Chapter 72

Andropause: The Missing Health

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INTRODUCTION

Testis has two important functions: (1) testosterone production and (2) spermatogenesis. Male hypogonadism refers to decreased testosterone production or sperm production or both. It is now well accepted that in men serum testosterone levels decline progressively with aging. This decline is associated with changes in body composition; diminished physical energy, muscle strength, and body function; diminished sexual function; depressed mood; and decreased cognitive function. Similar findings can be found in the young people with androgen deficiency and are improved with testosterone replacement therapy (TRT). However, the physiological and clinical significance of the aging-associated decline in serum testosterone levels in men is not very clear, particularly because testosterone levels may remain within the normal range for young men.

The word “andropause” is formed by combining two Greek words: “Andras” in Greek meaning human male, “Pause” in Greek meaning a cessation. Andropause is a condition that comes about when “masculinity” declines. Therefore, andropause is a syndrome in which the changes accompanying aging are associated with the signs and symptoms of androgen deficiency in the older male (traditionally age >50 years). Signs and symptoms are accompanied by a low serum testosterone level.

This is not same as the mid-life crisis. Other terms such as viropause, male menopause, male climacteric, androclise, androgen decline in the aging male (ADAM), aging male syndrome (AMS) late onset hypogonadism, partial androgen decline in the aging male (PADAM) have gained some importance.

HISTORY

- Sixteenth century Chinese text of Medicine provided a series of symptoms believed to be the male equivalent of menopause.
- In 1889, at age 72, distinguished French neurologist and physiologist Charles E Brown-Sequard reported in “Lancet” the rejuvenating effects of self-administered extracts of dog and guinea pig testes.
- Brown-Sequard administered five subcutaneous doses of extract prepared from dog testicles over a 3-day period. This was followed by five more injections of extract from guinea pig testes over the following 18 days. He reported in “Lancet”...
- “The day after the first subcutaneous injection, and still more after the two succeeding ones, a radical change took place in me... condition became quite manifest.”

- In 1935, Butenandt and Ruzicka received the Nobel prize in Chemistry after synthesizing testosterone in the laboratory.
- In 1946, Werner published a landmark paper in The Journal of the American Medical Association (JAMA) entitled “The male climacteric.” Climacteric is characterized by nervousness, reduced potency, decreased libido, irritability, fatigue, depression, memory problems, sleep disturbances and hot flushes.

PATHOPHYSIOLOGY

The production of testosterone in men is controlled by the hypothalamic-pituitary-gonadal (HPG) axis. Gonadotropin-releasing hormone (GnRH) is secreted from the hypothalamus. It stimulates the pituitary gland to release luteinizing hormone (LH), which acts on testicular Leydig’s cells to produce testosterone.

Ninety eight percent of the testosterone in plasma is bound to protein, 65% to sex hormone binding globulin (SHBG) and 33% to albumin. Only 2% of testosterone exists free in the serum. The non-SHBG-bound form of testosterone, along with free testosterone, constitutes the biologically active fraction of testosterone. The HPG axis is complex and interacts with a number of other endocrine systems, whose production of hormones is also affected by aging. Of these other hormones affected by aging, the important are the weak androgenic hormones (i.e. dehydroepiandrosterone and its sulfate) released from the adrenal gland. With aging these hormones decline. The pineal hormone melatonin is also secreted in reducing amounts with aging, which is responsible for the disturbances of sleep and biorhythms. These phenomena are attributed to some extent to the declining levels of serum testosterone with aging. The levels of growth hormone also decline with aging leading to a decline in muscle mass and strength, again the features seen in those with hypoadrogenism.

The levels of estrogens and corticosteroids in men do not show significant changes with aging. Recently, it has been found that a hormone produced by adipocytes, leptin, may act in conjunction with androgens in maintaining a lean body mass. Decreased level of hormone produced by adipocytes, leptin, may act in conjunction with androgens in maintaining a lean body mass. Decreased level of hormone produced by adipocytes, leptin, may act in conjunction with androgens in maintaining a lean body mass. Decreased level of hormone produced by adipocytes, leptin, may act in conjunction with androgens in maintaining a lean body mass. Decreased level of hormone produced by adipocytes, leptin, may act in conjunction with androgens in maintaining a lean body mass.

With aging, there is also impairment in Leydig’s cell function and decreased HPG axis sensitivity. About 7% of men between 40 years...
and 60 years of age, 20% of those between 60 years and 80 years of age, and 35% over 80 years have total concentrations below the low normal level of 350 ng/dL. This decline is very gradual (compared to the rapid hormone decline in women during menopause). The effects of andropause are less dramatic in men in comparison with the effects of menopause in women.

OTHER FACTORS CONTRIBUTING TO SYMPTOMS OF ANDROPAUSE
Factors such as smoking, obesity, alcohol use, sedentary lifestyle patterns and various chronic illness states accentuate the testosterone decline. Smoking increases total serum testosterone levels. Obesity correlates with total testosterone levels. Obese men have reduced total testosterone and SHBG levels (63% lower in very obese and 25% lower in mildly obese). Decline in the free testosterone level is less prominent. Alcohol results in a 19–27% reduction in testosterone levels. Further, older men have less circadian variation in testosterone than younger men. Thus, a fall in the morning levels is more prominent.

SYMPTOMS ASSOCIATED WITH ANDROPAUSE

Physical
- Baldness of head
- Reduced body hair, especially axillary and pubic area
- Decreased muscle mass and increased body fat
- Reduced body strength and stamina
- Feeling of weakness or tiredness
- Decreased testicular size
- Enlarged prostate
- Urinary discomfort and/or difficulties
- Backache, joint pains and stiffness

Cardiovascular
- Increasing risk of heart attack
- Increased levels of insulin, cholesterol and triglyceride
- High blood pressure
- Diminished elasticity of coronary artery
- Diminished strength of the heart muscle

Mental
- Low or negative mood, feeling irritable and insecure
- Inner unrest

Sexual
- Feeling overstressed
- Lack of concentrating power
- Memory deficits
- Reduced intellect and critical thinking

TREATMENT OF ANDROPAUSE (FLOW CHART 1)
Treatment with TRT is applied for men with symptoms of andropause and low serum testosterone levels in the absence of contraindications, such as men with history of carcinoma of the breast, known or suspected carcinoma of the prostate, severe benign hypertrophy of prostate (BPH)-related bladder outlet obstruction and liver dysfunction.

Libido
Testosterone replacement improves libido and at least quality of erections in older men. Sildenafil improves erectile function in older men. Some older men with low testosterone do not respond to sildenafil treatment until testosterone is replaced and others obtain firmer erections after testosterone replacement because testosterone is essential for the synthesis of nitric oxide synthase. Dehydrotestosterone (DHT) has been shown to enhance the ability to maintain erections.

Body Composition and Frailty
Testosterone replacement increases muscle mass. This occurs even in older persons who are not hypogonadal. The effect of testosterone on strength is less clear. Testosterone improves strength at least in the upper extremities. Testosterone definitely decreases fat mass. It seems to reduce abdominal subcutaneous adiposity to a greater extent than visceral obesity.

Behavioral Effects
Testosterone replacement reverses the memory disturbance to some extent. Testosterone produced improvement in spatial and working memory, and effects on verbal memory are controversial.

Low testosterone levels have been related to depression. Testosterone replacement does not improve depression. It may increase positive and decrease negative mood parameters.

Bone
Bone mineral density is increased at both the lumbar spine and femoral neck. The increases at the lumbar spine are more robust than those at the femoral neck.

Cardiovascular Disease
Testosterone decreases cholesterol and low-density lipoprotein cholesterol levels, and high-density lipoprotein cholesterol. The decline in high-density lipoprotein cholesterol is counterbalanced by an increase in hepatic lipase, which results in an increased clearance of cholesterol. Overall testosterone seems to have no deleterious effects on the cardiovascular system, but long-term studies are necessary for confirmation.

Administration of Testosterone Replacement Therapy
Replacement of native testosterone is ineffective due to rapid hepatic catabolism after oral ingestion. Oral testosterone is associated with
abnormal liver function tests. Injectable testosterone is considered safe but fluctuations in testosterone levels may yield variations in libido, sexual function, energy and mood, and patients may be inconvenienced by the need for frequent testosterone injections. Nongenital transdermal patches offer a convenient, although more costly, means of testosterone replacement and have demonstrated safety and efficacy in androgen-deficient men. Newer forms of administration, such as patches and gels, are generally well tolerated except for skin irritation. A new sustained- and controlled-release testosterone buccal system (TBS) contains testosterone 30 mg that adheres to the buccal mucosa and releases testosterone. Because venous drainage from the oral cavity flows directly to the superior vena cava, transbuccal delivery of testosterone bypasses hepatic first-pass catabolism. Buccal administration, therefore, is a rational method of testosterone delivery. The TBS was designed to rapidly adhere to the buccal mucosa and slowly form a gel.

Symptomatic andropause is managed by testosterone supplementation. Testosterone can be administered in oral, parenteral or transdermal forms. The parenteral salts (enanthate and cypionate esters) are safe, effective and relatively inexpensive and can

**Flow chart 1: Algorithm of management of andropause**

**Suspected hypogonadism: signs, symptoms, osteopenia**

**Morning total testosterone (T): LH and FSH**

- Normal or low total T and elevated LH and FSH
  - Repeat total T, LH, and FSH
    - Normal: Follow symptoms
    - Abnormal: Start androgen replacement therapy

- Low total T (< 200 ng/dL) and Low or nil LH and FSH
  - Repeat total T, LH, FSH
    - Normal: Follow symptoms
    - Abnormal: Evaluate for hemochromatosis and hyperprolactinemia (iron studies and prolactin)

- Total T 200–350 ng/dL and low or nil LH and FSH
  - Repeat total T, LH, and FSH (consider bioavailable testosterone or free T by equilibrium dialysis)
    - Abnormal: Follow symptoms
    - Normal: Evaluate accordingly

- Age < 60 years
  - Visual changes, headache, evidence of central (secondary) hypothyroidism, or total T < 200 ng/dL
    - Yes (to any): Pituitary MRI or CT, Trial of androgen replacement therapy
    - No (to all): Trial of androgen supplementation

- Age ≥ 60 years
  - Normal prolactin and iron studies

**Abbreviations**: T, Testosterone; LH, Luteinizing hormone; FSH, Follicle stimulating hormone
be used in a dose of 200–300 mg every 2–3 weeks. The main drawback of parenteral administration is high serum levels during the first week of treatment followed by a rapid fall. Undecanoate of testosterone is costly and has to be taken with fatty meals for lymphatic absorption to avoid first passage through the liver. Transdermal preparations (patches) are effective but are more costly. Dermatitis may occur with this form of testosterone supplementation.\textsuperscript{3,4}

Adverse effects include acne, oiliness of skin, erythrocytosis, gynecomastia, leg edema, exacerbation of sleep apnea and skin reactions to testosterone injections and patches.

**Testosterone Replacement Therapy and Prostate Specific Antigen**

Prostate specific antigen (PSA) levels are lower in andropausal men and are restored to normal after TRT. Rise of PSA level after TRT in andropausal men are usually less than 0.5 ng/mL, and rise of greater than 1 ng/mL over a period of 3–6 months are unusual.\textsuperscript{5}

**Testosterone Replacement Therapy and Erythrocytosis**

Erythrocytosis is the most common adverse event during TRT. It is also the most common cause of TRT discontinuation. If hematocrit rises greater than 54% TRT should be stopped until hematocrit has fallen to less than 50%. TRT may be restarted at a lower dose after evaluation of the patient for hypoxia and sleep apnea.\textsuperscript{5,6}

**Monitoring Men Receiving Testosterone Replacement Therapy**

Monitoring is done to ensure that:

- Testosterone levels are within the mid-normal range.
- Clinical features are improving.
- Adverse effects are minimal.

**Emerging Treatment**

- An intramuscular formulation of testosterone, undecanoate (Nebido) given every 3 weeks is in phase III pharmacokinetic studies.
- An implantable pellet system (Tesopel) can result in physiological testosterone levels with very little fluctuation over 4–6 months, but requires a minor surgical procedure.

**REFERENCES**