ANDROPAUSE – DOES IT EXIST?

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INTRODUCTION

In recent years, attention has been focused on a previous non-entity – the male menopause, also known as andropause. While some have assumed that it represents a distinct entity similar to the female menopause, others have questioned the existence of such an entity itself. The vexed controversy extends to its definition, diagnosis and beyond, and has implications for treatment and follow-up. This review provides a framework for understanding the current thoughts on the problem that will be of practical relevance to the general practitioner.

GONADAL REGULATION AND PHYSIOLOGY

An understanding of the physiology and regulation of the gonadal axis as well as the effects of testosterone on the human adult male would provide a scaffold for the discussion on andropause.

The Leydig cells in the intertubular tissues of the testes secrete testosterone. The synthesis and secretion of testosterone is under the control of Luteinizing Hormone (LH) from the anterior pituitary gland. FSH acts primarily on Sertoli cells and is necessary for the initiation of spermatogenesis. FSH also stimulates the production of androgen binding protein which maintains high intra-tubular testosterone concentration, thus allowing sperm maturation. Both FSH and LH are in turn under the control of GnRH (Gonadotrophin Releasing Hormone) from the hypothalamus. GnRH stimulates the synthesis and release of LH and FSH (Follicle stimulating Hormone) whilst testosterone inhibits it. The pulsatility of GnRH secretion is crucial for the secretion of the gonadotrophins and hence, testosterone. Testosterone can exert direct pituitary effects on LH and FSH secretion along with their effects on GnRH secretion. In addition, FSH directly stimulates the Sertoli cells to secrete inhibin, which in turn can selectively inhibit FSH release from the pituitary gland without affecting LH release.

Testosterone is the most important sex hormone in the male, playing a key role in keeping men both physically and psychologically healthy. Key roles for testosterone in the adult male include:

- Maintaining sex drive, sexual function and sperm production
- Increasing muscle mass
- Maintaining mood and energy levels
- Growth of facial and pubic hair.

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With advancing age, both free and total testosterone levels fall. This decline starts as early as the 3rd decade of life. The decline in testosterone secretion may be due to a decrease in Leydig cell mass in the testes, a dysfunction in hypothalamo-pituitary homeostatic control or both. In addition, many chronic diseases are also accompanied by a low testosterone level including chronic liver disease, chronic respiratory and cardiac conditions, all of which are more common with increasing age[1].

In a longitudinal follow-up study of 890 healthy men, the prevalence of hypogonadism as defined by a total testosterone of less than 11.3 nmol/L (325 ng/dL) increased with age from 12% in men in their 50s to 19%, 28% and 49 % in men in their 60s, 70s and 80s respectively. The decline in testosterone with age is even more pronounced when free testosterone was measured, a consequence of increasing sex hormone binding globulin with age[2]. This is in stark contrast to menopause which is universal among women and occurs dramatically and within a short time-frame, whereas the decline in testosterone secretion appears to be a lot more gradual and affects many, but certainly not all, men.

EFFECTS OF LOW TESTOSTERONE IN AGEING MEN

The case for andropause has frequently been put forth because of some similarities to hypogonadism in younger men in terms of symptomatology. This includes affective symptoms such as irritability, depression, anger, decrease in energy levels, as well as physical symptoms such as weight gain, loss of muscle bulk, and increase in adiposity and erectile dysfunction. There is no doubt that such symptoms do increase with age and this has been attributed to the decrease in androgen levels with age. However, what is not certain is whether the age-associated decrease in testosterone levels has clinical significance and whether it indicates hypogonadism.

Sexuality

Male ageing is frequently associated with decreased sexual interest and potency. This has been attributed to androgen deficiency[3]. However, erectile dysfunction in elderly men is often of non-hormonal aetiology, as is libido. It would thus be difficult to tease out the component that androgen deficiency contributes to. While testosterone replacement has been shown to increase libido[4], this is not true for potency[5].

Body Composition

The increase in central and upper body fat deposition and the reduced muscle bulk and strength with advancing age in addition to low testosterone levels, could also be explained by an age related decline in growth hormone concentrations, which also increases sex hormone binding globulin resulting in a decrease in bioavailable testosterone.

Testosterone replacement in hypotestosteronaemic men has been shown to improve fat mass, muscle bulk and strength[6]. Older men (>65 years) with low-normal serum testosterone levels who were given testosterone replacement in the form of a testosterone patch to increase the serum testosterone to the mid normal range of young men, experienced a decrease in fat mass in the arms and legs and an increase in lean body mass in the trunk. This was not, however, associated with any improvement in muscle strength nor in tests of physical function such as time taken to climb 12 stairs[7].

Profound hypotestosteronaemia in young men is associated with accelerated bone loss and osteoporosis. Testosterone replacement in older men with normal testosterone levels did not result in a significant increase in bone mineral density (BMD) at the lumbar spine. However, if the pre-treatment testosterone level was low, a significant increase in lumbar spine BMD was found[8].

Cognition and Mood

There is evidence for a correlation between testosterone levels and cognitive ability, especially spatial and mathematical skills[9]. However, there are currently no studies to address this specifically in the elderly. Testosterone administration has also been shown to enhance certain visual-spatial skills[10] but not memory[11].

A recent large study among older men (50-89 years old) showed that bioavailable testosterone was inversely correlated with depression score[12]. Some authors have demonstrated an improvement in mood, energy and sense of well-being with androgen substitution in hypogonadal men. This occurred only when testosterone levels were below the normal range. Once a minimally adequate testosterone level was achieved, further increase did not further improve mood[13].

Lipids

Testosterone administration to older men with low to low-normal testosterone levels decreases total and low-density lipoprotein (LDL) cholesterol, thus theoretically reducing cardiovascular risk[14]. No influence on cardiovascular mortality has been reported thus far.

In summary, while many aging symptoms in men are suggestive of androgen deficiency, it should be borne in mind that many of these symptoms are multi-factorial in origin. In addition, testosterone supplementation in older men seems to have benefits on muscle mass, BMD, lipid profile, libido and mood only in men with subnormal testosterone levels; no effects are generally seen above a certain threshold level of testosterone.

PROBLEMS WITH DIAGNOSING ANDROPAUSE

Yet another problem in andropause is its diagnosis. Many of the symptoms of androgen deficiency are vague and non-specific. In addition, many elderly men have testosterone levels within the normal range of young adults and have normal LH levels. It is also unclear whether the requirements of testosterone in elderly men are equal to that of younger men. Moreover, even in young men, it is not clear whether testosterone concentrations in the normal range are required for full androgenic effects in the various androgen-sensitive organs[15]. A normal hormone level may not necessarily mean a normal physiological effect.

Androgen deficiency in older men has most frequently been defined using normal ranges in young males. A diagnosis is made when testosterone is less than 11 nmol/L (319ng/dL) and/or free testosterone less than 0.225 nmol/L (6.5 ng/dL), which represent the lower 1% in healthy young males[16]. One more thing to keep in mind is that the assay for free testosterone may not be reliable depending on the type of assay used[17]. These definitions are arbitrary and symptoms of hypogonadism should also be present.

Also, other causes of hypogonadism should be actively sought after, rather than attributing the low testosterone levels solely to the aging process. A complete history (including a history of testicular trauma or injury, presence of other chronic illnesses) and physical examination are crucial. Serum prolactin, LH and FSH levels should be included as part of the diagnostic workup.

TREATMENT OF ANDROPAUSE

Proponents of the treatment of andropause suggest treating all men with symptoms of androgen deficiency regardless of testosterone levels. A more conservative approach would be prudent, since testosterone replacement is not free of adverse effects. The aim of treatment would be to increase testosterone to the mid-normal range of young men, and more importantly, to alleviate the symptoms attributed to androgen deficiency.

Adverse Effects of Testosterone Supplementation

The most important side effect of androgen supplementation in elderly men is the exacerbation of prostatic disease. Testosterone supplementation induces an increase in the volume of the prostate, with a modest increase in the levels of prostate specific antigen (PSA)[14]. Obstructive benign prostatic hyperplasia is a contraindication to testosterone supplementation, as is prostatic carcinoma since most of these are androgen sensitive. The problem arises in the case of a sub-clinical prostate carcinoma, which is only detectable by prostatic biopsy, a common occurrence in elderly men. There is no evidence that physiological levels of testosterone can stimulate the growth of a sub-clinical carcinoma. In the face of the androgen sensitivity of clinical carcinomas, caution will still need to be exercised.

Red cell mass is increased with testosterone supplementation[14]. Up to a quarter of treated subjects develop polycythaemia requiring phlebotomy[4,11].

Other side effects include sleep apnoea, water and sodium retention, gynaecomastia and rarely, hepatotoxicity.

Modalities of Testosterone Replacement (Table 1)

Testosterone undecanoate is the only orally active form of testosterone. It needs to be taken 3-4 times a day since

Table 1: Testosterone Delivery Modalities

Preparation	Dose	Monitoring of Testosterone	Remarks
T. Enanthate / Cyprionate	IM 200-250 mg 2 weekly. Start at 100mg 2 weekly and build up to minimize side effects.	Check serum testosterone 3-4 days before next dose.	Most common preparation used in Singapore.
Testoderm (4mg/day, 6 mg/day)	Start 6 mg/day patch over scrotal area. Use 4mg/day patch if scrotal area cannot accommodate 6 mg patch. Should be worn for 22-24 hours per day.	Check serum testosterone 3-4 weeks after daily use, 2-4 hours after application.	Currently not available in Singapore.
Testoderm TTS	5 mg/day patch applied over arms, back or buttocks. DO NOT apply over scrotal area.	Check serum testosterone as for testoderm.	Currently not available in Singapore.
Androderm (2.5mg/day, 5 mg/day)	Start with one 5mg/day patch or two 2.5mg/day patches applied nightly for 24 hours. Apply patch over back, abdomen, upper arms or back. DO NOT apply over scrotal area.	Check morning serum testosterone after application the previous evening.	Currently not available in Singapore.
1% Testosterone Gel (Androgel) (2.5 g and 5 g packets containing 25 mg and 50 mg testosterone respectively)	Start with 5g Androgel applied once daily (preferably morning) over shoulders, upper arms or abdomen.	Check serum testosterone 14 days after starting therapy.	DO NOT shower/swim for at least 5-6 hours after application. Not available in Singapore.
Testosterone Undecanoate (Andriolw)	Initial dose: 120 – 160mg/day in divided doses for 2-3 weeks. Maintenance dose: 40mg 3x/day.	Check serum testosterone 3 months after maintenance dose.	Not as popular in Singapore because of erratic absorption and cost.

testosterone levels fall to pre-treatment levels 6-8 hours after ingestion. Absorption is also variable and the dose required should be adjusted based on plasma levels and clinical effects. Other orally active synthetic androgens/anabolic steroids (e.g. Fludroxymesterone) are either only weakly active or hepatotoxic.

The most commonly used form is the intramuscular administration of testosterone esters in oily depot, enanthate and cyprionate. Doses of 200-250 mg bi-weekly are generally prescribed. This yields supraphysiologic levels of testosterone in the 1st 2-3 days following the injection, followed by a steady decline to sub-physiologic levels just before the next injection[18]. Such fluctuations in testosterone are unpleasant and often accompanied by changes in energy, mood and libido. Transient supraphysiologic levels increase the frequency of side effects. Thus, when initiating therapy, it is a good idea to start with lower doses and slowly build up to the maintenance dose so that the side effects are more tolerable. The frequency of intramuscular injections may be unacceptable for some. Despite this, giving a lower dose of testosterone more frequently is preferred over a higher dose less frequently as a smoother serum testosterone profile is obtained with the former.

Transdermal preparations in the form of patches (scrotal and non-scrotal) and gels have been made available in recent years. Currently, 3 testosterone transdermal systems are marketed: a system applied to the scrotum that has no permeation enhancers [Testoderm, 6 mg, ALZA Corporation, Palo Alto, CA] and two systems that contain permeation enhancers for application to appendage or torso skin [Androderm 2.5 mg and 5 mg, SmithKline Beecham Pharmaceuticals, Philadelphia, PA; Testoderm TTS, 5 mg, ALZA Corporation, Palo Alto, CA]. Transdermal patches, when applied at night, provide physiological levels of testosterone both in young and elderly hypogonadal men. Peak levels are attained 2-4 hours after application, declining to 2/3 of peak levels 22-24 hours after application[19]. The most common side effect seen is that of local skin irritation, a problem that could be exacerbated in our hot and humid climate. An added advantage of the patch is that therapy can be stopped immediately if necessary.

A 1% hydro-alcoholic testosterone gel is now available in some countries. The gel comes in foil packets and is applied over the shoulders, upper arms or abdomen. Testosterone may be transferred to another person if there is close vigorous contact. Methods of reducing this transfer include washing with soap and water after application of gel and covering the site of application with clothing after the gel dries.

Monitoring of Therapy

Regular inquiries into symptoms – both of amelioration of symptoms attributed to androgen deficiency and side effects of therapy – are vital.

Patients on testosterone therapy should be monitored to ensure that testosterone levels are within the normal range. Dose or frequency (in the case of injections) would need to be adjusted if levels exceed 500 ng/dL or are below 200 ng/dL.

6-monthly digital rectal examinations (DRE), haematocrit and PSA levels should be carried out. An abnormal DRE, an increase in PSA of > 2ng/ml or an absolute value > 4 ng/ml would necessitate a urologic evaluation with transrectal ultrasound and prostate biopsies. A haematocrit of > 55% warrants evaluation for hypoxia and sleep apnoea. Therapy should also be withheld or the dose reduced.

Measurement of bone mineral density would be useful in hypogonadal men who are osteopenic.

CONCLUSION

It is ironic that as concerns regarding the safety of oestrogen replacement therapy in post-menopausal women increase (especially with the recent publication of the Women's Health Initiative Study), the interest in male hormone replacement therapy is also increasing. Indeed, while some elderly men are likely to suffer from hypogonadism and its symptoms and may thus benefit from its treatment, it remains to be determined whether long term hormone supplementation in otherwise healthy men would be safe and efficacious. In the absence of clear-cut evidence, prudence is advocated and androgen supplementation limited to men with confirmed hypogonadism and for the treatment of specific symptoms. Close supervision should also be carried out in these men, and treatment is to be terminated should serious adverse events occur or if an expected benefit is not observed.

REFERENCES

1. Morley JE, Melmed S. Gonadal Dysfunction in Systemic Disorders. Metabolism 28:1051-73, 1979.
2. Harman ME, Metter J, Toben JD, Pearson J, Blackman MR. Longitudinal Effects of Aging on Serum Total and Free Testosterone Levels in Healthy Men. J Clin Endocr Metab. 86:724-31, 2000.
3. Pfeilschifter J, Scheidt-Nave C, Leidig-Bruckner G, et al. Relationship between circulating insulin-like growth factor components and sex hormones in population based sample of 50-80 year old men and women. J Clin Endocr Metab 81:2534-40, 1996.
4. Hajjar RR,Kaiser FE, Morley JE. Outcomes of long term testosterone replacement therapy in older hypogonadal males : a retrospective study. J Clin Endocr Metab. 82:3793-6, 1997.
5. Morley JE. Management of Impotence : Diagnostic considerations and Therapeutic Options. PostGrad Med 93:65-72, 1993.
6. Brodsky IG, Balagopal P, Nair KS. Effects of Testosterone Replacement therapy on muscle mass and muscle protein synthesis in hypogonadal men. J Clin Endocr Metab 81:3469-77, 1996.
7. PJ Snyder, H Peachy, P Hannoush, JA Berlin et al. Effects of Testosterone Treatment on Body Composition and Muscle strength in men over 65 years of age. J Clin Endocr Metab 84:2647-53, 1999.
8. PJ Snyder, H Peachy, P Hannoush, JA Berlin et al. Effects of Testosterone Treatment on Bone Mineral Density in men over 65 years of age. J Clin Endocr Metab 84:1966-72, 1999.
9. Christiansen K,Kussman R. Sex hormones and cognitive function in men. Neuropsychobiology 18:27-36,1982.
10. Cherrier M, Craft S, Plymate S, et al. Effects of testosterone on cognition in healthy older men. Endocrinology Abstracts 98:2-643, 1998.
11. Sih R, Morley JE, Kaiser FE, Perry III HM, Patrick P, Ross C. Testosterone replacement in older hypogonadal men : a 12 months randomized controlled study. J Clin Endocr Metab 82:1661-7.
12. Barrett-Connor E, von Muhlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressive mood in older men. The Rancho-Bernardo study. J Clin Endocr Metab. 84:573-7.
13. Wang C, Swerdloff RS, Iranmanesh A et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, body composition parameters in hypogonadal men. J Clin Endocr Metab. 85:2839-53, 2000.
14. Tenover JS. Effects of Testosterone supplementation in the aging male. J Clin Endocr Metab. 75:1092-8, 1992.
15. Bagatell C, Heiman JR, Rivier RE, Bremner WJ. Effects of endogenous testosterone and oestradiol on sexual behaviour in normal young men. J Clin Endocr Metab. 78:711-6, 1994.
16. A. Vermeulen. Androgen Replacement Therapy in the Aging Male – a critical evaluation. J Clin Endocr Metab 86:2380-90, 2001.
17. SR Plymate. Which Testosterone assay should be used in older men? Therapeutic Perspective – Issues in Testosterone replacement in Older Men. J Clin Endocr Metab 83:3435-48, 1998.
18. Nieschlag E, Cuppers HJ, Wiegelmann W, Wickings ES. Bioavailability and LH suppressive effects of different testosterone preparations in normal and hypogonadal men. Horm Res :7:134-41, 1976.
19. Yu Z, Gupta SK, Hwang SS, Cook DM, Duckett MJ, Atkinson LE: Transdermal testosterone administration in hypogonadal men: Comparison of pharmacokinetics at different sites of application and at the first and fifth days of application. J Clin Pharmacol, 37:1129, 1997.