REVIEW ARTICLE

Andropause - A Debatable Physiological Process

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Introduction

It is well accepted that males have andropause in their life cycle and recently andropause like menopause is attaining significant attention. Common age of onset of symptoms of andropause is 51-60 years but as early as 35 years have been reported in literature (1). Andropause is characterized by alteration in physical, sexual and intellectual domains that correlate with and can be corrected by alteration in androgen milieu (2).

Nomenclature : Andropause is a term of convenience describing complex symptoms in aging men who have low testosterone (T) level due to its gradual decline in secretion. "Androclise" instead of andropause, is a better term as pause means abolish and clise means decline (3). Different names like male climacteric, male andropause, androgen deficiency in aging men, penopause, viropause, age dependent decrease in plasma testosterone and low testosterone syndrome has been used in literature as synonym with andropause (4,5).

Cause of Andropause Hormonal deficiencies : Age related morphological and neurochemical alternations in suprachiasmatic nuclei of hypothalamus lead decline not only in testosterone level but also in other hormones as show in (Table- 1) .Out of all these hormones, low testosterone level with aging is more widely recognized and investigated hormonal alteration.

Changes in testosterone level with age : Multiple cross sectional and longitudinal studies have shown that testosterone production increases rapidly with onset of puberty and after the age of 40 years there is slow decline in plasma testosterone level, 1-2% per year (6). Changes in T level with age are shown in (7) (Fig 1). In addition to age factor, number of other factors like heredity, obesity, stress, depression, smoking, ingestion of alcohol, poor diet and hygiene can attribute to lowered testosterone level in aging men (1).

Table.1 Hormonal changes associated with aging

GHRH-LH/FSH/T	CRH-ACTH-DHEA	GHRH-GH/1GF-AXIS
↑LH*, ↑FSH ↓T ↓ free T ↓SHBG	No change in ACTH	GHRH message and receptor ↓DHEA & DHEAs ↓GH secretary pulse ↓circulating GH ↓ serum 1GF-1

(*↓ LH pulse amplitude and ↓ responsiveness to GnRH. GHRH-Growth hormone releasing hormone, CRH-Corticotrophic releasing hormone)

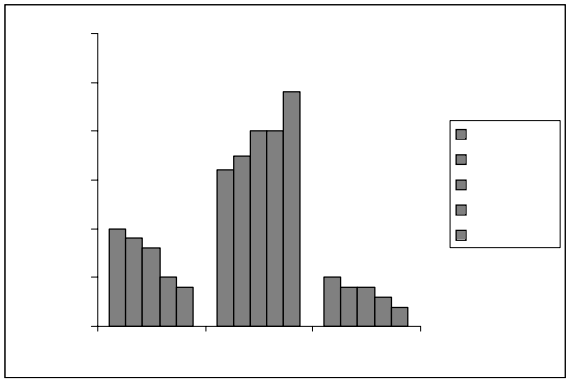

Fig. 1. Hormonal alteration with aging

Physiology of decline of testosterone hormone with age

There is no clear-cut consensus about the endocrine mechanism of decline of T level with aging. Age associated decline in T level has a mixed testicular and hypothalamic origin. Therefore the cause of decline may be at :

1. Central level
2. Peripheral level
   (a) Testicular changes
   (b) Blood- hormone binding protein change.

Changes at central level (Hypothalmo-pituitary level): There are studies, which show that there is

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reduction of GnRh releasing neuronal cellular mass with age (6) which results in decreased GnRh secretion at each pulse and decreased episodic frequency of high amplitude pulse, which ultimately causes decline in circadian rhythm, testosterone level and elevating LH.

Changes at peripheral level

(a) Testicular changes: Histological evidences of decreased number of leydig cells in aging testicles impaired testicular perfusion and decreased steroid response to stimulation by beta HCG or LH can be attributed to decreased testosterone level in aging men (8,9).

(b) Blood- hormone binding protein change: With advancement of age there is increase in testosterone binding carrier protein (SHBG) which results in low level of free biologically active testosterone (10).

Pathogeneses of Andropause

Contrary to menopause, andropause is not obligatory event in men, and when it occurs, its pathogenesis and hormonal aspects vary. Clinical domains attributed to andropause are as given below:

1. ***Lean body mass and muscle strength (Body composition) :*** Sarcopenia is a constant feature in aging person and it can reach as much as 1% per year. Mobility impairments due to sarcopenia are usually the first cause of disablement in elderly men (11).
2. ***Bone mass :*** The role of androgen in patho-physiology of bone in older individual is not much clear. It has been found that osteoblastic activity decreases with age, which may compound to the bone loss (2). Decline in other hormones (growth hormone and insulin like growth factor) with age may also be responsible for decrease in bone mineral density (12).
3. ***Haemopoiesis :*** Androgen have stimulatory effect on erythropoiesis, reticulocyte count and hemoglobin level. Thus lowered androgen level leads to the impairment of these values.
4. **Sexual behavior :** Change in some of the neurotransmitters and neuromodulators play determinant role in sexual behavior in elderly men. Erectile dysfunction in old age appears to be the result of penile fibrosis and impaired vasodilator activity (13).

Symptomatology

In contrast to menopause, the andropause has insidious onset and slow progression and also the clinical picture is not as clear as in menopause. The symptoms of andropause are almost similar to that of hypogonadism and are multifactorial in origin. The clinical picture is characterized by alteration in 3 domain.

Physical : Less endurance for physical activity, excessive weight gain, frequent fall on ground, tendency of increased fracture, dry and coarse skin decrease sexual body hair, takes larger time to recover from disease, recurrent infections and anaemia.

Psychological : Irritability, indecessiveness, depression lack of confidence, forgetfulness and insomnia.

Sexual : Decrease libido, reduced interest in sex, takes longer time to erect, full erection does not get as firm as it happens earlier, force of ejaculation is weaker and testicular shrinkage

Diagnosis of Andropause

Best screening test for andropause is to assess serum total testosterone and if it is less than 300ngm/dl the patient is considered as hypogonadal. However before labeling him as andropausal, pathological causes of hypogonadism must be ruled out by measuring serum prolactin, serum TSH, gonadotroph levels. If serum total T level is normal then one must measure free or bioavailable T (free plus albumin bound) because total T level may be normal due to age related rise in SHBG level. If free T is low with raised SHBG and there is raised gonadotroph then this confirms the diagnosis of andropause. A practical diagnostic algorithm is shown.

If suspected or at risk of hypogonadism then serum total testosterone (STT) determination should be carried. If STT is low then prolactin, TSH, LH/FSH levels should be estimated. If prolactin is raised then investigate for prolactinoma. Low levels of THS suggest hypothyroidism and low levels of LH/FSH suggest pituitary failure. If STT levels are normal then free testosterone, SHBG andLH/FSH should be carried. If found low suggest andropause which require testosterone supplementation, whereas if found high suggest pituitary problem.

Treatment of Andropause

Although other hormones and non hormonal factor may play role in causation of the symptoms but the effect of testosterone replacement therapy (TRT) on these symptoms has confirmed the role of testosterone in these age associated phenomenons, however these effects attributed to T supplementation may in fact be mediated by interaction of other hormonal system.

Testosterone Replacement Therapy (TRT) : Testosterone preparations are available in many forms like oral tablets, intramusclar injections, subcutaneous implants, scrotal and non scrotal patches and skin gel.

Oral : Fluxomesteron (5-20 mg daily), methyl testosterone (10-30 mg daily) and testerone undecanoate (120-240mg daily).

Advantages : No hepatotoxicity, can maintain circadian rhythm.

Disadvantages : ↓↓ HDL and cholestrol, supraphysiological level of DHEA and rarely GI side effects.

Intramuscular : Test.propionate and test cypionate (200-400 mg every 3-4 week) and T enanthanate (200-400 mg every 4 week).

Advantages : Cost effective, good clinical response Improvement in libido, potency and energy level, no significant change in cholestrol and HDL level.

Disadvantages : Painful, require frequent visit, not maintain circadian rhythm, altered DHEA and estradiol ratio, supraphysiological level of testosterone causing gynecomastia and breast tenderness.

Subcutaneous implants : Testosterone pellets (200 mg pellets, 3 inserted once every 4- 6 month).

Advantages : Safe, acceptable to patients, maintain bone mineral density and good for long term use.

Disadvantages : Do not restore circadian rhythm and require surgical procedure for insertion.

Transdermal patches : *Scrotal patch* - Testoderm (One patch daily(4-6 mg T/ day). *Non scrotal* - Androderm [Two patches daily (2.5 mgT/D)] and testoderm (One patch(5mgT/D)

Advantages : Improved sexual functions, haematocrit, lipid profile,PSA level and normal serum DHT level.

Disadvantages : More expensive, inconvenient site, repeated shaving of scrotal skin, ↑↑ DHT level, dermatitis and chemical burn.

Skin Gel (42) **:** Androgel, AA 2500 gel, 100 mg/d.

Advantages : Applied over large area of skin, all above plus less skin irritation.

Indication : Elderly men having symptoms of hypogonadism with serum testosterone level less than 300 ngm/dl and raised SHBG and gonadotrophin level are suitable candidates for TRT.

Contraindications : *Absolute :* Prostate carcinoma, mammary carcinoma and prolactinoma.

Relative : Polycythemia, clear-cut atherogenic lipid profile and benign prostatic hypertrophy ?

Effects of TRT : Benefit versus risk of TRT are summarized in table-2.

Table 2. Benefits versus Risks of TRT

Benefits	Risks
Physical	
▯ Increase in muscle mass strength	▯ fluid retention especially in patients with cardiac failure or hypertension
▯ increase in bone mineral density	▯ gynecomastia
▯ increase body fat and decrease in visceral fat	▯ acne / oily skin
Intellectual	▯ polycythemia
▯ improved sense of well being	▯ hyperviscosity syndrome
▯ improvement in spatial cognition	▯ decrease in HDL level and cholestrol level
▯ effect in quality of life	▯ sleep apnea
Sexual	▯ aggravating prostate cancer
▯ development and maintenance of secondary sexual characteristic	▯ impaired endothelial depended vasodilatation
▯ improvement in libido and sexual function.	▯ aggressive behaviour?

Lipid Profile : The effects of TRT on lipid profile are conflicting. There are evidences which support that TRT produce favourable lipid profile (14). On the other hand some evidences indicate excessive increase in LDL cholesterol following exogenous administration of testosterone. Transdermal T replacement in hypogonadal men resulted in an 8% decrease in HDL cholesterol and 9% increase in total cholesterol/HDL cholesterol ratio (15). Administration of testosterone in patients with peripheral vascular disease and ischaemic heart disease resulted in increases in coronary artery diameter, coronary and cerebral circulation (16). However a recent study reported that long term TRT in hypogonadal men is associated with impaired endothelial dependent dilatation (15). The relationship between the T and cardiovascular risk studies have shown a decreases in atherogenic fraction of LDL with TRT (17) .

Bone : Although the effects of TRT on bone in men are less known as compared to that of estrogen replacement in women. But there are studies, which have shown increase in bone mineral density with TRT in elderly men (18). TRT also decreases markers of bone resorption and increases markers of bone formation (19).

Body composition : TRT results in decrease in visceral fat and increase in lean body mass (20).

Haemopoiesis : TRT stimulate haematopoiesis and the mean increase in haematocrit in andropausal men is about 7% (21). Anemia is corrected in 50% of treated patients but androgen induced polycythemia may lead to hyperviscosity syndrome (22) resulting in heart failure and stroke which is one of the major risk of TRT.

Sleep Apnea : Short term TRT may cause the decrease in hypoxic ventilator drive (23) however long term study failed to show any such association (24).

Libido and cognition : The effects of TRT on libido are conflicting (17). One study showed that sexual behavior is T dependent (25,26). Whereas in another study no effect of biweekly T enanthate administration on elderly men with erectile dysfunction was found (27). Some Studies have shown improvement in mood and sense of well being and decreased anxiety in hypogonadal men (28) and in elderly receiving T therapy. Testosterone replacement also enhance spatial cognition in elderly men (29).

CNS : New insights into the physiological effects of T on androgen sensitive brain glial cells and astrocytes showed that testosterone reduces neuronal secretion of beta amylopeptide, the major protein, plaques of patients with Alzheimer's disease (30,31). Recently one study documented that T treatment increases the cerebral perfusion in addition to the improvement in cognitive function (32).

Prostate : There is a controversy regarding the TRT in elderly men and its effects on prostate. Although the T is the main circulating androgen but its metabolite DHT is major androgen for prostatic growth as the prostate has the receptor for it . Many studies have shown no significant association between the testosterone level and occurrence of prostatic cancer (33). Earlier studies supported the view that androgen administration results in modest but significant increase in prostatic volume and Prostate specific antigen (PSA) (34). But in one study, 3 month TRT did not increase prostate volume in elderly men although majority did have increase in PSA level (35).

Thus it proves that androgen supplementation does not result in serious prostate disorder. Further as different regions of prostate have different degree of sensitivity so prolonged administration of testosterone can result in disproportionate growth of periuretheral part of gland (36), leading to symptoms of urinary obstruction with out increase in prostate size. TRT is absolute contra indication in-patient with prostate cancer (but not BPH).

Treatment Guidelines : As TRT is associated with major risk of prostrate cancer and polycythemia etc it must always be administered only by very responsible physician (andrologist) and it should not be used as tonic for vague complaints.There are some pre-requisites which should be kept in mind before starting the therapy and the patient should be monitored carefully after starting the therapy.

(a) Prerequisites : Complete medical examination

(i) General examination including per rectal examination.

(ii) Laboratory tests like haematocrit, lipid profile, cardiac function tests, liver function tests and measurement of PSA level.

(iii) Trans rectal ultrasound.

(b) Monitoring :

- Initially patient should be seen after 3 months and at that time following should be undertaken :–

History of response to therapy, digital rectal examination, lipid profile, haematocrit, liver function tests

If stable, then these should be repeated twice a year.

- Serum PSA level should be initially measured after 6 months of therapy and then annually.
- After one year of therapy if patient is stable he must be followed annually for hemoglobin, liver function tests, lipid profile, serum calcium, bone density, psychological evaluation.
- Serum testosterone will fluctuate especially with intramuscular injection. Clinical response is better guide for dose requirement rather than serum testosterone level.

Conclusion

Andropause is a syndrome of physical,,sexual and psychologic symptoms in aging men. Age related decline in T level is supposed to be the potential cause of symptoms. Restoring T level to physiologic level ameliorate symptoms associated with andropause. However unlike the proven benefits of hormone replacement therapy in women, the effects of TRT in men are equivocal and major associated risk is development of prostrate cancer. So whether these elderly men should be substituted with androgens or not still remains controversial and needs further probing.

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