PROBLEMS OF ANDROPAUSE AND POSSIBLE REMEDIES

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Andropause or PADAM (partial androgen deficiency in aging males) or ADAM (androgen deficiency in aging males) or AAAD (aging associated androgen deficiency) or late onset hypogonadism is a clinical condition characterized by a partial deficiency of bio-available androgens and/or its decreased sensitivity in target tissues affecting reproductive activity that has a similarity with female menopause. This state of hypogonadism leads to a decline in physical energy and altered state of well-being, irritability, occasional sweating, sexual dysfunction and various metabolic alterations. These changes may have deleterious effects on muscle mass, bone density, cardiovascular efficiency, lipid profile and eventually cognitive functions. The diagnosis of andropause depends mainly on clinical features and laboratory investigations. As the onset is gradual and many of the symptoms are common with elderly persons, diagnosis is difficult. The common treatment is testosterone supplementation, which has positive effects on improving the symptoms and quality of life. This therapy has some reported side effects that are also to be considered during long-term use. Awareness about the condition may help to diagnose it earlier and multi-dimensional long-term studies are required to elucidate the mechanism of the symptoms and its possible prevention through Testosterone Replacement Therapy (TRT).

As the reproductive life of female ends at the onset of menopause, male reproductive life also becomes meager with the emergence of a condition commonly known as Andropause. The condition is also termed as PADAM (partial androgen deficiency in aging males) or ADAM (androgen deficiency in aging males) or AAAD (aging associated androgen deficiency) or late onset hypogonadism (Snyder, 2014). With advancement of age androgen levels gradually decline that is reflected by alteration in physical and mental domain. Fundamental gender differences in gonadal physiology underlie the wide disparities between men and women in the natural history of human reproductive aging (Handelsman, 2006).For this reason some authors consider the term andropause as a misnomer (Morales *et.al*.,2000) since, during this condition androgen secretion does not cease but gradually decreases, whereas in females 'menopause' completely arrests female reproductivity. Nevertheless, the term 'andropause' is still continued to be used by laymen as well as clinicians.

Epidemiological Aspects: Though the magnitude of the problem has not been clearly defined, but population projections indicate that the diseases associated specifically with aging will increase significantly in the first half of this 21st Century. The UN estimates and projections of world population trends during a 75 years period are shown in the following

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figures (Figs. 1 &2). In our life time life expectancy will increase by 30 years and the number of elderly persons will triple and WHO estimates of non-reproductive older population will be about 15% by 2025 (Morales, *et.al.,* 2000). Thus, the study of problems associated with non-reproductive population in the future world is socio-biologically very much significant.

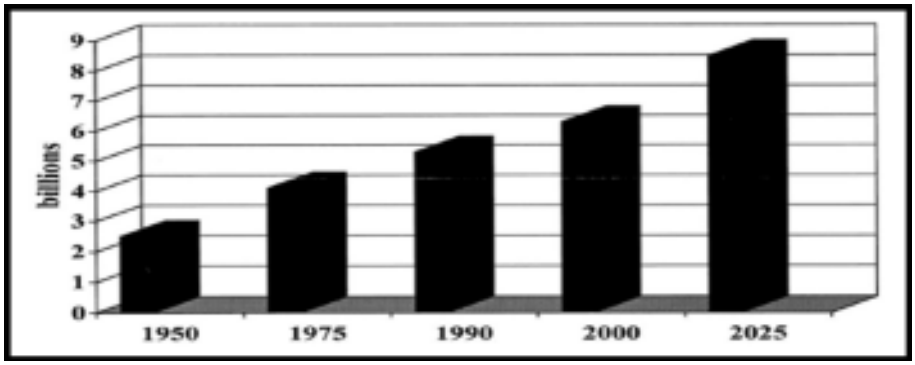

Fig. 1: United Nation's predictions for world population growth (in billions) within lifetime (75 years) (United Nation's document, 1995)

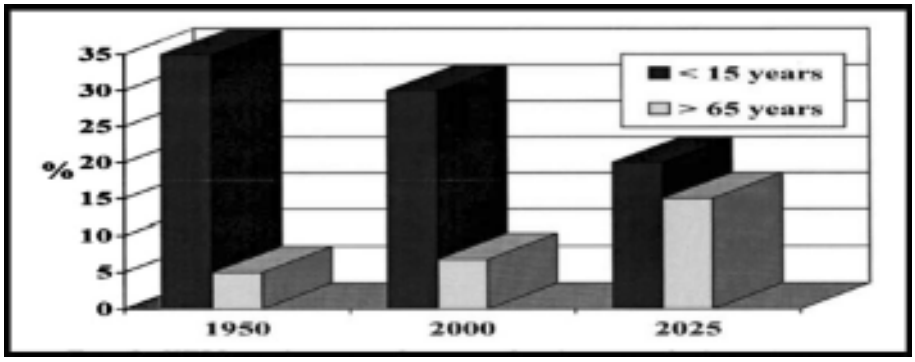

Fig. 2: WHO estimates of non-reproductive populations (younger than 15 and older than 65 years within 75 years span (WHO Technical reports, 1995)

Considering different points in view regarding testosterone action on different target organs including sexual organs, International Society for the Study of the Aging Male (ISSAM) in 1997 defined: "Andropause is a clinical condition characterized by a partial deficiency of androgens in blood and/or a decreased genomic sensitivity in target tissues. This state of hypogonadism leads to a decline of physical energy, an altered state of well-being, a sexual dysfunction and various metabolic alterations. These issues may have deleterious effects on muscle mass, bone density, lipid profile and eventually cognitive functions" (Tremblay, 1998).

SIGNS AND SYMPTOMS

The signs and symptoms that were adopted by ISSAM as universal signs of andropause on different organ systems apart from gonads are as follows :

A) **Vasomotor and Nervous symptoms**: These include insomnia, nervousness, episodes of sweating, hot flushes similar to those of menopause.

B) **Mood disorders and cognitive function**: Among these irritability and lethargy, low mental energy, depressive symptoms, decreased sense of well being, difficulties with short term memory and unusual fright are most prominent.

C) **Body composition and masculinity** : Decreased vigor and physical energy, diminished muscle mass and strength, decreased bone mineral density, increased osteoporosis, abdominal obesity are the common symptoms (Ward, *et.al.*, 2011).

D) **Sexuality :** Decreased desire for sex, reduction of sexual activity, poor erectile function, limited quality of orgasm, weakness of ejaculation, loss of sexual body hair are the signs of sexuality in andropause (Kabir *et.al.*2008).

Among the above symptoms the body compositional alterations lead to decreased balance, low physical function and increased risk of fall and fracture. This leads to increased frailty and decreased independence leading to disability. The decreased bone mineral density and increased osteoporosis also contribute to this disability (Roubenoff and Hughes, 2000).

The hypothalamo-pituitary-testicular (H-P-T) system including reproductive activity is also adversely affected in andropause that can be summarized under the following parameters:

FERTILITY: Though male fertility theoretically persists until death, less that 1% of all births are fathered by men over the age of 50 yrs. This is true even in those countries where life expectancy exceeds 70 yrs. of age such as Australia, Germany etc. This is shown in Fig. 3 (Handelsman, 2006). In an Irish study where pooled fertility data of all husbands according to age across all wives' ages were taken, a moderate negative effect (~10%-20% per decade) on annual birth rate was found as husband's age increased from 40-45yrs to over 60 yrs (Fig. 4) (Anderson, 1975).

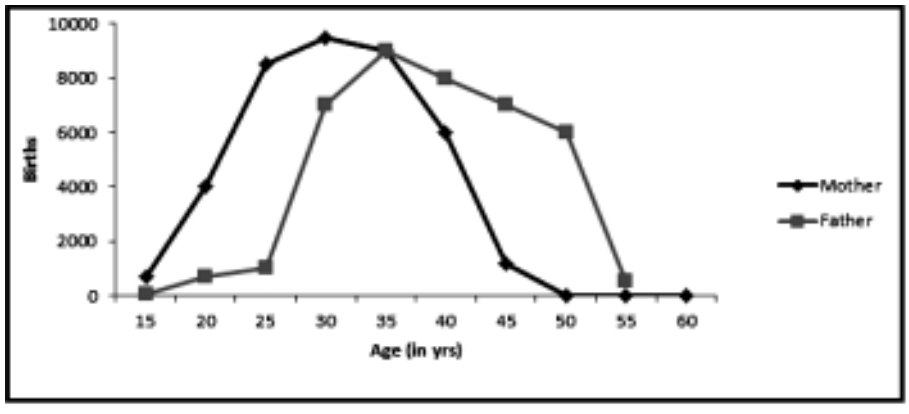

Fig. 3: Persistence of male fertility in some European Countries (Handelsman, 2006)

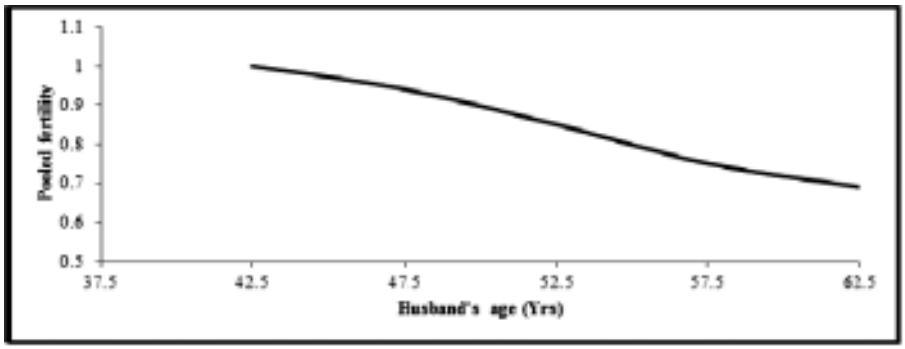

Fig. 4: Pooled fertility of all husbands according to age across all wives' ages (Anderson, 1975)

SPERMATOGENESIS : The little information available suggests that spermatogenesis though declines with increasing age but not severely. Testicular volume (largely seminiferous tubular volume) decrease about 25%. Daily sperm production rate is approximately 30% less in aged men than younger men. Percentage of sperm motility is lower in older men. Serum Inhibin B (a reflector of Sertoli cell function) in older men are about 75% of that in younger men (Snyder, 2014).

SEX STEROIDS AND GONADOTROPHIN CONCENTRATION: Serum testosterone (T) decreases with an increase in age (Fig. 5). The onset, speed and depth of the decrease are variable and generally, mean serum testosterone decreases approximately 10% in each decade after the age of 50 years (Morales, *et.al*., 2000). The diurnal variation of serum T (peak at 8 a.m. and nadir at 8 p.m.) is also less pronounced in older men (Fig. 6). Though exact level of testosterone varies immensely among person to person the bio-available testosterone which is the sum of free testosterone and albumin bound testosterone is comparatively less in olders (Snyder, 2014). These results are not always found in case of total testosterone as it includes SHBG (sex hormone binding globulin) bound testosterone which is not bio-available but increases with advancement of age (Vermeulen, *et. al*, 1995) . Moreover, diurnal variations of serum T is the main indicator of testosterone mediated activity (Plymate, *et.al*., 1989), proving a compromise in androgenic activity during andropause (Travison, *et.al.*, 2007).

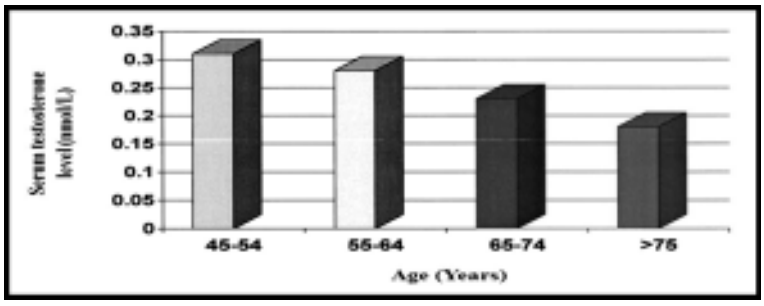

Fig. 5: Decrease in plasma free testosterone relative to age (Vermulen, et.al., 1995)

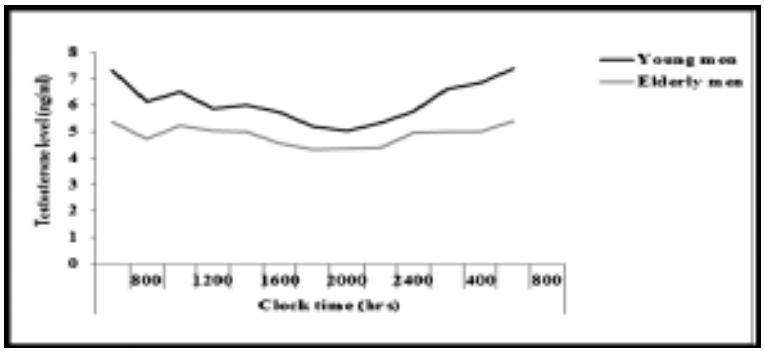

Fig. 6: Diurnal variation of serum testosterone in young versus older men (Bremner, et.al., 1983)

Serum concentration of LH and FSH increase with increasing age – LH increases by 0.9% per year and FSH by 3.1% per year after 50 years of age. This increase suggests that a degree of primary hypogonadism is responsible for the decline in serum T. Moreover, LH secretory burst amplitudes and LH response to a bolus dose of GnRH is less in elderly men than young. This indicates that T decline is a result of primary as well as secondary hypogonadism (Wu, *et.al*., 2008).

The extra-gonadal androgens secreted mainly from adrenal cortex are DHEA (dehydroepiandrosterone) and DHEAS (dehydroepiandrosterone sulfate) –which also decrease – by the 5th decade of life DHEA level decrease less than 30% of those in younger men and this declining DHEA parallel a decrease in well-being (Herbert, 1995).

The above central and peripheral endocrine alterations result in disruption of the regulatory mechanisms of the H-P-T axis which not only suppresses reproductive activity but also deteriorates the quality of life (Morales, *et al,* 1994).

DIAGNOSIS

The diagnosis depends mainly on clinical features and laboratory investigations. The patient presents with the features of impotence. The practical diagnostic algorithm for biochemical evaluation of men suspected of andropause is shown in Fig. 7.

TREATMENT

Since andropause is manifested mainly due to decline in androgen levels in blood, androgen (testosterone) replacement therapy is the choice of treatment available these days (Weksler, 1996, Brawer, 2004, Hijazi, *et.al.*, 2005, Snyder, 2014). As the onset of andropause is gradual and there is a controversy on established normal testosterone levels for different age groups, supplementation of testosterone has not been proved to be completely safe and long-term placebo-controlled trials are needed to establish the safety of the therapy (Weksler, 1996, Rhoden *et.al*., 2004). However, T-replacement therapy (TRT) is widely in practice on andropausal men throughout the world (Tenover, 2003).

The goal of TRT can be divided into two major areas: improvement in symptoms and restoration of alterations in normal physiology. Improvements in symptoms include improved psycho-sexual function, physical activity, quality of life and overall mood. Restoration of

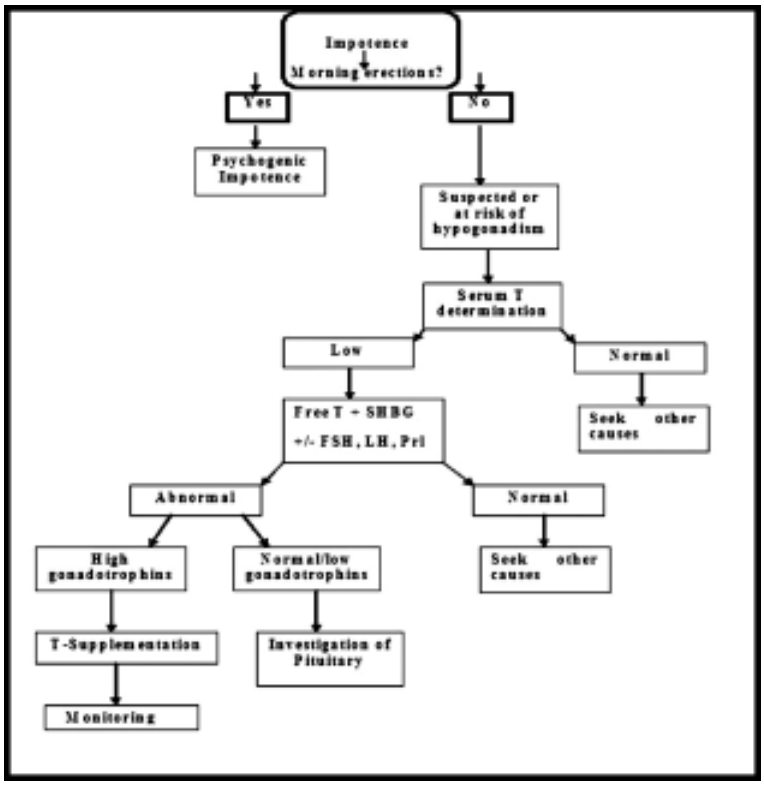

Fig.7: Practical diagnostic algorithm of andropause (Adapted from Morales, et.al. 2000)

organ systems that have suffered deleterious effects due to a hypogonadal state include improvement of bone mineral density, body composition , strength and cognitive function (Brawer, 2004, Srinivas-Shankar, *et.al*., 2010).

Since TRT has been proved to be efficient in treating andropause related symptoms, different modes of testosterone treatments are now-a-days available such as oral agents, injectable formulations, trans-dermal patches, trans-dermal gels and buccal tablets (Fernandez-Balsells, *et.al*., 2010). Among these most accepted mode is application of trans-dermal gels because of their ease of administration. Though it is expensive, this is the preferred modality of therapy today (Steidle, *et.al*., 2003) . The commonly used TRT modalities and formulations are given in Table1.

Risks of TRT: Though TRT is the available treatment, the patient with biochemical evidence of low testosterone and some or all of the symptoms of andropause must be informed of the potential risks and benefits before treatment. The absence of long-term placebo-controlled trials renders definitive evidence of safety of supplemental androgens unknown (Brawer, 2004).Potential risks factors based on sporadic reports should be described to the patient. These are mentioned in the Table 2.

Table 1
Commonly used TRT modalities and preparations (Adapted from Brawer, 2004)

Mode	Preparations	Trade Name	Manufacturer
Injectable	Testosterone cypionate cypionate	Depo-testosterone	Bio-Technology General Corp, New Jersey
	Testosterone enanthate	Delatestryl	Bio-Technology General Corp, New Jersey
Oral	Fluoxymesterone	Halotestin	Pharmacia & Upjohn, Michigan
	Methyltestosterone	Metandren	Novartis Pharma Switzerland
	Testosterone undeconate	Andriol	Organon Oss, The Netherlands
Transdermal	Testosterone Patch	Testoderm Androderm,	Alzacorp CA Watson Pharma, Inc., NJ
	Testosterone Gel	Androgel® Testim®	Solvay Pharma, PA AuxiliumPharma, PA

Table 2
Potential Hormone-related and non-hormone-related adverse effects of TRT (Tenover, 2003)

Hormone Related Adverse Effects of TRT	
Promotion of fluid retention	
Increase in cardiovascular disease risk	
Precipitation or worsening of sleep apnea	
Gynecomastia	
Polycythemia	
Fluctuations in mood	
Increased rate of development of benign or malignant prostate disease	
Non-Hormone Related Adverse Effects of TRT	
Preparations	**Effects**
Testosterone undeconate	Gastro-intestinal bloating and irritation
Injectable esters	Pain at site of injection
Implantable pellets	Pain or infection at site; extravasation of pellet
Scrotal patch	Local site irritation
Nonscrotal patch	Local site skin irritation, sometimes significant
Transdermal gels	Occasional mild skin irritation

Management: The Canadian Andropause Society, Canada first recommended the management of andropausal patient which was later on adopted by ISSAM and they universally recommended the adopted management schedule. These are—

1. Patients receiving TRT should have a clear indication for it, based on clinical symptoms and physical manifestations of hypognadism.
2. Serum Testosterone level, haematocrit level, lipid profile, prostatic antigen (PSA) and other relevant investigations to be done.
3. Digital rectal examinations for prostatic hypertrophy to be done during TRT.
4. Prostatic cancer, Breast cancer and sleep apnea are absolute contraindications for TRT.
5. TRT should be continued on a long-term basis.
6. Initially, patients should have a follow-up after three months with prior attention to:
   a) Critical assessment of response to therapy
   b) Digital rectal examination
   c) PSA (> 4ng / ml, referred to urologist)

Then follow-up of the patients should be done on half-yearly basis (Kabir, et.al., 2008) .

CONCLUSION

Paternity at an advanced age is well known from older celebrities fathering children, such as— Pablo Picasso (68 yrs), Marlon Brando (70 yrs), Rupert Murdoch (72 yrs), Charlie Chaplin (73 yrs), still there is clear evidence that advancing age is associated with decline in several hormone levels prominently sex steroids (Handelsman, 2006). Direct causality between declining androgen levels and andropause is yet fully established. Early diagnoses and treatments improve the sense of well-being and prevent the metabolic,skeletal and other complications. Further multi-dimensional long-term studies are required to fully establish the causality of the disease and evaluate the safety of Testosterone replacement therapy (TRT).

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