Overview of Andropause: risk factors, effects and management

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ABSTRACT
Background: The andropause is a complex of symptoms in ageing men who have low testosterone levels. There is a scarcity of data about the symptoms of the andropause. Ongoing research has resulted in the development of ideas about this complaint, from the clinical syndrome to diagnoses with the aid of disease-targeted questionnaires.
Objective: To describe the andropause and associated health effects in men and to determine the prevalence of this problem. Also, to highlight the risk factors of the andropause and methods of treatment.
Review of literature: The andropause refers to a general decline in male hormones, including testosterone and dehydroepiandrosterone, in ageing men. This decline has been related to changes such as loss of libido, depression and sexual dysfunction. There are many factors that affect testosterone levels in older males, such as inherited factors, obesity, smoking and alcohol abuse. Ageing has been associated with an abundance of concomitant diseases, in particular, rheumatoid arthritis, cardiovascular disease and lung cancer. Also, the andropause has a negative impact on men's general wellbeing and quality of life. There is evidence that hormone replacement therapies for men may improve the quality of life of affected older men.
Conclusion: There is a connection between low testosterone levels and andropause symptoms. Awareness programmes on the effects of this condition and ways of prevention could alleviate the more adverse consequences of the andropause. Testosterone replacement therapy may be considered to treat the symptoms of ageing males whose testosterone levels are mildly reduced, also determining the side effects of testosterone replacement therapies.

Keywords: andropause, testosterone, ageing, male, hypogonadism, male hormones, testosterone replacement therapy.

1 INTRODUCTION

THE Andropause Society, in relation to the andropause or male menopause, states "Testosterone reduction or deficiency in men is a common problem from the age of 40 or above" [1]. After the age of 40 years, the level of testosterone reduces and the andropause relates to the age at which a pathogenic edge is reached [2].
Testosterone, characterized as a male hormone, is responsible for most male sexual components, it is produced in the testicles and controlled by glands in the brain [3]. It has been established that testosterone decreases by roughly 1% every year after the age of 30. In men of various ages, the prevalence of hypogonadism is around 20% in men in their 60s, for whom an androgen inadequacy is in biochemical evidence, and this increases to 50% of men in the eighth decade of life [4].
Signs of male ageing or andropause are comparable to menopausal complaints in women [5]. The deteriorating general and sexual condition of men was initially recognized in 1944 by Hellers and Meyers, who related it to diminished testosterone levels and were the first to utilize the term 'male menopause' [6].
Recently, the concept of the andropause has gained public attention and mentions in medical journalism [7]. As men age, their levels of testosterone drop progressively. Also, the concentricity of free and bioavailable testosterone drops aggressively in every decade after the 30s [8], [9], [10]. These symptoms can include: low libido, lack of vitality, erectile dysfunction, postprandial drowsiness, memory weakness, loss of pubic hair, sadness, irritability, diminished endurance, loss of facial hair and trouble at work [11]. However, these symptoms are not specific enough, which makes it hard to clinically differentiate the andropause from ageing [12]. The long-term impact of hypogonadism includes effects on the brain and cardiovascular system. Excessive utilization of anabolic steroids can result in premature andropause, which leads to a shutdown of the pituitary gland. Different causes of premature andropause include: testicular infections, diabetes and obesity [13].
There are many causes of testosterone reduction in old age. Common impacts of change, fewer Leydig cells and changes related to age in the dynamics of the hypothalamic-pituitary-gonadal (HPG) axis together result in diminished testosterone production in old age [14]. Various studies propose that old men with low levels of testosterone serum could benefit from testosterone replacement therapy for better muscle, bone and psychosexual capacities [15]. Additionally, fasting might impact on testosterone creation through a decrease in gonadotropic testicular control [16].
The aim of this study is to explore the prevalence and effects of this problem on ageing men and treatments for the symptoms and associated effects.

2 OBJECTIVES

1. To describe the andropause and associated health effects in men.
2. To determine the prevalence of this health problem worldwide and regionally.
3. To highlight the risk factors of an accelerated andropause.
4. To describe ways to treat the andropause in men.

3 REVIEW OF LITERATURE

3.1 Andropause: Definition And Magnitude Of The Problem

The andropause or "male climacteric" is characterized as "a clinical and biochemical disorder related with ageing and portrayed by a set of typical symptoms, additionally testosterone deficiency"[19]. It is becoming a worldwide concern, as the total populace of old age males increases. Around 33% of men over 60 years of age and over 80% of men in their 80s and older recognize psychological and physical changes alluded to as "the Andropause syndrome" [20]. An American study found that around 5% of 4 to 5 million males tested and found to have low testosterone levels are treated in order to increase their libido [21]. Andropause identifies with moderate but consistent lessening of the production of testosterone and dehydroepiandrosterone (DHEA) in middle-aged men, and the explanations behind that reduction include a decline in Leydig cells [7]. "Leydig cells originate inside the testis postnatally. Their development is a continued procedure which involves gradual conversion of progenitors into mature type of cells" [22]. "The Testosterone hormone is responsible for the secondary Y sex features that show up during maturity. It potently impact on sexual desire, arousal, and libido stimulating" [23]. Additionally, it is an anabolism hormone that boosts metabolic procedures within the immune system, muscles, brain, bone marrow (erythropoiesis) and bones [24].

The hypothalamic-pituitary-gonadal (HPG) axis controls the male production of testosterone hormone. The hypothalamus excretes Gonadotropin releasing hormone (GnRH). The pituitary gland is stimulated by testosterone to release luteinizing hormone (LH). Then, LH acts on Leydig's cells to stimulate testosterone release [25], [26]. The testosterone found in plasma is 98% bound to protein, 33% to albumin as well as 65% to sex hormone-binding globulin (SHBG). On the other hand, only around 2% of testosterone rests freely in serum. Another form of testosterone, known as non-SHBG-bound, constitutes the biologically active part of testosterone, besides free testosterone. The HPG axis is complex and reacts with several other endocrine systems, whose creation of hormones is also influenced by old age [25], [9].

Of these different hormones influenced by ageing, the serious are weak androgenic hormones (i.e. dehydroepiandrosterone and its sulfate) released by the adrenal gland. With old age these hormones decrease. The pineal hormone melatonin is also secreted in decreasing amounts with old age and is responsible for sleep and biorhythm disorders [27]. These phenomena relate to some extent to dropping levels of serum testosterone with old age. The levels of growth hormone also decline with old age, leading to decreases in muscle mass and strength, again these features are seen in those with hypoandrogenism [28].

Estrogen and corticosteroid levels in men do not see significant changes in old age. Lately, it has been found that a hormone delivered by leptin, adipocytes, may work in conjunction with androgens to maintain a lean body mass. Diminished total testosterone levels are only seen in men in the 6th decade of life [25], [9]. Reductions in free testosterone levels occur earlier (a 1% decrease for each year between the ages of 40 and 70). This reduction is due to increasing SHBG concentrations, at a consistent rate of 1.2% per annum. The free portion of testosterone reduces in inverse proportion to the increase in the number of testosterone-binding sites on SHBG [29].

With old age, there is also weakness in Leydig's cells' function and diminished HPG axis sensitivity. Around 7% of males between 40 and 60 years, 20% of those between 60 and 80 years, and 35% over 80 years of age have total concentrations under the ordinary low level of 350 ng/dL [26]. There is little awareness of the term andropause [30]. In a study done in Nigeria on adult males, knowledge about the andropause was less than experience of certain symptoms of it. This suggests that awareness of this syndrome has to be raised in men so that they can manage it or seek treatment for the changes and morbidities related to this disorder [20]. Another study done in Kuwait on awareness of the andropause found that more than half of the participants (59.2%) claimed that they had not heard about it, while (36.0%) men had heard about it [18]. A clinical study was done in Toronto, Canada, and in Los Angeles, USA about the effects of the andropause on men's quality of life, it found that andropause symptoms, such as depression, loss of libido, impotence and a lack of energy. have a negative impact on men's wellbeing. The study also noted that men with an androgen deficiency were unaware that they were undergoing the andropause until they were clinically diagnosed [31]. A population study in Massachusetts on ageing males found that about 4% of men between 40 and 70 years of age had low testosterone levels [32].

3.2 Factors Associated With Testosterone Levels In Males

Many factors affect the level of testosterone in older males. Inherited factors play a vital part so that men in the same family increasingly have similar testosterone levels when compared to unrelated people [33]. A high body mass index (BMI) or obesity appear to affect androgen levels, as there is an inverse relation between levels of testosterone and BMI [33], [34]. Also, caloric limitation incites a lowering of testosterone levels by inhibiting the GnRH pulse generator [35]. Smoking raises testosterone levels in males of any age compared to non-smokers [33], [34], [36]. Chronic alcohol abuse can prompt diminished levels of testosterone; also, estradiol levels increase in direct synchronization with stages of alcohol abuse [33], [34], [36]. Systemic or chronic illness diminishes testosterone levels, probably by stress-induced secretion of the corticotropin releasing factor, which inhibits the secretion of GnRH [33], [34], [37]. Reductions in testosterone because of illness have been shown, in particular for rheumatoid arthritis [40], [41] and lung cancer [42[, [43]. The development of man climacteric

as an organic and treatable disorder started to be taken seriously in the late 1930s and early 1940s [38). Diagnoses of the andropause were based on clinical symptoms evaluated via the utilization of more or less complex questionnaires that sought the subjective opinions of patients [41]. The ADAM (Androgen Decline in Ageing Males) questionnaire is a helpful clinical screening tool that "identifies a complex symptoms related to the age-related decline in testosterone hormone that may be amenable to therapeutic intervention" (Table 1) [44]. The principal indications of decrease in testosterone are generally ambiguous: reduced subjective levels of energy, rises in irritability, mood swings, decreases in cognitive performance, loss of erections in the early morning. These symptoms often mimic other conditions. Complaints include infertility, in body and beard hair, increase in body fat, lower muscle mass, gynecomastia, changes in testicle size and signs of osteoporosis [46]. These may occur regardless of whether decay in hormone levels is straightforwardly connected to the development of disease presentation, such as cardiovascular disease, among older men [47]. An issue with recognizing the andropause is that, in men, the changes are extremely steady and may develop over several years, unlike in females where the menopause can occur within months [41].

Men whose testosterone lack is caused by an abnormality in the testes often display increased follicle-stimulating hormone (FSH) levels, increased Luteinizing hormone (LH) levels and reduced sperm production. Different conditions are trauma to the testes, orchitis, radiotherapy, chemotherapy and testicular tumours [48]. Also, men may have low testosterone due to chromosomal abnormalities or genetically based conditions [13]. There are various causes, including: generalized vascular diseases, such as diabetes and probably problems caused by heavy smoking, diseases when the immune system is aggressive and damages the testes, such as variations in systemic lupus erythematosis and viral infections such as mumps [16].

3.3 The Impact Of The Andropause On Men's Health

A cross-sectional study that examined the connection between low levels of testosterone, depression and falls in 482 men found that symptoms of depression were closely related to testosterone levels [49]. Different studies have shown that the andropause cannot be differentiated from specific psychological symptoms, but can be related to depressive symptoms that are not considered pathologic [50].

In a large, multicentre study [The Netherlands (Boxmeer), Korea (Seoul), France (Auxerre) and the United Kingdom (Birmingham)], it was found that males who had an International Prostate Symptom Scale (IPSS) score of eight to thirty-five would probably have erectile dysfunction, and a score of zero to four on the Sexual Function Inventory [51], after modifying for country and age (odds ratio [OR] 1.39, 95% CI 1.10–1.74) [52]. Males who had high blood pressure (OR 1.38, 95% CI 1.09–1.75) and diabetes (OR 1.57, 95% CI 1.09–2.25) also were more likely to have an erectile dysfunction score of zero to four. The relationship between levels of testosterone serum and erectile dysfunction has not been clearly demonstrated in epidemiological studies. Serum free-testosterone concentrations relate to impeded relaxation of cavernous endothelial and corporeal smooth muscle in response to vasoactive challenge, independent of age [53]. With increasing age, muscle mass declines and fat mass increases. In another study, the New Mexico Ageing Process, the best predictor of loss of muscle mass and strength (sarcopenia) was the free form of testosterone. Different predictors included physical activity, caloric intake, age and insulin-like growth factor (IGF) 1 [54], [55]. Males fracture their hips roughly 10 years after females do [56]. When males fracture their hips they have a higher death rate than women. Minimal trauma hip fracture is related to low levels of testosterone [57], [58]. The relationship of testosterone to bone is less clear in men. Different studies have demonstrated that treatment with testosterone can increase bone mineral density [59], [60]. The 5-alpha-reductase inhibitor does not block this impact of testosterone. There is no doubt that the aromatization of testosterone to estrogen is a significant reason for the beneficial outcomes of testosterone on bone. This effect has been plainly shown in persons with innate aromatase inadequacy [61]. Recent studies comparing males with coronary heart disease (CAD) and males with normal coronary angiograms have demonstrated that males with coronary heart disease (CAD) have significantly lower concentrations of bioavailable testosterone than men with normal coronary angiograms [62]. The commonness of hypogonadism in a populace of men with CAD is about twice that noticed in the overall public [63]. Testosterone hormone in men has been shown to cause dose dependent vasodilation both in vitro and in vivo. When testosterone is implanted into the vasodilation ensues, and left coronary artery flow increases [64].

3.4 Testosterone Replacement Therapy

The andropause is due to a lack of bio-available or free testosterone. Therefore, the obvious treatment would be to replace testosterone for affected individuals [46].

An effect of treatment is that the rest of the endocrine system must be adjusted. This may include the management of thyroid hormone, dia- or physiological doses of cortisol. Some new studies on ageing show that the administration of optimal doses of human Growth Hormone (hGH) may also be very useful when this is inadequate [65].

Various testosterone medicine techniques have been devised [66]. Testosterone can be used from one to three weeks as injections. The main issue with this approach is that testosterone levels differ from supraphysiologic and decrease over each period of treatment. This approach has been used effectively for over seventy years. Long-acting undecanoate injections of testosterone have been given in both Europe and Asia [67]. This therapy is like to involve testosterone pellet implant therapy , these can be embedded for four to six months. Patches of testosterone can increase

the rate of skin agitation, so that alcohol is part of the process. Hydroalcoholic gels contain 1 per cent of testosterone, and these are well-known in America. They cause less skin agitation and agree better with patients. Dosages vary from 50 to 100 mg of gel every day, and 3-year safety data for this type of treatment have been declared [68]. This study found there were positive consequences of treatment on libido, fat, bone and muscle in males from 19 to 67 years of age [69]. Testosterone taken orally is primarily absorbed through the lymphatic system; consequently, it avoids the impact of high dosages of testosterone on the liver in a first pass. It has had widespread usage around the world and there is 10-year security information for it [70]. There is little evidence to suggest the utilization of dehydroepiandrosterone as an androgen replacement [71], [72]. Injectable androgen or Nandrolone has been utilized effectively to enhance power in both men and women [73].

When a testosterone treatment start, there is often a general feeling of well-being. This is because of metabolic changes in different body systems [74]. Testosterone may also have an effect on mood stabilization [75]. This can occur in one of two ways: a patient's enhanced anabolic status can boost his general feeling of prosperity, which may then enhance his mood, lift depression and have a calming impact on irritability; or there may be an immediate impact on the brain [76]. Also, males whose desire for many activities has waned might experience a surge of new motivation inducing them to take initiatives long forsaken. All of this can result in a new sense of self, in renewed self-confidence [77]. Many studies have demonstrated no change in HDL levels, [74],[79] a few have shown slight reductions [80] and some, in hypogonadal men, have demonstrated that treatment with testosterone prompts a rise in levels of HDL [81]. Also, in many studies involving remedial trials of testosterone, neither increases in prostate-specific antigen (PSA) levels nor clinically significant changes in prostate gland volume have been seen [82], [83] In one study of 13 men, there was no adjustment in prostate size following 3 months of treatment with testosterone, but PSA increased [74].

The main side-effect of testosterone is an excessive increase in hematocrit. When hematocrit increases to more than 55, testosterone treatment ought to be withheld. Testosterone can additionally be related to worsening sleep apnea [78]. Also, parenteral testosterone management has minimal harmful effects on the liver [84]. Testosterone treatment may also encourage (usually mild) skin inflammation. Men may gain weight because of both an increase in lean body mass and liquid retention [85].

4 CONCLUSION

Several studies have demonstrated that it is important to educate the general population about the symptoms of the andropause, especially men. They need to get more data about it from healthcare providers, social media and health organizations. Additional data about andropausal signs and symptoms, treatment and screening would help men to accept this change and cope with it.

The andropause is a fact and testosterone replacement therapy can significantly address metabolic abnormalities, physical symptoms and quality of life.

However, there need to be large long-term clinical trials to estimate the long-term risk versus benefit profile of testosterone replacement therapies in older men.

Evidence on the merits and efficacy of treating symptomatic males is now beginning to accumulate. Although the number of reports describing positive clinical or biochemical responses to treatment with testosterone is increasing, the numbers of males studied are comparatively small, and treatment duration is generally comparatively short. Also, there is a need for a large study to determine the side-effects of testosterone replacement therapies. And a large study to determine the side-effects of using testosterone replacement therapies is needed too. Any strategy to decrease the risks and symptoms of andropause should be combined with a suitable lifestyle, such as a balanced diet, regular exercise, and tobacco and alcohol consumption in moderation. These will help to maintain the highest quality of life and achieve the ultimate goal of allowing dignified healthy ageing.

ACKNOWLEDGEMENT

I thank my supervisor for her helpful and insightful comments on this review article.

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ANNEX

Table 1 *ADAM (Androgen Decline in the Aging Male) Questionnaire (44).*

ADAM (Androgen Decline in the Aging Male) Questionnaire	Yes	No
1. Do you have a decrease in libido (sex drive)?		
2. Do you have a lack of energy?		
3. Do you have a decrease in strength and/or endurance?		
4. Have you lost height?		
5. Have you noticed a decreased "enjoyment of life"?		
6. Are you sad and/or grumpy?		
7. Are your erections less strong?		
8. Have you noted a recent deterioration in your ability to play sports?		
9. Are you falling asleep after dinner?		
10. Has there been a recent deterioration in your work performance?		

NOTE: A positive questionnaire result is defined as a "yes" answer to questions 1 or 7 or any other three questions (4 5).