Male Andropause : A Myth or Reality

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Abstract

Male andropause, male climacteric or viropause is a condition in which men suffer from complex symptomatology due to low androgen level with aging. After the age of 40 years testosterone level starts declining and andropause corresponds to the age at which a pathogenic threshold is reached. This review summarizes the etiology, consequences, screening, diagnosis, monitoring of androgen deficiency in aging male (ADAM). The pros and cons of testosterone replacement therapy (TRT) in elderly male have been discussed. Currently oral, transdermal, transbuccal, intramuscular, and subcutaneous implants are available for clinical use. The choice is made by physicians based on therapeutic indication and patient preferences.

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Key Words : Andropause; Aging male; Testosterone replacement therapy

Introduction

Science has extended life and life expectancy of the Indian male has increased from 45 to 67 years in last five decades. Approximately 100 million men in India are above the age group of 40 and this figure is expected to double in the next decade. By 2010, India will have 49 million men above 65 years, accounting for 18% of world's elderly male [1]. Aging related health problems have hence gained interest in the medical community. Healthy aging men undergo a variety of hormonal changes, including decreasing plasma androgen levels. Attempts to describe these changes as the 'male menopause' or the 'male climacteric' are now generally regarded as inaccurate, since the precipitous changes that occur in women are lacking in men [2]. Unlike menopause, the decrease in testicular function in men is gradual and many associated symptoms are vague and nonspecific. Unlike females, decrease in biologically active androgen levels in aging male is not profound and many elderly men have free androgen level in the low normal range [3]. Terms such as "late onset hypogonadism" (LOH) [4], partial androgen decline in aging male (PADAM) [5], androgen decline in aging male (ADAM) [6] 'low testosterone syndrome' have gained some acceptance, but the term currently being used by the WHO and which also seems most appealing to aging men themselves is 'andropause' or viropause'.

Etiopathogenesis

Testosterone is metabolised to dihydroxytestosterone (DHT) by 5- α reductase and to estradiol by aromatase. Ninety-eight percent of the circulating

testosterone is bound to plasma proteins, the remaining 2% is free. Approximately 40% of bound testosterone is tightly bound to sex hormone binding globulin (SHBG) [3]. Plasma levels of SHBG increase with age and this is associated with a relative estrogenic dominance in plasma and progressive decrease in bioavailable testosterone with aging [7]. The rest of testosterone is weakly bound to albumin and is readily available to the tissues when needed [3]. Bioavailable testosterone refers to albumin bound plus free testosterone [8]. The androgen index (100 x total testosterone/SHBG) is another measure of bioavailability [3].

In a cross sectional analysis, free testosterone fell by a mean of 1.2% per year between ages 40 and 70 years and albumin-bound testosterone by 1% per year, whilst SHBG increased by 1.2% per year, resulting in a 0.4% per year decline of total testosterone [9]. However reduction in total testosterone is not observed in men until the sixth decade. Other studies have similarly shown that overall annual decrease of total testosterone and bioavailable testosterone are 1-2% and 2-3% respectively [10,11]. While age associated decrease in testosterone levels is well established, it is relatively modest and does not occur in every man [12]. About 15-25% of men over the age of 50 years will experience serum testosterone levels well below the threshold considered normal for men between 20 and 40 years of age [13].

The aetiology of testosterone decline with aging is multifactorial. Combined effects of decline and alteration in Leydig cells and age related changes in dynamics of

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hypothalamic-pituitary-gonadal (HPG) axis contribute to decreased testicular production with aging [8]. Other factors also have an impact on serum testosterone levels, including hereditary factors, obesity, diet, stress, depression, chronic diseases such as diabetes mellitus, chronic liver disease, sleep apnea syndrome, rheumatoid arthritis and medications such as glucocorticoids, smoking and alcohol intake [8].

Screening and Diagnosis

Aging men often present with a variety of vague non-specific symptoms that may be associated with testosterone deficiency (Table 1). For symptom assessment a rating scale has been developed, the 'Aging Males Symptoms' (AMS) questionnaire (Table 2) [14]. As it is not cost effective to screen all cases for low plasma testosterone levels, a screening questionnaire has been developed (Table 3). This identifies patients with low testosterone levels with high sensitivity (88%) and adequate specificity (60%). In subjects identified by the questionnaire, testosterone deficiency should be confirmed by laboratory measurements [15]. The most widely accepted parameters to establish the presence of hypogonadism are the measurement of total testosterone and free testosterone calculated either from measured total testosterone and SHBG or measured by a reliable free testosterone analysis method. A serum sample should be obtained between 0700 and 1100 hours [16]. Practical diagnostic algorithm for biochemical evaluation of men with suspected andropause is shown in (Fig. 1) [6,17]. Previously it was believed that androgen deficiency is present only in aged men and not in younger individuals. However recently Organon, US based health care company did a perception study among men in the 40 plus age category across the four metros of Mumbai, Delhi, Kolkata and Chennai and found that almost 75% of these men experience undesirable changes. Indian Andropause Society highlights that 40-plus Indian could need monitoring. The UK and Canadian andropause societies recommend monitoring men's health from the age of 30 against the earlier 50 [1].

Table 1

Consequences of decreased testosterone

1. Decreased libido, decreased performance
2. Poor response to PDE-5 inhibitors
3. Decline in muscle mass and strength
4. Cognitive decline particularly visuospatial memory
5. Negative thinking
7. Mood changes – increased irritability / anger, depression
8. Decreased BMD resulting in osteopenia and osteoporosis
9. Increased visceral fat
10. Chronic fatigue and sleep disturbances

Testosterone Replacement Therapy (TRT)

Recent interest in testosterone therapy has been fuelled not only by increased medical awareness of the

Table 2

Aging males symptoms questionnaire

Which of the following symptoms apply to you at this time? Please mark the appropriate box for each symptom, for symptoms that do not apply, please mark 'none'

1. Decline in your feeling of general well-being (general state of health, subjective feeling)
 2. Joint pain and muscular ache (lower back pain, joint pain, pain in a limb, general backache)
 3. Excessive sweating (Unexpected/sudden episodes of sweating, hot flushes independent of strain)
 4. Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, sleeplessness)
 5. Increased need for sleep, often feeling tired
 6. Irritability (feeling aggressive, easily upset about little things, moody)
 7. Nervousness (inner tension, restlessness, feeling fidgety)
 8. Anxiety (feeling panicky)
 9. Physical exhaustion/lacking vitality (general decrease in performance, reduced activity, lacking interest in leisure activities, feeling of getting less done, of achieving less; of having to force oneself to undertake activities)
 10. Decrease in muscular strength (feeling of weakness)
 11. Depressive mood (feeling of weakness)
 12. Feeling that you have passed your peak
 13. Feeling burnt out, having hit rock-bottom
 14. Decrease in beard growth
 15. Decrease in ability/frequency to perform sexually
 16. Decrease in the number of morning erections
 17. Decrease in sexual desire/libido (lacking pleasure in sex, lacking desire for sexual intercourse)
- Have you got any other major symptoms?
If yes, please describe: Yes No

Scale : 1 = None, 2 = Mild, 3 = Moderate, 4 = Severe, 5 = Extremely severe

Severity of complaints : Scores : 17-26 : No complaints; 27-36 : few complaints; 37-49 : moderate complaints ; >50: severe complaints

Table 3

The St Louis University ADAM questionnaire?

Test is considered positive if answers are "Yes" to question 1, question 7, or any 3 other questions.

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

Practical and Diagnostic Algorithm for biochemical evaluation of men with suspected andropause [6,19].

Fig. 1 : Practical and diagnostic algorithm for biochemical evaluation of men with suspected andropause [6,19].

effects of hypogonadism, but also by media attention regarding hormone replacement therapy in both men and women, the marketing of new topical testosterone formulations, and the desire of “baby boomers” to maintain vigor and health into their mature years [18].

Although reports indicate that TRT may produce wide range of benefits for hypogonadal men including improvement in libido, bone density, muscle mass, body composition, mood, erythropoietosis and cognition, considerable controversy remains regarding indications for testosterone supplementation in aging males [18]. However there is a general agreement that total testosterone level above 12 nmol/L (346 ng/ dl), or free testosterone levels above 250 pmol/L (72 pg/ ml) do not require substitution [14]. Similarly, based on the data of younger men, there is consensus that serum total testosterone levels below 8 nmol / L (231ng/dl) or free testosterone below 180 pmol/ L (52 pg/ ml) requires substitution. Since symptoms of testosterone deficiency become manifest between 8 & 12 nmol /L, trials of treatment can be considered in those in whom alternative cause of these symptoms have been excluded [5].

Despite this controversy, testosterone supplementation has increased substantially over the past several years, with an increase of more than 500% in prescription sales of testosterone products since 1993

[19]. Common testosterone preparations based on the route of administration , their recommended doses and their side effects are depicted in Table 4.

Patients must be involved in the selection of the type of testosterone preparation. Patient’s compliance is of utmost importance as the treatment is usually of long duration, often for life. Majority of experienced clinicians aim for the mid-to upper normal range in order to optimize the response to treatment. No dose adjustments are required if adequate clinical response is obtained. The oral delivery is difficult because of rapid first-pass metabolism and the short half-life of those formulations [20]. Depot injections can be painful and do not yield the circadian variations in testosterone levels found in healthy young men. Therefore, testosterone is usually administered transdermally using reservoir patches or topically applied gels [21]. If the maximal recommended dose of transdermal therapy has been prescribed without achievement of adequate serum testosterone levels, consideration should be given to changing to intramuscular injection therapy. With injection therapy, peak serum levels are obtained 2-5 days after injection and the levels often return to baseline by 10 to 14 days after the injection [18]. It is also important for patients receiving testosterone therapy that estradiol remain within normal concentrations. In a comparative trial,

Table 4**Testosterone preparations, recommended doses, advantage, side effects and cost**

Route of delivery	Generic name (Formulation)	Trade name	Dose	Advantage	Disadvantage
Oral	(i) Testosterone Undecanoate	a) Andriol Testocaps (40 mg)	a) 120-200 mg/day in divided doses for 2-3 weeks. Maintenance dose 40 mg TDS	a) Increased insulin sensitivity, improved lipid profile, increased myocardial circulation, increased calcitonin.	a) Short half life requires frequent dosing. Prolonged use may cause hepatotoxicity and altered lipid profile.
	(ii) Mesterolene	b) Proviron Restore (25mg)	b) 100-150 mg daily	b) Estrogen antagonist - Does not aromatize, Does not inhibit gonadotrophin secretions or spermatogenesis	b) Rapidly reduced to inactive metabolite and does not provide complete supplementation.
Injectable	(i) Testosterone Cypionate	a) Depot – Testosterone	a) 200-400 mg every 2 weeks IM or 100mg / week	Good clinical response	a) No circadian variation in serum testosterone levels. Supra physiologic levels in first 2-3 days with greater frequency of side effects. Suppresses LH levels in 33% cases
	(ii) Enanthate	b) Testoviron Depot	250-500 mg/ 3 rd week		
Buccal	Testosterone Bioadhesive buccal system	Striant	2 x 30 mg daily	-	-
Subcutaneous	Testoderm Implants	-	1200 mg every 6 months	-	-
Transdermal	i) Testosterone Patch	a) Androderm Testoderm TTS (2.5mg)	2.5 mg twice daily	a) No injections b) Mimics circadian variation. c) Good clinical response d) Does not require frequent office visits.	a) Local skin irritation b) Inadequate levels
	ii) Testosterone Gel	b) Androgel Testogel Cernos Gel (1 %) 5 gm/10 gm unit (10 mg testosterone / gm)	1% testosterone in 5-10 g Gel once daily. Gradually increased to 7.5-10gm		
	iii) Transcrotal patch	c) Testodrem (6 mg)			
	iv) Spray	Testospray (12.5 mg testosterone/spray)	50-100mg/day shoulder/upper arm		

estradiol levels remained within the normal range 81% of time with transdermal delivery and 35% of time with intramuscular delivery ($p < 0.001$) [21].

Risks of TRT

Perhaps the most controversial topic in the ongoing discussion of TRT is the risks involved. Despite the belief that testosterone is a risk factor for cardiac diseases, few studies support a causal relationship between the two [18]. Indeed, several studies suggest that higher testosterone levels may actually have a favorable effect on the risk of cardiovascular disease [22]. Although

studies of TRT have not demonstrated an increased incidence of cardiovascular disease or cardiac events, prospective, large scale, placebo controlled studies are required for definitive assessment of long term effects of TRT on cardiovascular health. The contraindications of TRT are given in Table 5.

Although available data regarding the relationship of TRT to lipid profiles is inconsistent, it is suggested that TRT within the physiologic range is not associated with worsening of lipid profile [18].

Higher testosterone levels appear to act as a stimulus for erythropoiesis. Although a rise in the haematocrit is

Table 5**Contraindication for TRT****Absolute contraindication :**

- (1) Preexisting cancers of prostate or breast.
- (2) Haematocrit > 55%

Relative contraindication

- (1) Haematocrit >52%
- (2) Severe obstructive sleep apnoea
- (3) Severe congestive heart failure
- (4) Severe urinary obstructive symptoms due to BPH.

generally beneficial for patients with anaemia, elevation above the normal range may have grave consequences, particularly in the elderly, since an attendant increase in blood viscosity could aggravate vascular disease in the coronary, cerebrovascular or peripheral vascular circulation. The risk of haemoconcentration is higher if the patient also has a condition that may itself be associated with an increased haematocrit such as chronic obstructive pulmonary disease [18].

Injections appear to be associated with a greater risk than topical preparation. Although untoward events are unlikely with mild erythrocytosis of relatively short duration, the haematocrit or hemoglobin level should be regularly monitored in men receiving TRT. It is reassuring that no testosterone associated thromboembolic events have been reported till date [18].

It is well recognized that the development of benign prostatic hyperplasia (BPH) requires the presence of androgen and men with hypogonadism may occasionally have increased voiding symptoms with TRT [18].

Currently available data obtained from relatively small studies support the short term safety of TRT with regard to risk for possible development or stimulation of sub clinical carcinoma prostate (CaP), although the long term risk remains undetermined [23].

In fact it should be recognized that CaP becomes more prevalent exactly at the time of man's life when testosterone levels decline. Proper monitoring with serum prostate specific antigen (PSA) and digital rectal examination (DRE) should promote early diagnosis and potential cure of "unmasked" CaP identified during TRT [18].

Oral preparations except testosterone undecanoate, have been reported to lead to hepatotoxicity and neoplasia, benign and malignant. Intramuscular and transdermal preparations are not associated with hepatic dysfunctions and hence routine liver function test (LFT) monitoring appear unnecessary for men on such forms of TRT [18].

TRT contributes to sleep disordered breathing by central mechanisms rather than by any anatomical changes in the airway [3].

The other miscellaneous effects of TRT include breast tenderness and swelling in few cases. Testicular size and consistency often diminish and fertility is compromised due to down regulation of gonadotrophins.

Transdermal preparations may be associated with a variety of skin reactions mainly erythema/pruritus. Acne, oily skin and flushing are minor inconveniences. TRT is to be used cautiously in men with congestive heart failure or renal insufficiency [18].

Monitoring Drug Therapy

Monitoring is mandatory to ensure that :

- (1) Testosterone levels are within the normal range.
- (2) Symptoms are improving.
- (3) Side effects and potential health risks are minimized.

Once TRT is initiated, first follow up is recommended at one to two months to assess the efficacy of treatment with consideration of dose escalation in cases of inadequate clinical response associated with suboptimal testosterone levels. Voiding symptoms are to be documented by history or by the use of measures such as the international prostate symptoms score (IPSS). Any history of sleep apnea should be ascertained [18].

A physical examination, including DRE of the prostate, serum PSA level and hematocrit should be performed at 3,6,12 months and then annually [5,24]. Lipid evaluation is optional.

An abnormal DRE, an increase in PSA of more than 0.75ng/ml/year, total increase during treatment in PSA of more than 2 ng/ml or PSA levels greater than 4 ng/ml require urologic evaluation for possible prostate biopsy [25]. There is a proposal for a standardized monitoring algorithm which recommends urologic referral for possible biopsy for patients with an increase in PSA of more than 1ng/ml during the first six months of treatment or more than 0.4ng/ml per year thereafter [26].

Hematocrit rise above the reference range (more than 52%) warrants evaluation for polycythemia and consideration should be given to temporarily withhold TRT, reduce the dose, or perform phlebotomy.

Recent Advances

A promising advancement in this field is the development of specific androgen receptor modulators, a new family of synthetic non-steroidal molecules displaying selective preferential activities for androgen receptors in tissues such as muscle, bone and central nervous system while avoiding the undesirable effects in other tissues, such as the prostate. One such molecule improved several properties of bone [27, 28]. Since they are not 5 alpha reductase enzyme substrates, they are not converted to dihydroxy- testosterone and hence have

no proliferating activity in the prostate [8].

Conclusion

The phenomenon of andropause is a reality and TRT can significantly improve physical symptoms, metabolic abnormalities (e.g. strength, insulin resistance, cognitive function, bone mineral density) and quality of life. However large scale long term clinical trials are needed to assess the long term risk versus benefit profile of TRT in ageing men. Despite the broad range of testosterone therapy on offer, the short acting transdermal testosterone gel appears to be better suited for aging androgen deficient men [29]. Of course any ongoing strategy to reduce the symptoms and risks of andropause should incorporate life style approaches such as optimal balanced diet, regular exercises, stress management with tobacco and alcohol consumption in moderation. These will help us to achieve the ultimate goal of providing dignified healthy ageing, and maintain highest quality of life, thereby adding life to years and not simply years to life.

Conflicts of Interest

None identified

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