Chapter

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Andropause — How Relevant?

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INTRODUCTION

In day-to-day practice it is not unusual to encounter male patients in their 50s or older who come to physician for loss of libido, erectile dysfunction, unexplained fatigue, behavioral problems, loss of muscle mass and some times unexplained bony fractures. These symptoms can be vague and can vary a lot among individuals. Some men find it difficult to admit that there's even a problem. And often physicians didn't always think of low-testosterone levels as a possible culprit. So these factors often lead doctors to conclude that symptoms were related to other medical conditions, depression or were simply related to aging and often encourage their patients to accept that "they were no longer spring chickens" while in fact sole cause for this entire symptom complex may be Andropause. "Term Andropause refers to a state of lowered androgens levels"[1]. Some prefer to use term "Androclise" instead of andropause as pause means abolish and clise means decline and there is gradual decline in testosterone levels in andropause[2]. Different names like male climatric, androgen deficiency in aging males (ADAM), penopause, viropause, age dependent decrease in plasma testosterone and low testosterone syndrome have been used in literature as synonym with andropause[3,4].

Androgens are a group of hormones that include testosterone, dehydroepiandrosterone, and androstenedione among others. It is a misnomer to call them as male hormones as they are present in both males and females albeit in different amounts. There is undeniable evidence that aging results in lowering of androgen levels.

PHYSIOLOGY OF TESTOSTERONE REVISITED

Testosterone is the principal androgen of which 95% is made by the testes; the adrenals produce rest of androgens mainly in the form of dehydroepiandrosterone. Pituitary gland secretes LH and regulates production of testosterone while FSH primarily affects spermatogenesis. Testosterone has got only a supplementary role in regulating spermatogenesis[5]. Testosterone is synthesized from cholesterol at the rate of approximately 6 mg / day (normal range 5-15 mg / day depending on age) and metabolized to dihydrotestosterone (DHT) by 5-alpha reductase and undergoes aromatization to estradiole by aromatase, and is excreted in the urine. Testosterone can be bioconverted into these two other steroids at target tissues throughout the body, this conversion essentially regulates all testosterone activity since the rate of conversion can be modified by the levels of these steroids.

Dihydrotestosterone (DHT) binds more readily to androgen receptors than testosterone conversion is noted at prostate, seminal vesicles, pubic and scrotal skin, axillae, gingival tissues and to a slight degree in skin of the back, biceps, ribs and thighs in both men and women. DHT is four times more potent than testosterone as an anabolic agent this conversion of testosterone to DHT increases the action of testosterone. Testosterone has both anabolic and androgenic effects. DHT is linked to prostate hypertrophy and male alopecia[6].

Estradiol: There are three estrogens acting on both females and males (E1, Estrone; E2, estradiol; E3, Estriol) 25% of these are made by the testes, whereas 75% is bioconverted in liver and brain from testosterone. 98% of circulating Testosterone is bound to plasma protein while remaining 2% is free testosterone and is responsible for biological activity. 40% of bound testosterone is bound to sex hormone binding globulin (SHBG) and rest is weekly bound to albumin and is readily available to tissues when needed. Bioavailable testosterone includes both free testosterone and testosterone that is loosely bound to albumin[7].

In men between the ages 40 and 70 years, each year total testosterone level declines by about 1.6%, free testosterone by 2% and bioavailable testosterone by about 2 to 3%, While on the other hand level of sex hormone binding globulin (SHBG) increases by 1.6% per year. This decline in testosterone level with aging is associated with an increase in FSH and to a lesser extent LH hence fertility in man may not be affected in andropause although number of sperms, their morphology and motility may be affected. It is mind blowing to note that on the basis of total testosterone measurement 20% of men older than 55 years are hypogonadal. However, when bioavailable testosterone levels are measured 50% of men older than 50 years could be defined as hypogonadal[8].

PATHOPHYSIOLOGY OF ANDROPAUSE

Hypogonadism (i.e. lower testosterone levels) that occurs with aging seems to result from both primary hypogonadism and secondary hypogonadism (hypothalamic- pituitary failure).

Primary hypogonadism: Involves decrease in number of Leyding cells in the testes subsequent to aging leading to reduction in testosterone production.

Secondary hypogonadism: When the messages from the brain to the pituitary gland are not strong enough or frequent enough to stimulate the Leydig cells to secrete testosterone[9]. Precise reason for this pituitary malfunction is not known although there are studies which show that there is reduction of GnRH releasing neuronal mass with increasing age[10]. Beside this, the change in serum hormone binding globulin (SHBG) level in blood also plays a role as it is a well known fact that with advancing age SHBG increases by 1.6% per year which results in low levels of free bioavailable testosterone[11].

If testosterone levels are normal, and a man is experiencing signs of andropause, the hormonal culprit is usually estrogen, both men and women have a specific ratio of testosterone to estrogen. Young men may have a ratio of testosterone to estrogen of 50:1. The ratio drops to 20:1 or even as low as 8:1 with normal aging. When estrogen levels in a man increase, the effects of testosterone are negated. Within the body, there is an enzyme called aromatase, it converts certain amounts of testosterone into estradiol (an estrogen).With aging, a man's body produce larger amounts of aromatase, larger amounts of aromatase mean more conversion of testosterone to estradiol. This will change the ratio of testosterone to estrogen, besides this there are many other contributory factors for hyperoestrogenemia[12] these are:

Obesity: Studies indicate that obesity is directly related to hyperestrogenization in both sexes. All fat cells contain aromatase, so an increase in fat cell population will cause an increase in the conversion of testosterone into estrogen, this will alter the testosterone estrogen ratios. Obesity is also known to lower testosterone levels at all ages[13].

Zinc deficiency: Zinc inhibits the levels of aromatase in the body. If zinc levels are inadequate, the levels of aromatase rise[14]. Zinc is also necessary for normal pituitary functions. Without zinc, the pituitary gland cannot release the LH and FSH that stimulate the testes to produce testosterone, while zinc is necessary for testosterone production, testosterone too is necessary to maintain levels of zinc in body tissues.

Liver function: Estrogen is metabolized in liver, there are a number of factors that can prevent or decrease this from happening. Use of alcohol is known to cause diminished liver functions specially in cirrhosis of liver. Normal aging can also lessen liver function.

Alcohol: Alcohol consumption causes significant rise in estrogen levels in the body. Women can have a dramatic rise in their estrogen levels after just one drink. Men although do not show such a dramatic rise, but levels of estrogen increases with chronic liver cell dysfunction, not only this alcohol decreases zinc levels in the body which in turn may contribute in lowering of testosterone levels.

Drugs: The side effects of some drugs can have a negative effect on levels of testosterone and increase the effects of andropause. One example is diuretics, which can diminish levels of zinc in the body, other important drugs in this category are cimetidine, digoxin and spironolactone.

IS THIS A NEW PHENOMENON?

Answer to this question is Yes and No. In fact, andropause was first described in medical literature way back in the 1940s. So it is not really new, but our ability to diagnose it properly is! Sensitive tests for bioavailable testosterone weren't available until recently, so andropause has gone through a long period of hibernation where it was under diagnosed and under treated. Now that men are living longer, they are concerned with their quality of life and hence there is heightened interest in andropause and this has led to advance our approach to this important life stage which was identified so long ago.

HOW DOES IT DIFFER FROM MENOPAUSE?

Unlike menopause man don't have a clear cut sign post such as cessation of menstruation to mark this transition, which generally occurs in women during their mid forties to mid fifties, men's transition is much more gradual and expand over many decades. Fertility in men may not be affected in andropause while menopause results in shut down of the ovaries and bring about cessation of reproductive activity.

CLINICAL MANIFESTATIONS

Unlike menopause andropause has insidious onset and slow progression of symptoms typical picture is characterized by alteration in three main domains.

Physical

Androgen deficiency causes loss of muscle mass, sarcopenia is a constant feature of aging and can reach as much as 1% per year. These losses can leave an andropausal man with feelings of fatigue, less endurance for physical activity and mobility impairment which is usually the first cause of disablement in elderly men[15]. Because of muscle mass depletion, men often experience multitude of generalized aches and pains throughout their bodies. Decline in other hormones such as growth hormone and insulin may also be responsible for decrease in muscle mass and bone mineral density[16]. Excessive weight gain, frequent fall on ground, tendency for fractures with trivial injuries.

Physical examination should include measurement of weight, body mass index (BMI) waist hip ratio and body fat distribution. Dry and coarse skin, decreased sexual body hair over face, axillae and groin, presence of spider telengiectasia are some of the important observations in these persons. Testes should always be examined its size could be measured with an orchidometer. Androgens are known to have stimulatory effect on erythropoiesis hence decreased levels of testosterone leads to anemia and thrombocytopenia. Tendency for recurrent infections is also observed. Prostate examination should always be done as part of screening for andropause.

Andropause and osteoporosis: Decrease in bone densities form an integral part of aging it has been found that osteoblastic activity decreases with age which may compound to the bone loss[17]. Bone density in men between the ages of 40 to 70 decreases by up to 15% this is a concern, as a person with low bone density is at risk for bone fractures. In Canada 20 to 30% of osteoporotic fracture occur in men. Common fracture sites are the hips, wrists, spine and ribs. Particularly devastating seem to be hip fractures, up to one-third of patients never seem to regain full mobility. With advancing age and declining testosterone levels, a man's risk level is similar to women. One in eight men over the age of fifty has osteoporosis. Presence of kyphotic spine on examination may be suggestive of osteoporosis. Two important consequences of osteoporosis are often seen as a slow but progressive rounding of the shoulders as well as a loss of height and back pain

Andropause and cardiovascular risk: It is now well accepted that women's risk of atherosclerosis, increases after menopause. Estrogen replacement therapy seems to reverse this trend. New evidence suggests that a similar phenomenon occurs in men as their testosterone levels diminish with age[18]. While research is not as complete as for women, the clinical findings point to an association between low-testosterone levels and an increase in cardiovascular risk factors in men. A cause and effect relationship has not yet been established in large clinical trials. Further clinical research is needed into this important area of study. Perhaps the most dangerous consequence of hypogonadism in men is myocardial infarction (MI). In one study serum testosterone levels were found to be about 90 ng / dl lower in patients who had suffered MIs than in those who had not. High blood levels of testosterone might protect against atherosclerosis, especially in men over sixty years of age[19].

Psychological

Androgen deficiency can heighten feelings of irritability that can lead to aggression, hostility, and anger. It can affect cognitive functions, resulting in lack of mental energy, decreased sense of well-being and even depression. Indecisiveness, lack of confidence difficulty in concentration, forgetfulness and insomnia are some of the other important psychological manifestations of andropause.

Sexual

Androgen deficiency reduces libido in most men, sexual changes and loss of libido occur gradually. Erectile dysfunctions form integral part of andropause symptomatology and include prolonged length of time in achieving an erection, diminished force and volume of ejaculation, diminished rigidity of the erection and diminished pleasure. Most men who reach midlife will experience one or all of these to varying degrees. Most men do not experience impotence and majority of the time their fertility remains intact. Changes in some of

the neurotransmitters and neuromodulators play important role in overall sexual behavior in elderly individuals. Erectile dysfunction in andropause patients is most likely the result of impaired vasodilator activity and penile fibrosis[20].

DIAGNOSIS

Andropause is often under diagnosed because symptoms can be vague and can vary a lot among individuals. Some men find it difficult to admit that there's even a problem because of self ego, and often their treating physicians didn't always think of low testosterone levels as a possible culprit. Best screening test for diagnosis of andropause is to measure serum testosterone levels, but lab investigations should always be done in conjunction with thorough history and clinical examination and in presence of clinical diagnosis of andropause. Lab test alone may often lead to misdiagnosis.

Screening tools such as ADAM questionnaire[21] can be helpful in detecting symptoms of androgen deficiency although this tool is sensitive but not specific and may detect cases of depression or even hypothyroidism. Geriatric depression scale[22] and Folstein Mini Mental State examination can be used to screen for depression and cognitive disorders respectively[23].

Radioimmunoassay remains the most common method for measuring testosterone level. Normal testosterone levels range from 260 to1000 ng/dl, while free testosterone levels range from 50 to 210 ng/L. Because of pulsatile nature of release of testosterone in human body every 60 to 90 minutes, a single random testosterone sample provides a result within ± 20% of the true mean value only two-third of time; a pool of three samples spaced 20 to 30 minutes apart provide a more accurate assessment[24]. This daily fluctuation in serum testosterone level is attenuated in older individuals. Free testosterone level of less than 50 ng/L or total testosterone level of less than 260 ng/dl are diagnostic of androgen deficiency[25]. The Endocrine Society Andropause Consensus Statement has recommended treatment for patients with the symptom complex and total testosterone level of less than 200 ng/dl, a second measurement of serum testosterone should always be obtained before starting testosterone replacement therapy (TRT).

If initial testosterone level is low (<200 ng/dl) then serum prolactin, TSH, LH and FSH levels should be estimated to rule out pathological causes of hypogonadism. If prolactin level is raised then patient should be investigated for prolactinoma. Low levels of TSH suggest hypothyroidism while low levels of LH/FSH suggest pituitary failure. If serum total testosterone levels are normal and patient presents with strong clinical suggestion of andropause then Free Testosterone levels, Serum hormone binding globulin (SHBG), and LH/ FSH level estimation should be carried out, if these levels are found low it will suggest andropause whereas high levels would suggest pituitary problem[26].

If the initial lab assessment is found to be inconclusive in presence of symptom complex suggestive of andropause through search should be made for factors confounding andropause such as— chronic illnesses (diabetes mellitus, cirrhosis of liver, and CRF), clinical depression, other endocrinopathies (hypothyroidism, Cushing's syndrome), acute stress, hypothalamic pituitary tumor, medications (cimetidine, spironolectone, digoxin and antidepressants), rare conditions such as hemocromatosis, Kalmann's syndrome, Klinefelter's syndrome and Prader Willi's syndrome. In all these patients clinical status and testosterone levels should be monitored on follow-up visit[27].

Routine laboratory tests such as complete hemogram, liver function tests, renal function tests, lipid profile and prostate specific antigen (PSA) should always be done. In elderly individuals quite often nutrition is a big problem in such situation measurement of serum Zinc level may be of use as low serum Zinc level is a usual finding in these patients and because of its antiaromatase action supplementation of Zinc can be useful in treating andropause.

TESTOSTERONE REPLACEMENT THERAPY (TRT)

Once the diagnosis of andropause is confirmed and other organic causes of low testosterone are excluded, then testosterone replacement therapy (TRT) could be started. In many instances, testosterone replacement in men with andropause can be highly effective and beneficial. It is not for every man, of course, TRT must always be administered only by qualified physician/ endocrinologist and it should not be used as a tonic for vague complaints. There are some pre-requisites that should be kept in mind and patient should be monitored periodically after starting the therapy.

Pre requisites for starting the treatment: Normal medical examination, including per-rectal examination. Normal lab tests like hematocrit, lipid profile, renal function test, liver function test, and PSA levels, rectal ultrasound, if required.

Monitoring the patient: Patient should be seen every 3 months, response to treatment should be evaluated at

that time digital rectal examination, lipid profile, hematocrit, and liver function test should be performed, if found stable, these tests should be repeated twice a year, Serum PSA level should initially be measured after 6 months of therapy and then annually, after one year of therapy, if the patient is stable he must be followed annually with the above mentioned tests, along with these tests serum calcium, bone density measurement and psychological evaluation should be done. Clinical response is a better guide for dose adjustment rather than frequent serum testosterone levels.

Modes of Treatment

Testosterone supplementation: Treatment with male hormone testosterone is available as oral tablets, skin patch (scrotal and non-scrotal), skin gels, injection and subcutaneous implants with very good results. Normally patient with andropause require very small doses of hormone as they have some production of their own.

Oral preparations: Fluxomesteron (5-20 mg daily), Methyl testosterone (10-30 mg daily) and Testosterone undecanoate (120-240 mg daily) *Advantages* causes no hepatotoxicity, maintains circadian rhythm. *Disadvantages*—decreased HDL levels, increased levels of DHT, rarely GI side effects.

Transdermal patches: Scrotal Patch-Delivers 4 to 6 mg natural testosterone per day, has to be applied over shaved scrotum every time. Testoderm (one patch / day). Non scrotal patch – Could be applied any where on the body, Androderm (Two patch of 2.5 mgT / day). Testoderm (One patch 5 mg / day), *Advantages*-Better improvement in sexual functions, no change in lipid profile, no increase in PSA levels, normal serum DHT levels. *Disadvantages*-More expensive, Inconvenient site, Repeated shaving of scrotal skin, dermatitis and chemical burns.

Intramuscular injections: Testosterone Propionate, Testosterone Cypionate, Testosterone Enanthanate. Doses—200 to 400 mg every 3 to 4 weeks. *Advantages*—Cost effective, good clinical response, no significant change in HDL level. *Disadvantages*—Painful, does not maintain circadian rhythm, gynecomastia, breast tenderness.

Subcutaneous implants: Testosterone pellets 200 mg each, 3 pellets are inserted subcutaneously every 4-6 months, *Advantages*—Safe, acceptable, maintains bone mineral density, good for long-term use. *Disadvantages*-Require surgical procedure for insertion, do not restore circadian rhythm.

Skin gel: Androgel, AA 2500 gel (100 mg / day), *Advantages*—Safe, acceptable to patients, maintains bone mineral density, good for long-term use, less irritation as compared to patches. *Disadvantages*—Has to be applied over large area of skin, large dose is required hence costly.

Sub lingual testosterone: Cyclodextrine, not easily available fast acting and effective. One tablet daily to be kept sublingually for few minutes, has got good acceptability among patients and minimal side effects.

Lifestyle Modifications

Of course, any ongoing strategy to reduce the symptoms and risks of andropause should incorporate lifestyle approaches such as optimal diet, regular exercise, stress management and the reduction of tobacco and alcohol intake. In elderly patients who seem to be malnourished may have low serum zinc levels and would require zinc supplementation therapy.

Contraindications to TRT

Absolute: Carcinoma of prostate—In men who have an existing cancer of the prostate, testosterone can promote its growth. This is why testosterone replacement is not recommended for men with prostate cancer. Mammary carcinoma and presence of prolactinoma are also absolute contraindications for TRT therapy.

Relative: Polycythemia—Testosterone is known to enhance erythropoiesis hence in patients of polycythemia it may lead to hyperviscosity syndrome resulting in heart failure and stroke. Hyperlipidemia— In some clinical studies excessive increase in LDL cholesterol has been observed following TRT, while others have demonstrated favorable lipid profile hence it is better to be cautious in patients with altered lipid profile.

BHP: As prostatic carcinoma is absolute contraindications for TRT and to differentiate BHP from carcinoma especially in early stage is quite often difficult hence use of TRT in BHP patients should better be avoided; serum PSA levels may be of great use in this situation.

What Could be Expected from TRT

With testosterone therapy, one's attitude improves, reinforcing self-esteem and self-confidence at work, as well as an increased energy at home and in social activities. Most men feel more vigorous, experience improved energy levels, mood, concentration, cognition, libido, sexual performance and an overall sense of well-

being. These effects are usually noted within 3 to 6 weeks. Use of TRT has shown conflicting results on various systems of body, few of these observations are as follows:

Lipid profile: There are evidences to support that TRT produces favorable lipid profile[28]. Transdermal testosterone replacement in hypogonadal men resulted in 8% increase in HDL cholesterol and 9% increase in total cholesterol / HDL cholesterol ratio[29]. Administration of testosterone in patients with peripheral vascular disease and ischemic heart disease resulted in increase in coronary artery diameter, coronary and cerebral circulation[30].

Bone: There are studies to show increase in bone mineral density with TRT in elderly men[31]. TRT also decreases markers of bone resorption and increases markers of bone formation[32].

Haemopoiesis: Testosterone is known to stimulate erythropoiesis, mean increase in hematocrit in andropausal men on TRT is about 7%[33]. Anemia is corrected in about 50% of treated patients. But androgen induced polycythemia may lead to hyperviscocity syndrome and related problems.

Cognition and libido: The effects of TRT on libido are conflicting. One study showed that sexual behavior is testosterone dependent[34], whereas in another study, no effect was observed in elderly men with erectile dysfunction[35]. Some studies have shown improvement in mood and sense of well-being and decreased anxiety after treatment with testosterone replacement. It also enhances spatial cognition[36,37].

CNS: Recent studies have shown role of testosterone in reducing neuronal secretion of beta amylopeptide, a protein found in plaques of patients with Alzheimer's disease[38]. TRT has also been found to increase cerebral perfusion in addition to improved cognitive functions.[39]

Prostate: Effect is controversial. Studies have shown no significant association between testosterone level and occurrence of prostatic carcinoma[40]. While earlier studies supported the view that testosterone administration results in modest increase in prostatic volume and prostate specific antigen[41]. Prolonged administration of TRT can result in disproportionate growth of periurethral part of prostate[42], leading to symptoms of prostatic obstruction.

ILLEGAL USE OF TESTOSTERONE REPLACEMENT

Androgen use is very prevalent in society. Much of this is due to androgen abuse among athletes and body builders, where black market androgen abuse has reached epidemic proportions. Indeed, in various studies of high school boys, it has been found that 4-12% had used androgens at least once. Current polls indicate illegal use of testosterone replacement, by the following: 96% of professional Football Players, 80-99% of male body builders , 11% of High school football players, 6.6% of High school senior males.

Dangers of Androgenic Steroid

Androgens if used indiscriminately are not at all safe drugs hence their use should be extremely judicious by experts only, many countries have strict prescription norms for these drugs but unfortunately these drugs are easily available in India in absence of well defined norms. If used without proper considerations as mentioned earlier they may create lot of problems these are as follows—Kidney diseases, Increase in serum LDL levels, while serum HDL level decreases, Hypertension, cardiovascular disease, Stunted growth, Depression, aggression, Acne., Male pattern baldness, Gallstones. *In males*: Testicular atrophy, Decreased sperm production, Gynecomastia. *In female:* Hypertrophy of clitoris, Facial hair, Deepening of voice, Peliosis hepatitis (blood-filled cysts in liver) and Cholestatic jaundice[43] their misuse should be discouraged.

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