

## Review

# Andropause: Can it be properly diagnosed?

**\*Inegbenebor, U and Ebomoyi, M.I.**

Department of Physiology, School of Basic Medical Sciences, University of Benin, Benin City, Edo State, Nigeria.

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**Though it has been difficult to accept that men could be subject to sex hormone fluctuations like women, it has been established that men develop clinical features secondary to low testosterone levels in later life. These clinical features have been grouped into a symptom complex called andropause, and referred to as the male version of menopause. Hypogonadism, partial androgen deficiency in men and relative hypogonadism have been used synonymously with andropause by various authors. This paper critically examines the criteria for diagnosis and suggests new criterion, which is expected to properly distinguish a benign and reversible condition currently called andropause from an irreversible condition currently called acute andropause, which is the true male version of female menopause.**

**Keywords:** Andropause, diagnostic criteria, hypogonadism

## INTRODUCTION

Andropause is a syndrome of aging men with physical, sexual and psychological symptoms. These include weakness, fatigue, reduced muscle mass, reduced bone mass, impaired hematopoiesis, oligospermia, sexual dysfunction, depression, anxiety, insomnia, memory impairment and reduced cognitive function (Lund et al., 1999). Andropause occurs in men between 40 to 45 years of age. There are no clear-cut signposts like cessation of menstruation in women. However, there is a drop in testosterone level like the drop in estrogen level in women. Body changes are gradual in men and they are often accompanied by changes in attitudes and moods, fatigue, loss of energy, loss of sex drive and loss of physical agility. The precipitating factors of andropause include alcohol, injuries or surgery, medications, obesity and infections (Lund et al., 1999).

### Male versus Female gonadal programming

The male gonadal programming is quite different from that of the female. Unlike women, men continuously produce spermatocytes even when blood testosterone level declines at the rate of one percent per year starting from the age of 40 years (Lund et al., 1999). The female cannot produce oögonia beyond 28 weeks of gestation

and must function with a declining pool of oocytes (Bullock et al., 2001). There is therefore a programmed obsolescence of the female genital apparatus for producing sex hormones, which eventually manifests in menopause. Though 20 percent of men between 60 and 80 years of age are said to have testosterone below the lower limit of normal, there is no agreement on the threshold level of testosterone that is considered hypogonadal (Lund et al., 1999). However, most laboratories give a normal range of 260 - 1000 ng/dl for total testosterone and 50-210 ng/l for free testosterone (Morley and Perry, 1999).

### Testosterone level during aging

Testosterone levels decline gradually with age in men. The clinical significance of this decrease is debated. Testosterone levels can be measured as free (that is bioavailable and unbound) or total. In the United States of America, male total testosterone levels below 200-300ng/dl from a morning sample are generally considered low. However these numbers are not typically age adjusted, but based on an average of a test group which includes elderly males with low testosterone levels. Therefore, a value of 300ng/dl might be normal for a 65 year old male but not normal for a 30 year old.

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\*Corresponding author E-mail: [maureenebomoyi@yahoo.com](mailto:maureenebomoyi@yahoo.com)

### Leydig cells and ageing

There appears to be an increasing resistance of the leydig cell to the effect of luteinizing hormone as man ages. There is therefore a decreasing production of testosterone coupled with an increasing blood level of luteinizing hormone (Hardy and Schlegel, 2004).

Chen and other researchers investigated luteinizing hormone signal transduction in (brown Norway rat) leydig cells and reported that Luteinizing Hormone-stimulated adenylate cyclase activity declines with aging (Chen et al., 2004).

It appears that the level of leydig cell resistance varies in different men and with age, so that the expected high level of gonadotropins, typical of end organ resistance, manifests in different men at different ages. A situation where the testosterone level is very low, and follicle stimulating hormone and luteinizing hormone levels are very high is seen only in men whose testes have been destroyed by disease or trauma. It is also possible that situations like this might be seen, if men were to live over 120 years. Since testosterone levels decrease by 10% 1 every decade from the age of 40 years due to increasing resistance to gonadotropins, one would expect testosterone levels to decrease from its value at 40 years (100%) to an extrapolated value of zero percent at 140 years of age. Follicle stimulating hormone would increase from its value at 40 years at the rate of 2.7% every decade till it gets to maximum value (100%) at andropause.

### Spermatogenesis in ageing men

Though spermatogenesis continues throughout life in the normal male, there is evidence that there is a decline in the quantity and quality of semen produced in males above the age of 45 years. In a study on the effect of age on semen quality using patients referred to an andrology outpatient clinic in a retrospective study covering a period of 3 years, it was found that the percentage of morphologically normal spermatozoa (- 44%,  $P < 0.01$ ) and semen volume (- 29%,  $P < 0.0005$ ) were significantly lower in older than in younger men. Moreover, serum testosterone levels were significantly reduced in the group of older men (median: 300 vs. 360 ng/dl -17%,  $P < 0.005$ ) (Jung et al., 2002). In another study, normal morphology according to the World Health Organization criteria was significantly lower in patients aged more than 45 years. From a linear regression analysis, semen volume, sperm concentration and motility decreased by 0.01 mL, 2.1%, and 0.27%, respectively, per year, and the FSH level increased by 0.27%. Sperm concentration and motility decrease and FSH levels increase with age. Normal sperm morphology decreases from 45 years old (Pasqualotto et al., 2005). The most widely used reference values for human semen and sperm variables

were developed by the World Health Organization (WHO) to help assess the fertility status of men interested in reproduction (typically a younger population).

259 men were investigated regarding primary (86.5%) or secondary (13.5%) infertility. Men with azoospermia had significantly higher concentrations of FSH and LH and lower concentrations of testosterone than those with spermatozoa. High concentrations of FSH and LH in serum were found in case of low sperm density. Men with low testicular volume had high concentrations of FSH and LH and low concentrations of testosterone. FSH was closely correlated with LH and also with total testicular volume. A negative correlation was found between both gonadotropins and testosterone. The correlation between LH and testosterone was stronger in azoospermic men than in those with spermatozoa in semen (Abramsson and Ducheck, 1989).

Current criteria for andropause, as currently described in medical literature, is a condition of low level of testosterone only (Tan and Pu, 2004). For this reason, andropause has been variously called hypogonadism, (Tan and Pu, 2004) partial androgen deficiency in men, (Morales et al., 2000) and relative hypogonadism (Tan, 2002). It has even been said that symptomatic hypogonadism is sometimes referred to as andropausal syndrome (Morales et al., 2000). Though some authors (Tan and Pu, 2004) recognize that blood levels of follicle stimulating hormone and luteinizing hormone could be elevated, such laboratory estimations are only to be carried out to rule out irreversible causes of low testosterone- the key point in diagnosis!

Acute andropause, which has a sudden onset, has features of azoospermia, impotence and hypergonadic hypogonadism. This is probably the male version of female menopause. Acute andropause may be due to autoimmune disease, viral infection, generalized vascular disease including diabetes mellitus, destruction of testes by trauma or disease and surgical removal of testes as in orchidectomy.

### Expected Diagnostic criteria

Testosterone secretion is regulated by a negative feedback control system. Hence too little testosterone allows the hypothalamus to secrete large amounts of gonadotropin releasing hormone with corresponding increase in anterior pituitary luteinizing hormone and follicle stimulating hormone secretion (Guyton and Hall, 2006).

The decline in testosterone levels with aging is associated with an increase in follicle stimulating hormones and to a lesser extent luteinizing hormone (Morley and Perry, 1999). In andropause, the leydig cells of the testes are expected to be maximally resistant to the effect of luteinizing hormone. Hence testosterone level should be low and be accompanied by high levels of

gonadotropins- follicle stimulating hormone and luteinizing hormone. Thus andropause must be a case of hypergonadotropic hypogonadism. Sperm count should be nil and the condition should be irreversible using currently available technology.

## CONCLUSION

The criterion commonly used in diagnosing andropause is defective since the parameter used is low testosterone level and not a combination of both low testosterone and high gonadotropic hormone levels (Luteinizing hormone and Follicle Stimulating hormone).

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