Andropause: An emerging World health problem

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Summary

Andropause is an emerging clinical concept that is gaining an increasing recognition, as the world becomes more aging. The clinical features though subtle are easy to identify and appropriate treatment of diagnosed cases will to a good extent alleviate a lot of age-related complaints and improve the general quality of life in the elderly men.

Low level of clinical suspicion secondary to inadequate knowledge about this clinical entity remains the major obstacle to appropriate treatment. In this review, the literature has been perused and the definition, epidemiology, pathophysiology, clinical features, diagnosis and treatment are outlined.

Key-words: ***Male aging, Androgen deficiency, Testosterone replacement therapy.***

Résumé

Andropause est un concept clinique qui vient d'emerger et elle gagne une reconnaissance progressive dans les temps modernes. Le traits caractéristiques cliniques quoique subtils sont facilement identifiable et une prise en charge adéquate des cas diagnostiques sera dans une large mesure alleger beaucoup de complaisants qui sont liés à l'âge et améliorent la qualité de vie en général chez des hommes âgés. Niveau bas de soupçon clinique secondaire à la connaissance inappropriée sur cette entité clinique demeure un obstacle majeur en ce qui est du traitement approprié.

Dans cette étude, la littérature a été lue attentivement et la définition, l'épidemiologie, la pathophysiologie, les traits cliniques, le diagnostic et traitement ont été indiqués.

Introduction

The last century witnessed a remarkable increase in life expectancy in both the industrialized and developing countries as a result of improvement in medical services, more healthy nutrition and better sanitation. Because of this, the number of elderly people has been growing faster than the population at large, thus making the world a fast aging society.[1] Age-related problems are therefore gaining interest in medical community and clinicians are being confronted with the increasing challenge of satisfying the desire of people not only to live longer, but to undertake an "active aging."[2]

With aging, changes occur in many parameters of endocrine and metabolic functions such as decrease in Growth Hormone secretion (somatopause),[3] decreased adrenal steroids (adrenopause)[3] and interestingly decrease in gonadal steroid production.[4] Over the years, menopause, a dramatic clinical syndrome of somatic and psychologic symptoms associated with a decline in circulating estrogenic hormones has been known and well described. It has however been suggested that a similar syndrome exists in men, referred to as andropause, male climacteric, low testosterone syndrome or androgen deficiency in the aging man (ADAM).[5,6]

Definition

Andropause has been defined, as the collection of signs and symptoms associated with the age-related decline in gonadal function in men.[7] In contrast to the rapid decline in ovarian function at menopause, at andropause the decline in testicular function and testosterone production is gradual.[7]

Epidemiology

Although all women undergo menopause, it is uncertain if every man experiences symptomatic decline in circulating androgen with aging. Prevalence of andropause varies extensively depending on the age group of the study population as well as the diagnostic criteria used. It has however been estimated that on the average, about 50% of healthy men above the age of 60 years have serum bio-available testosterone levels that are below the lower limit of normal for men aged 20 - 40 years.[2,5]

Pathophysiology

The most important male sex hormone is testosterone which is majorly produced by the testicular Leydig cells under the control of pituitary gonadotropin called luteinizing hormone (LH).[8] Testosterone is metabolized by the enzyme 5 -α reductase to dihydro-testosterone, which is the active metabolite. It is transported in the serum highly bound to sex hormone binding globulin (SHBG) and to a lesser extent, albumin. Only about 2% exists unbound as free testosterone.[5, 8]

Bio-available testosterone refers to non-SHBG bound form including free testosterone and is generally considered to be the biologically active fraction. It acts directly at the cellular level and is responsible for development of secondary male sexual characteristics. It also contributes to hair growth, muscle mass, bone density and erythropoiesis.[5, 8, 9]

Reduction in total testosterone is not usually noticed in men until sixth decade of life; however decline in free concentration is seen earlier, at a rate of approximately 1 - 2% per year between the ages of 40 - 70 years.[8] The etiology of testosterone decline is multi-factorial but testicular failure seems to be playing a major role. With advancing age, there is a gradual decline in the number as well as the secretory capacity of Leydig cells, thereby resulting in low testosterone production.[10, 11] Age-related histomorphological changes in Leydig and Sertoli cells in the testis have also been observed.[10, 12] Apart from this, the hypothalamus- pituitary

* Correspondence

- gonadal axis becomes less sensitive with age and elderly men seem to be unable to compensate for the reduction in circulating testosterone.[2] Also, it has been noticed that SHBG concentration increases at the rate of about 1 - 2% per year, thus reducing the concentration of the free hormone.[2]

There are other confounding extra-testicular factors that may contribute to testosterone decline in the elderly men. It has been shown that men with massive obesity had total serum testosterone level 63% lower than age-matched control.[5, 13] Reduction in free testosterone in this context however is less. A reversible dose-dependent reduction in testosterone concentration by about 27% as a result of alcohol use has also been documented.[5, 14] In addition, many acute and chronic medical illnesses, which are quite prevalent among the elderly men, can cause a reduction in testosterone production.[5]

Clinical features

There is a great variability in terms of perception and intensity of andropausal symptoms in elderly men. Some men with low serum testosterone are completely asymptomatic while some experience certain symptoms that they accept as normal accompaniment of aging or what they call "mid-life crisis."[8] For others however, age-related hypotestosteronaemia is associated with physical, psychologic and sexual symptoms.[8]

Loss of muscle mass (sarcopaenia), seen in elderly men and the resultant reduction in muscle strength has been attributed to hypotestosteronaemia.[3] It has been observed that thee is an average of 12kg lean body mas loss between ages of 25 and 70years. Over the same period, truncal adiposity is noticed with an increase in fat mass by 18 - 36%.[2, 15]

There is a positive correlation between bio-available testosterone concentration in elderly men with bone mineral density and hypotestosteronaemia resulting in accelerated bone loss and osteoporosis with an increased risk of pathological fracture.[2, 16]

Cognitive and mood disturbances are quite common in aging men.[17, 18] They experience chronic fatigue, irritability, depression, lethargy and sleep disorders. Others complain of hot flashes and night sweats.[19] Sexual dysfunctions like erectile dysfunction and reduced libido are common occurrences as well as some regression of secondary sexual characteristics.[10]

Diagnosis

Andropause essentially is a diagnosis of exclusion and pathological causes of androgen deficiency in the elderly must be ruled out before assuming it is age-related. Subtle chromosomal disorders like delayed diagnosis of Klinefelter's syndrome can simulate features of andropause and should be ruled out by karyotyping. Other causes of hypotestosteronaemia in adult include traumatic, chemical, infectious and neoplastic diseases of the testes. Post-pubertal mumps, torsion of the testes as well as certain drugs like ketoconazole, cimetidine and cytotoxic agents have been associated with gonadal dysfunction.[8]

The diagnosis of andropause requires the presence of some or all the symptoms and signs mentioned above plus a low free or bio-available testosterone level. There is no generally acceptable biomarker of testosterone and therefore clinical judgment must be supported by laboratory confirmation. Because of the high degree of individual variability seen in serum testosterone level and the normal circadian rhythm, at least two non-fasting samples taken in the morning, are needed to confirm hypotestosteronaemia.[8]

Serum gonadotropin estimation also assists in making diagnosis. Elevated serum LH level supports the diagnosis of testosterone deficiency of testicular orgin; although a sizeable proportion of hypogonadal elderly men have serum LH level in the normal range. This is due to the earlier mentioned age-related attenuation of the hypothalamic-pituitary sensitivity to low testosterone level. Other diagnostic studies that may be useful include FSH and prolactin levels as well as liver and thyroid function tests.

Treatment

The treatment of choice for symptomatic men with documented diagnosis of andropause is testosterone replacement therapy (TRT).[8] The goals of therapy are to relieve symptoms due to androgen deficiency, restore libido and sexual function; and improve the overall quality of life. Use of testosterone in elderly men however is highly controversial and the risks and benefits should be considered in selecting patients for this therapeutic option.

Beneficial effects of TRT

1. The anabolic effect of androgens is well known. TRT has been shown to increase bone mass density in all elderly hypogonadal osteopenic men. Increased lean body mass, leg muscle strength and upper body strength have also been noticed.[2, 7, 8, 20]

2. Total body fat mass as well as visceral fat decline with testosterone replacement in hypogonadal men and men with abdominal obesity.[7, 20, 21]

3. Testosterone therapy improves sexual function and attitude in men with hypogonadism. Studies have shown that the number of erectile events per day, mean duration of events and mean penile rigidity increased significantly during treatment periods as against during withdrawal periods. Sexual desire, arousal, orgasm and overall satisfaction all improved with testosterone replacement.[7, 22]

4. Androgen therapy increases haematocrit level and corrects anemia in elderly hypogonadal men.[7]

5. Effect of TRT on mood and cognitive functions are inconclusive. While some claimed improvement in these symptoms, others felt that there was no benefit with treatment.[7]

Adverse effects of TRT

Like any pharmacological agent, TRT has some potential and real adverse effects.[5] The effect of long-term testosterone administration on prostatic health is a major concern. This is

because testosterone is the key androgen for prostatic growth.[7, 21]

However, studies have shown that exogenous androgens do not initiate prostate carcinoma but may increase the rate of progression of an established case.[7] Reports on elevation of prostate specific antigen (PSA) level during treatment are largely anecdotal;[5, 23] neither does TRT initiate benign prostatic hyperplasia (BPH) but may cause it to progress.[5, 7]

The serum lipid profile is an important determinant of cardiovascular morbidity and mortality. The net effect of testosterone on serum lipids is rather complex and varies from individual to individual depending on the person's baseline lipoprotein profile.[5, 7] Importantly, no increase in angina pectoris, myocardial infarction or stroke was observed in elderly men placed on TRT.[24] Other recognised adverse effects include erythrocytosis, sleep apnea, gynecomastia and sometimes aggressive behaviour.[5, 7]

TRT therefore may be considered relatively safe for hypogonadal elderly men but before commencing therapy, baseline assessment of the prostate has to be carried out. This includes a digital rectal examination, baseline PSA level, trans-rectal ultrasound and biopsy.[5, 20]

Modalities of testosterone replacement

Testosterone comes in different formulations including oral, buccal, transdermal (patches or gel), intramuscular and subdermal implants. The intramuscular route is by far the most cost effective, though obviously not the most convenient.[8] Some oral preparations like 17-methyl testosterone are associated with hepatotoxicity hence the natural testosterone is preferred. Transdermal delivery system is recently emerging as the therapy of choice because of its convenience but it causes skin irritation in some users. Testosterone gel produces much less skin reaction.[7, 25]

Where TRT is considered inappropriate because of adverse effects, men with clinical andropause should be treated symptomatically. Phosphodiesterase-inhibitors like sildenafil can be given for erectile dysfunction, selective serotonin reuptake inhibitors without sexual side effects for depression etc.

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