Basaria S. "Trials of testosterone replacement reporting cardiovascular adverse events". *Asian Journal of Andrology* 20.2 (2018): 131-137.

12. Snyder PJ., *et al*. "Effects of testosterone treatment in older men". *New England Journal of Medicine* 374.7 (2016): 611-624.

13. Meyer EJ and Wittert G. "Endogenous testosterone and mortality risk". *Asian Journal of Andrology* 20.2 (2018): 115-119.

14. Yeap BB. "Testosterone and its metabolites: differential associations with cardiovascular and cerebrovascular events in men". *Asian Journal of Andrology* 20.2 (2018): 109-114.

15. Shores MM. "Testosterone treatment and cardiovascular events in prescription database studies". *Asian Journal of Andrology* 20.2 (2018): 138-144.

16. Anawalt BD and Yeap BB. "Conclusions about testosterone therapy and cardiovascular risk". *Asian Journal of Andrology* 20.2 (2018): 152-153.

17. Giovanni Corona G., *et al*. "Testosterone Replacement Therapy and Cardiovascular Risk: A Review". *World Journal of Men's Health* 33.3 (2015): 130-142.

18. Gagliano-Jucá T and Basaria S. "Testosterone replacement therapy and cardiovascular risk". *Nature Reviews Cardiology* (2019).

Volume 4 Issue 5 July 2019