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Review

Aging male syndrome

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Abstract. Aging Male Syndrome is a medical condition through which men could pass between the ages of 35 and 65, when testosterone levels in their body decline considerably. Androgen deficiency in the aging male has become a topic of increasing interest and debate throughout the world. In contrast to female menopause, the process of aging in the male genital system is slow and highly variable between individuals. The characteristic symptoms of Aging Male Syndrome include weakness, depression, fatigue and changes in body hair and skin, decreased sexual desire, decreased lean body mass accompanied by increased visceral fat, decreased bone mineral density. Aging Male Syndrome is usually diagnosed by testing the blood for testosterone levels. The usual treatment method for Aging Male Syndrome includes testosterone injections, testosterone patches, testosterone gels and oral preparations.

Key Words: aging, male, testosterone.

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Introduction

The 20th century was characterized by the transition from a high mortality and fertility demographic pattern to a low mortality and fertility pattern, which led to the rapid aging of the population. According to the provisions of the United Nations Organization, in 2050 the percentage of the population older than 60 will exceed for the first time that of children younger than 15, and the demographic structure of 13 countries will include more than 10% individuals older than 65 years of age. A consequence of this increase in mean life expectancy will be that the majority of women will live almost 1/3 of their lives with ovarian insufficiency and a high proportion of men will be confronted with a similar phenomenon due to partial endocrine deficiencies secondary to aging (Diczfalusy *et al* 1998).

References to "male menopause" appeared in the medical literature as early as the '30s. In 1939, Wermer described men aged over 50 who complained of memory disorders, decreased concentration ability, chronic fatigue, and decreased resistance to stress. The evidencing of low plasma testosterone levels in these men led to the formulation of the term "climacterium virile" (Wermer *et al* 1939). The article published by Heller and Myers in JAMA in 1944 was considered a landmark in the literature, as it demonstrated for the first time that symptoms related to decreased serum testosterone levels secondary to aging improve following testosterone replacement therapy, but do not respond to placebo therapy (Heller & Myers 1944).

During the course of time, various names have been given to this condition: Male Menopause, Male Climacteric, Androclise, Androgen Decline in the Ageing Male (ADAM), Testosterone deficiency syndrome (TDS) or Late Onset Hypogonadism (LOH). According to the recommendations of the World Health Organization (Paris 2003) and of the World Congress on the Aging Male (Prague 2004), the currently accepted terms that can be used, is either the Ageing Male Syndrome (AMS) or late onset hypogonadism (LOH) (Bhasin *et al* 2003).

Aging Male Syndrome is a medical condition through which men could pass between the ages of 35 and 65, when serum hormone (particularly testosterone [T]) levels decrease considerably, and which is associated with a number of somatic and psychic manifestations like: decreased sexual desire and increased incidence of erectile dysfunction; changes in the general state associating fatigue, depression, anger, sleep disorders, along with decreased intellectual capacity; decreased lean body mass and muscle strength, associated with increased visceral fat; increased incidence of metabolic syndrome; reduction of body hair and skin changes, such as increased facial wrinkles; reduced bone mineral density and appearance of osteoporosis (Keenan *et al* 2006). Aging Male Syndrome is also associated with increased risk of mortality (Khaw *et al* 2007; Haring *et al* 2010; Shores *et al* 2012).

The prevalence of low serum testosterone levels in elderly men is estimated to be around 25% (Harman *et al* 2001; Orwoll *et al* 2006; Wu *et al* 2010), while the prevalence of symptomatic androgen deficiency is 5.6% between 60 and 70 years, and over 18% in those over 70 years (Araujo *et al* 2004).

Hormonal changes related to aging

Testosterone is one of the essential conditions for male differentiation during embryonic development. Physiological levels of testosterone are required for the functioning of many organs and cells due to its stimulating effects in bone, bone marrow, muscle, liver, sebaceous glands, melanocytes, hair, spermatogenesis, prostate and erythropoietin producing cells (Suoranta 1971).

Testosterone is a steroid hormone secreted by the testis, which is subsequently converted to two major products: dihydrotestosterone (DHT) and 17 beta-estradiol (E). The conversion of T to DHT occurs by means of the enzyme 5a-reductase, while conversion to E involves aromatase, which is present in fat tissue, muscle, liver and kidney (Hugh *et al* 2007).

In the circulatory system, testosterone is found under three forms: free testosterone (fT), sex hormone binding globulin (SHBG)-bound testosterone, and albumin-bound testosterone. Testosterone is avidly bound to SHBG and is considered to be biologically inactive, while it is weakly bound to albumin, from which it is easily dissociated. Free testosterone and albumin-bound testosterone represent biologically active or bioavailable testosterone (Surampudi *et al* 2012).

Aging is associated with a progressive decrease in the secretion of testosterone due to cellular and molecular changes in all levels of its secretion regulation mechanism: hypothalamus (decreased secretion of gonadotropin releasing hormones – GnRH), pituitary gland (decreased secretion of luteinizing hormone - LH) and testis (Bremner *et al* 1983).

Primary changes in the testis lead to primary hypogonadism in the elderly and are caused by a decrease in the secretory capacity of Leydig cells (Copinschi *et al* 1995), an increase in lipofuscin deposits in Leydig cells (The Aging Male 2003), a decrease in the number of functional Leydig cells (Feldman *et al* 1994), an alteration of tissue perfusion secondary to atherosclerosis (Feldman *et al* 1994), a thickening of the basal membrane of seminiferous tubules (Monga 1999).

After the age of 50, serum testosterone levels decrease by 1% every year, and after the age of 60, 20% of men have serum testosterone levels below the normal limits. Moreover, serum free testosterone levels decrease with aging. After the age of 70, serum SHBG levels increase, resulting in decreased serum free testosterone concentrations (Kidd *et al* 2001). The increase in serum SHBG levels is caused by the increase in free estradiol levels, as a result of androgen aromatization, especially in fat and muscular tissue (Henkel *et al* 2005; Hugh *et al* 2007), hyperinsulinemia associated with insulin resistance (Kuhnert *et al* 2004), changes in growth hormone-insulin-like growth factor-1 (GH-IGF-1) axis (Plas *et al* 2000).

Another change in testosterone secretion related to aging is the change of the circadian rhythm of hormone secretion, with the flattening of the morning serum peak between 6 and 8 a.m. (Auger *et al* 1995).

With aging, a decrease in serum androgen levels secreted by the adrenal gland, in particular dehydroepiandrosterone (DHEA), is also found. Maximum DHEA secretion is found at the age of 30, after which it decreases rapidly. After the age of 70, serum DHEA levels represent 10-15% of the maximum levels found in all subjects during life (Auger *et al* 1995).

Aging is also accompanied by a decrease in the secretion of melatonin and a change in the profile of its circadian secretion. The tendency for earlier sleep onset, earlier morning awakening and a more fragmented and more shallow sleep period is representative of these alterations. This change in sleep influences in particular growth hormone (GH) secretion, which occurs during slow wave sleep [SWS] or non-rapid eye movement [NREM] episodes. In men, approximately 70% of daily GH secretion occurs during the NREM sleep phase. The duration of the NREM phase and implicitly, GH secretion, decrease with aging, which could explain the peripheral effects of hyposomatotropism in elderly men (Eskenazi *et al* 2003).

Sexuality and libido

A decrease in the frequency of sexual acts is seen after the age of 40, which becomes more marked during the sixth and seventh decades of life. It should be noted that the factors that influence the frequency of sexual acts are multiple, including sexual desire, opportunity, general health status, mobility and medication. If after the age of 40, only 15% of men report a loss of interest in sex life, the proportion of women is much higher. This is why the partner's loss of interest may lead men to give up regular sexual activity (Hugh *et al* 2007).

According to the Massachusetts Male Aging Study (MMAS), complete loss of erectile capacity is found in 5% of 40-year-old men and in 15% of 70-year-old men, while moderate erectile dysfunction occurs in 17% and 34% of these (Rolf *et al* 2002). The etiology of erectile dysfunction is multifactorial. Endocrine dysfunction is involved in less than 5% of cases (Hugh *et al* 2007). The most important cause is peripheral vascular diseases, diabetes mellitus, peripheral neuropathy, renal failure and smoking. MMAS has shown a 41% risk of erectile dysfunction in smokers, compared to only 14% in non-smokers (Rolf *et al* 2002). Other studies have demonstrated that 81% of elderly smokers or ex-smokers have sexual dynamic disorders (Rolf *et al* 1996).

An important function of the testis, which is distinct from androgen hormone synthesis, is that of spermatogenesis. The extent to which aging morphologically and functionally affects sperm characters (amount, number of sperm cells, motility) is under debate, as long as prospective longitudinal studies are not yet available.

The impairment of spermatogenesis is a long-term process, which develops over the course of several decades, but which may never reach levels resulting in infertility (Stern *et al* 2004). In the process of aging, men do not confront with a sudden dysfunction of Leydig, Sertoli cells or seminiferous tubules, but rather with a slow persistent decrease in sperm production, by 3 to 22% (Muller *et al* 2005). Only one third of men older than 60 and half of those older than 80 are infertile. Sperm cell motility is also influenced by aging. During spermatogenesis, zinc is actively incorporated in the flagellum and subsequently eliminated during epididymal maturation. As epididymal function is testosterone dependent, it is obvious that the elimination of zinc from the flagellum is also hormone dependent. This is why aging and the reduction of testosterone levels result in an epididymal dysfunction and thus, in a reduction of the motility of sperm cells by up to 37% (Rolf *et al* 2002; Laaksonen *et al* 2004; Smith *et al* 2006).

Morphological abnormalities of sperm cells have been described in 4-18% of men aged over 50. Regarding the number

of sperm cells, data are inconclusive, studies report an increase, a decrease or even no change in the number of sperm cells with aging (Simon *et al* 1992; Looker *et al* 1997; Cohen *et al* 1999; Isidori *et al* 2000).

Testosterone and metabolic syndrome

The association between abdominal obesity, the increase in serum lipids, hypertension and the alteration of carbohydrate metabolism is known as metabolic syndrome and represents an important cause of morbidity and mortality. People with metabolic syndrome have a three-fold risk of developing a major coronary accident or a cerebrovascular accident and a two-fold risk of dying from these causes compared to subjects without metabolic syndrome (Orwoll 1995).

Some epidemiological studies have proved the reverse proportional relationship between plasma testosterone levels and the prevalence of metabolic syndrome as well as of its various components, without being able to clarify the cause-effect relationship (Stanley *et al* 1991; Kamel *et al* 2001). However, intervention studies performed either by pharmacological testosterone deprivation (McElduff *et al* 1988) or by androgen replacement (Simon *et al* 1992) have supported the direct relationship between testosterone levels and the incidence of metabolic syndrome or of some of its components (Cohen *et al* 1999).

Meta-analysis of available cross-sectional data suggests that metabolic syndrome can be considered an independent association of male hypogonadism (Corona *et al* 2011).

Testosterone plays a role in the pathogenesis of metabolic syndrome through several mechanisms. Studies performed on stem cells have demonstrated the capacity of testosterone to regulate the composition of the organism by stimulating the differentiation of these cells towards myogenic lines and by inhibiting the development of adipogenic lines (Morley *et al* 2000). Other mechanisms involved are represented by the direct improvement in insulin sensitivity (Malkin *et al* 2004) or the reduction of leptin secretion in fat tissue and thus, the breakage of the self-perpetuating loop between leptin resistance and obesity (Goncharov *et al* 2005; Lunenfeld *et al* 2005).

Osteoporosis

Osteoporosis is a significant but poorly recognized cause of morbidity and mortality in elderly men. Data of the Third National Health and Nutrition Examination Survey (NHANES III) reveal the fact that 3-6% of men have osteoporosis and 28-47% have osteopenia. The clinical manifestations of osteoporosis in men differ compared to women: men develop osteoporosis 10 years later than women; bone mass loss is lower in men; osteoporotic bone fractures are less frequent compared to women; vertebral fractures are the consequence of severe trauma, compared to minor trauma in women; the mortality and morbidity associated with femoral neck fractures is higher in men (Nieschlag *et al* 2006).

The causes contributing to osteoporosis in elderly men are numerous, but the three most frequent causes are excessive alcohol use (15-20%), excessive glucocorticoid hormones (20%) and hypogonadism (Jockenhovel 2003).

Hypogonadism (primary or secondary) has been reported in 15-20% of men with vertebral osteoporosis (Plas *et al* 2000). In addition, the prevalence of hypogonadism has been reported to be 5 times higher in male elderly with femoral neck fractures (Turek *et al* 2006). Serum testosterone levels do not correlate with bone density in eugonadal men (Baum *et al* 2007). However, the mechanisms by which hypogonadism plays a major role in osteoporosis is still unclear. In the osteoblast, both androgen and estrogen receptors have been evidenced. Androgens might act through calcium metabolism regulating hormones, such as calcitonin. Moreover, it has been shown that bone tissue cultures have the capacity to convert testosterone to DHT, which suggests that DHT is the active androgen in bone (Hugh *et al* 2007). Long-term TRT in middle-aged men with LOH and MS determines a significant increase in both vertebral and femoral on bone mineral density related to increased serum T levels (Aversa *et al* 2012).

Diagnosis

The symptoms described in Aging Male Syndrome are extremely varied. Complaints can be generally grouped in four major categories: endocrine, somatic, sexual and psychic.

The Saint Louis University has drawn up a screening questionnaire based on these symptoms (Wald, 2008):

1. Have you noticed a reduction in your libido?
2. Have you noticed a reduction in your energy level?
3. Have you noticed muscle weakness?
4. Have you lost weight?
5. Have you noticed a reduction in your enjoyment of life?
6. Are you sadder?
7. Do you experience poorer erections?
8. Have you noticed a recent decline in you exercise capacity?
9. Do you feel tired after diner?
10. Have you noticed a decline in your work performance?

A positive result, i.e. the possibility of an androgen deficiency, is considered in the case of an affirmative answer to questions 1 or 7 or to any other three questions.

It could be useful also: Androgen Deficiency in Aging Male (ADAM) questionnaire (Gooren 2009), Aging Male survey (AMS) (Morales *et al* 2002), and MMAS questionnaire (Frajese *et al* 2005). All these questionnaires have high sensitivity, but they have low specificity (Morley *et al* 2006).

In patients with a suspicion of androgen deficiency, the determination of serum testosterone (total or free or bioavailable) is recommended.

The level of total testosterone is a good screening method, but the sensitivity of the detection of testosterone deficiency by this method is lower than by the level of free or bioavailable testosterone (Jara *et al* 2004). Sample taking is recommended between 7 and 11 a.m. Although there are no unanimously accepted lower limits, total testosterone values over 350 ng/dl or free testosterone values over 72 pg/ml are considered not to require replacement therapy, which is recommended at values lower than 250 ng/dl and 52 pg/ml, respectively. In the case of serum testosterone values below the lower limit, it is recommended to perform a second determination, along with the dosage of luteinizing hormone and prolactin (Vermuelen *et al* 2000; Makhsida *et al* 2005).

The determination of thyroid hormones, cortisol, DHEA, melatonin, growth hormone and IGF-1 is not recommended for the

assessment of uncomplicated hypogonadism; this should be reserved for the suspicion of endocrine dysfunction (Keenan *et al* 2006).

Treatment

Androgen supplementation in the elderly remains a controversial problem. Hormone replacement therapy should be initiated only after the objective demonstration of hormone deficiency, the exclusion of secondary causes of hormone dysfunction: HIV-infection (Sampson *et al* 2007), obstructive sleep apnoea (Klein *et al* 2005), Kallman's syndrome, Haemochromatosis, Thalassemia (Morton 2004) and the thorough evaluation of the risk-benefit relationship.

Absolute contraindications for androgenic hormone replacement therapy are the subjects with a history of severe lower urinary tract infection, untreated sleep apnea, prostate cancer, breast cancer, poorly controlled heart failure, IPSS (International Prostate Symptome Score) > 19 or subjects who still want this fertility. A hematocrit of more than 50% represents a relative contraindication (Bhasin *et al* 2010). Age per se does not represent a contraindication to this treatment (Keenan *et al* 2006). The dosage of the prostate specific antigen (PSA) (which should be lower than 3 ng/ml) and rectal touch are mandatory before the initiation of hormone replacement therapy (Keenan *et al* 2006). There are many preparations of testosterone available for the treatment of hypogonadism.

Androgen supplementation by intramuscular injections with testosterone can be made with testosterone enanthate or testosterone cypionate: 50-400 mg (average 200 mg) every 2-4 weeks (Nieschlag *et al* 2004); it can be also used testosteron undecanoat 1.000 mg as a loading dose, and than 1.000 mg at every 3 months (Nieschlag *et al* 2004).

The transdermal method of testosterone supplementation is repesented by testosterone gel (AndroGel 1%, Testim 1%) or transdermal testosterone preparations (patch: 2.5-5 mg/day).

Testosterone can be also supplemented by administration of oral preparations like alkylated androgens (methyltestosterone and fluoxymesterone) or testosterone undecanoat: 40-120mg/day) (Allan *et al* 2007).

Alkylated testosterone preparations are currently contraindicated due to hepatotoxicity and abnormal lipid profile (Keenan *et al* 2006; Gooren 2009).

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