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Review Article

Late onset hypogonadism of men is not equivalent to the menopause

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ABSTRACT

Some men between the ages 45 and 60 years develop complaints and symptoms reminiscent of menopausal complaints in women. So, parallels were sought between the changes in female and male endocrinology during that period of life. Indeed, men do show a decline of serum testosterone from age 40 to 50 years onwards but it is a slow decline of 1–2% per year and over time it may amount to hypogonadism. The mechanism of a decline in serum testosterone in men does not resemble the menopause; it is partially an aging neuroendocrine system with a less efficient testosterone production but equally or more important, the result of inhibition of testosterone production by metabolic factors in relation to visceral obesity. These effects are in part reversible with weight loss. A hypogonadal state in aging men has deleterious effects. Mortality of all causes is highest in men with low testosterone impacting on their metabolic state leading to diabetes mellitus, cardiovascular disease, osteoporosis, and sexual dysfunction. Normalization of testosterone in aging hypogonadal men has a beneficial effect on the above pathologies. The fear that testosterone treatment of elderly men would lead to prostate disease has not been substantiated in studies. So, while men do not have a 'menopause', testosterone deficiency in old age deserves serious attention.

Contents

1. Introduction 52
2. The pathophysiology of declining testosterone levels with aging 53
3. Late onset hypogonadism and treatment with testosterone in elderly men 53
   3.1. The relationship between testosterone and metabolism 54
   3.2. Osteoporosis 54
   3.3. Sexual functioning 54
   3.4. Lower urinary tract symptoms, erectile dysfunction, and testosterone 55
4. Safety of testosterone therapy 56
   4.1. Prostate 56
   4.2. Cardiovascular disease 56
5. Conclusion 56
   Contributors 56
   Funding information 56
   Competing interest 56
   Provenance and peer review 56
   References 56

1. Introduction

When men reach their late 40s to early 60s, some experience a reduction in libido and sexual functioning, weight gain, fatigue, depression, and other emotional symptoms which bear some similarities to the female menopause. This has instigated research

Abbreviations: T, testosterone; LH, luteinizing hormone; ED, erectile dysfunction; LUTS, lower urinary tract symptoms; BPH, benign prostate hyperplasia.

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whether these complaints presenting at the age of menopause in women, could possibly be related to age-related changes in the male endocrine reproductive system.

Probably the first scientific documentation of declining vitality and sexual functions and its relation to male hormones is from the eminent French physiologist and neurologist Brown-Séquard (1889) who injected himself with aqueous extracts from dogs' testis and felt rejuvenated [1].

In the 1930s the chemical structure of testosterone (T) had been identified and since the 1940s there was a renewed interest in male aging and its potential relationship with male hormones (for review: [1]). Werner (1939) introduced the term 'male climacteric' but stipulated that this only could be reliably diagnosed when urinary output of gonadotropins was elevated. In 1944, Heller and Myers identified symptoms of what they also labeled the "male climacteric" including loss of libido and potency, nervousness, depression, impaired memory, the inability to concentrate, fatigue, insomnia, hot flushes, and sweating. These authors found that their subjects had lower than normal levels of T, and that symptoms decreased dramatically when patients were given replacement doses of T (for review: [1]).

It was Bauer in 1944, who argued that 'male climacteric' was a misnomer and the symptoms of the 'male climacteric' were simply the expression of testicular insufficiency. Meanwhile terms like 'male menopause' or 'andropause' or in the popular press 'penopause' became en vogue. Especially, andropause, meaning 'the end of being a man' and therefore an inappropriate term, became widely used. In 2001 the Endocrine Society convened a workshop on andropause and until 2003 the term was used in the Journal of Clinical Endocrinology & Metabolism. Other journals accept the term up to the present day [1].

In 1994 at the andrology workshop of the Austrian Urology Society, the term 'partial androgen deficiency of the aging male' with its acronym PADAM was introduced. The term drew no parallel with the female menopause and recognized that not all men become T deficient in old age and when they become T deficient, its pattern was unlike the menopause [1].

Subsequently the term 'late-onset-hypogonadism' found its way into the literature, stressing that late-onset-hypogonadism is a hybrid form of primary and secondary hypogonadism corresponding to the pathophysiological facts of the age-related decline in gonadal and/or hypothalamic–pituitary function, eventually manifesting in clinically relevant hypogonadism.

New insights that this syndrome was not limited to aging subjects prompted some authors to propose the term 'T deficiency syndrome' but this term has not found wide use. But the notion that the phenomenon of declining serum T was not necessarily linked to a defined period of the aging process found wider support in studies. In a study of men aged 40 years or older with good to excellent health, no decrease of serum T was observed although obesity and former smoking had a depressing effect on serum T. This probably indicates that the age-related decline in blood T accompanying non-specific symptoms in older men may be due to accumulating age-related co-morbidities rather than a symptomatic androgen deficiency state [2].

From an endocrine viewpoint, any similarity between the female menopause and the decline of serum T levels in men has not been supported by scientific findings. Nevertheless, the (patho)physiology of T in aging men has appeared to be a subject that deserves serious attention. T deficiency in advanced age has serious health implications. And normalization of serum T appears to have a large number of beneficial effects, even though the final verdict is not yet out. In traditional medical thinking the etiology of prostate disease is linked to T but this view is up for revision. Several studies now document that T administration to elderly men is acceptably safe.

2. The pathophysiology of declining testosterone levels with aging

The menopause was originally believed to result from 'exhaustion of the ovary', but it is becoming clear that neuroendocrine mechanisms are involved in the loss of reproductive capacity in women [3]. The basis of the decline of T in aging men is partially explained by neuroendocrine mechanisms, all leading to a diminished stimulation of the pituitary to produce the stimulatory hormone of the peripheral endocrine gland. There are also testicular factors contributing to the decline of T production with aging (for review: [4]). Healthy elderly men maintain high frequency, but low amplitude LH secretion patterns. Further, there is evidence that, with the same circulating levels of testicular steroids, the feedback signal to the hypothalamus is stronger than in younger men, thus diminishing output of LH when T levels decline [4]. Administration of human chorionic gonadotropin to elderly men produces a diminished response of T compared to young men, particularly in obese men [5], pointing to an impairment of testicular steroidogenesis. But an important part of the decline of serum T in men is explained by metabolic factors. Synthesis of sex hormone binding globulin and T are highly correlative biochemical processes. Hyperinsulinism associated with adiposity suppresses synthesis of SHBG and thus, levels of circulating T [4]. Weight loss is associated with a proportional increase, and weight gain a proportional decrease, in testosterone and SHBG. Free T showed a curvilinear relationship to weight change; only those who gained or lost $\geq$15% of weight showed a significant change (in the same direction as testosterone) [6].

In addition, insulin [7] and leptin [5] exert suppressive effects on testicular steroidogenesis and may contribute to further disruption of pulse amplitude of LH diminishing stimulation of the testicular steroidogenesis. Further, conversion of T to estradiol in adipose tissue resulting in elevated serum estradiol, may contribute to inhibition of androgen biosynthesis via central feedback mechanism involving the hypothalamic–pituitary-gonadal axis [8]. It is well recognized that adipocytes secrete a host of adipokines that regulate a variety of metabolic processes in endocrine, paracrine, and autocrine fashion. Thus, adipocytokines, secreted by visceral fat modulate the hypothalamic–pituitary–testicular axis and inhibit T production [9]. Modulation of GnRH secretion by kisspeptins, produced by adipose tissue causes significant lowering of circulating levels of T. Several clinical studies confirm the inverse relationship between visceral obesity and depressed serum testosterone. In one study of elderly men with serum T levels $\leq$12.1 nmol/L, 71% were obese and 96% had an elevated waist circumference [10] and in another study 62% were obese and 97% had an elevated waist circumference [11]. But, unlike the menopause with its rather abrupt decline of female sex steroids, in men there is a gradual decline of serum T, in a number of cases below the threshold values for male hypogonadism.

3. Late onset hypogonadism and treatment with testosterone in elderly men

Part of the lower than normal serum T in elderly men can be reversed in obese individuals. Lifestyle intervention, along with better nutritional counseling and physical activity reduces weight and conjointly raises T levels [12]. Unfortunately, these goals are only rarely achieved in daily medical practice. Obesity seems to be a treatment-resistant entity. Following bariatric surgery, the increase in T levels parallels weight loss. However, the recovery of T concentration is more pronounced in younger than in older patients, indicating an age-related impairment of the hypothalamic–pituitary–testicular axis [13].