Chapter

56

Testosterone as a Therapeutic Tool

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INTRODUCTION

Testosterone preparations have been available for many years and have been used by physicians primarily to treat sexual problems. In a recent study it has been reported that 43 percent of women and 31 percent of men experience sexual dysfunction[1]. There has been a five fold increase in the prescriptions of testosterone over the last decade. The most common indication for androgen therapy is hypogonadism in men, but other potential uses of testosterone therapy are emerging[2,3]. Also, androgen abuse has become common among athletes[2]. Controversy surrounds the use of testosterone even today even though several issues have been resolved. Safety and effectiveness of testosterone therapy is not clearly established. Physicians need to be familiar with physiology, pharmacology, clinical indications, and adverse effects of this agent which is being prescribed much more often today than before. We need to clearly understand the risks and benefits of testosterone treatment.

TESTOSTERONE PHYSIOLOGY[3]

Androgens include Testosterone, DHT and Androstenedione. Testosterone serves as a prohormone for Dihydrotestosterone (DHT) and Estradiol. Testosterone is produced by the Leydig cells of the testis under the influence of Leuteinizing hormone (LH) from the pituitary gland. Testosterone can act directly on target cells, or indirectly by conversion to dihydrotestosterone by the 5α-reductase enzymes. It can also be aromatized to estradiol. Both testosterone and dihydrotestosterone bind to the androgen receptor, but dihydrotestosterone has a much greater affinity for the receptor and is therefore a more potent androgen. Mechanism of action

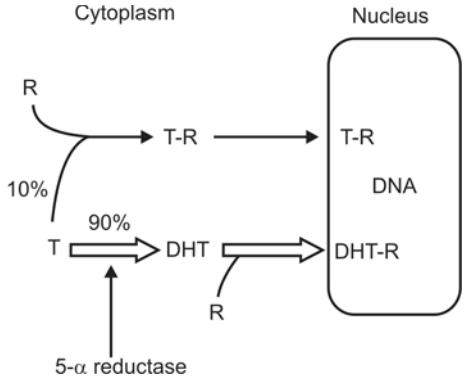

Fig. 1: Mechanism of action of testosterone and dihydrotestosterone at cellular level. R-Receptor; T-Testosterone; DHT-Dihydro Testosterone

of testosterone and dihydrotestosterone at cellular level is demonstrated through Fig. 1. 98-99% of testosterone circulates in the blood bound to the sex hormone binding globulin (SHBG) and is not available to the tissues. SHBG levels can be low in conditions like obesity which results in low total testosterone levels. Free testosterone estimations may be more relevant in these conditions to assess testicular function.

Testosterone levels in adult men decline at an average rate of 1 to 2 percent per year reaching hypogonadal range in over 50% by the age of 80 years. This change can be caused by the normal physiologic changes of aging, testicular dysfunction, or hypothalamic-pituitary dysfunction[2,3].

BIOLOGICAL ACTIONS[2,3]

Testosterone is the predominant androgenic hormone and has a range of biological actions. The

classical effects of testosterone are the induction and maintenance of secondary sexual characteristics and preservation of libido, sense of well-being, lean mass, and bone density. It stimulates prenatal differentiation, pubertal development of secondary sexual characters, its maintenance in adults and spermatogenesis. Testosterone also has a key role in stimulating and maintaining sexual function in men. Testosterone replacement in men with hypogonadism improves several aspects of sexual behavior. However, testosterone administration in men with erectile dysfunction but normal gonadal function is usually not beneficial. Testosterone increases lean body mass, and body weight. It acts through the androgen receptor to increase the size of muscle cells, without affecting their number. Dihydrotestosterone is believed to increase sebum production in the sebaceous glands. Testosterone increases the synthesis of clotting factors, hepatic triglyceride lipase and other enzymes. Exogenous testosterone administration is associated with decreased HDL levels. Hypogonadism is an important risk factor for osteoporosis in men suggesting an important role for testosterone in increasing bone mass. Testosterone is also believed to increase erythropoietin production thus promoting erythropoiesis. Also, several lines of evidence suggest that testosterone has favorable immunomodulatory properties. The greater incidence of immune-mediated disease in women and androgen deficient men has been attributed to the immunosuppressive effects of androgens compared with estrogens. Current *in vitro* evidence suggests that testosterone may suppress the expression of the proinflammatory cytokines TNF alpha, IL-1, and IL-6 and potentiate the expression of the anti-inflammatory cytokine IL-10[2,3]. Physiological effects of testosterone and dihydrotestosterone is illustrated in Table 1.

Table 1: Physiological effects of testosterone and dihydrotestosterone

- Growth of genitals in a boy
- Spermatogenesis
- Growth of facial, pubic and axillary hairs
- Muscular development
- Growth of larynx and deepening of voice
- Inhibition of bone growth
- Thickening of skin, loss of s.c. fat
- Behavioral changes in men
- Nitrogen retaining effect
- Increased erythropoietin secretion
- Increased LDL and decreased HDL
- Immunomodulatory and anti-inflammatory action

Table 2: Testosterone preparations

Testosterone preparations	*Dose*
Testosterone aq. suspension	50-100 mg / 2 weeks
Testosterone esters:	
• Testo. propionate	25-50 mg / 3 times a week
• Testo. phenylpropionate	40-60 mg / 1 or 2 week
• Testo. cypionate	100–200 mg / 2 weeks
• Testo. enanthate	250 mg / 2 weeks
Orally active preparations:	
• Testosterone undecanoate	120 mg / day or twice daily
• Methenolone	
• Methyl testosterone tab.	
• Fluoxymesterone	
• Mesterolone	
Transdermal	
Scrotal patches	
Testoderm	Once daily
Non-scrotal patches	
Androderm	1-2 patches /day
Testoderm TTS	(back, abdomen, thigh)
Gel	
1% testosterone gel	On shoulder or abdomen once daily
Implants	Wall of abdomen / thigh

Testosterone Preparations

Since testosterone is degraded quickly by the liver, it must be altered chemically to produce clinically useful preparations. Three types of modifications are used (Table 2) :

1. Esterification of the 17 hydroxy position
2. Alkylation at the 17 hydroxy position
3. Modification of the A, B, or C positions[2,3]

Testosterone is commonly esterified at the 17-hydroxy position[2]. The resultant compounds are hydrophobic and are released gradually from oily vehicles. After injection, testosterone is hydrolyzed from the ester at the site of injection and is metabolically identical to endogenous testosterone. Serum testosterone concentrations are high for the first few days after an injection but often fall to base-line levels before the next injection. Because of extensive first-pass hepatic metabolism, esters other than testosterone undecanoate must be injected intramuscularly. Testosterone may be alkylated at the 17-hydroxy position, giving rise to androgens that are more resistant to hepatic metabolism[2,3]. Many of these compounds are sufficiently resistant to degradation that they can be administered orally, and they form the basis

for many regimens used by athletes and body builders. In general, these androgens are weaker than testosterone or testosterone esters, and they can cause hepatic dysfunction.

Testosterone patches, worn on the scrotum and replaced daily, are available for the treatment of men with hypogonadism. After the patch is applied, serum testosterone concentrations rise to the middle of the normal range and then decrease slowly to the low end of the normal range over a period of approximately 24 hours.

A patch that can be used on nonscrotal skin has recently become available. This patch is very effective and eliminates the problems of scrotal application, although it may be associated with more frequent skin problems at the site of application. Both scrotal and nonscrotal patches are more expensive than other formulations of androgen. Crystalline testosterone can be formulated in implantable pellets, which provide serum testosterone concentrations in the normal range for up to four months.

Clinical Indications for Testosterone Therapy

Various clinical uses of testosterone are listed in Table 3.

Hypogonadism in Adults

Hypogonadism is defined as a low serum testosterone level coupled with any of the following signs and symptoms i.e. Sexual symptoms, including decreased libido, erectile dysfunction, difficulty achieving orgasm, anemia, depressed mood, diminished bone density, diminished energy, sense of vitality, or sense of well-being, diminished muscle mass and strength, impaired cognition, increased fatigue[4].

There are no consistent guidelines for the level of total testosterone that defines hypogonadism; the American Association of Clinical Endocrinologists (AACE) definition of hypogonadism in males is of a total testosterone level less than 200 ng per dl[4].

Table 3: Clinical uses of testosterone

- Testicular failure: Primary and secondary
- Chronic illness
- Burns
- Osteoporosis
- Long-term corticosteroid therapy
- Pituitary dwarfism
- Carcinoma of breast
- Hereditary angioneurotic edema
- Anemia (refractory)
- Menopausal syndrome

Treatment with testosterone gel, transdermal patch, or intramuscular injection is indicated for men with low total testosterone levels who have symptoms of hypogonadism[5].

The goals of androgen replacement in men are to induce or maintain secondary sexual characteristics, sexual behavior, muscle development, and male habitus[6]. Studies have shown improvement in libido and sexual function in hypogonadal men[7]. The bone mineral density of hypogonadal men decreases as testosterone levels decrease, potentially increasing the risk of fractures[8]. Testosterone replacement is associated with increase in bone mineral density but effects on fractures have not been demonstrated[8]. Lean body mass increases after treatment in these patients although muscle strength does not improve[6,9]. No positive effects on mood or cognitive behavior have been reported. But, improvements in quality of life have been found in trials[9]. Testosterone therapy does not restore spermatogenesis in hypogonadal states but the ejaculate volume may return to normal[10]. Because they are long-acting and do not have toxic effects on the liver, testosterone enanthate and testosterone cypionate are the preparations of choice for the treatment of hypogonadism[11]. A regimen of 200 mg given intramuscularly every 10 to 14 days is frequently used.

Effectiveness of therapy is best assessed clinically. Increased libido, energy, and strength is demonstrable within days to weeks after the start of therapy. Changes in physical appearance takes longer to be visible and may take six months. In older men the prostate should be examined before the start of therapy along with prostate specific antigen (PSA) and again 3-6 months after starting treatment[11,12].

Hypogonadism in Delayed Puberty

Delayed puberty may be due to hypogonadism (primary or secondary) or constitutional delay in growth and puberty. Sometimes this may be very difficult to distinguish and a period of observation may be required to settle the issue. In patients with greater concern, testosterone enanthate injections 50-100 mg i.m. can be given for 3 months without deleterious effects[13,14]. This would help linear growth and development of secondary sexual characters.

However, if hypogonadism is indicated by clinical and biochemical features long-term testosterone

replacement is indicated from age 14 years. This is given as testosterone enanthate injections 50-100 mg every 2-4 weeks for 6-12 months and then gradually increased to 200 mg / every 2-4 weekly[13,14].

Healthy Older Men with Decreased Bioavailable Testosterone

There is a lot of controversy about the aging old men and the male andropause. Growing evidence indicates that some aging men have reduced production of testosterone associated with decreased libido, impotence, decreased growth of body hair, decreased muscle mass, fatigue, increased risk of myocardial infarction, and decreased bone mass with osteoporosis. Recent evidence suggests that this is related to the age related decline in testosterone which responds to testosterone replacement therapy[5,12,15-17].

Data from long-term studies are needed to clarify the use of testosterone replacement in aging men. Short-term studies have demonstrated that testosterone replacement treatment may result in improved lean body mass, increased hematopoiesis, decreased low density lipoprotein (LDL) levels, improved libido, and improved well-being in older men with low testosterone levels[10]. Generally, prostate size and prostate-specific antigen (PSA) levels do not change[7]. Testosterone therapy can improve quality of life in aging men because aging is accompanied by declining testosterone levels that may contribute to decreases in muscle mass, bone density, libido, stamina, and cognition[6-8,13,15].

However, routine recommendation of the use of testosterone in this setting would depend on further studies establishing a favorable risk to benefit ratio. At least six important adverse effects need to be considered - Increased risk of prostate cancer, increased risk of clinically significant benign prostatic hypertrophy (BPH)[18]. Stimulation of erythropoiesis, which could cause adverse effects due to hyperviscosity of the blood, increased risk of sleep apnea, increased risk of cardiovascular disease, Increased risk of aggressive behavior or inappropriate sexual behavior[18]. Data are insufficient to determine whether testosterone replacement therapy would increase, decrease, or have no effect on cardiovascular disease incidence.

HIV-infected and AIDS Patients

Hypogonadism is highly prevalent in HIV-infected patients and has been associated with the late stages of AIDS and AIDS wasting. Testosterone replacement, with the exception of the transscrotal delivery patch, has been observed to have a beneficial effect on lean body mass and body weight in hypogonadal and eugonadal men with the AIDS wasting syndrome[9,19-22]. In hypogonadal men with AIDS treated with testosterone replacement therapy, researchers noted a positive effect on depression scores[20]. Testosterone replacement in HIV-infected men with low testosterone levels is safe and is associated with a 1.35-kg gain in lean body mass, a significantly greater reduction in fat mass than that achieved with placebo treatment, an increased red cell count, and an improvement in role limitation due to emotional problems[20]. Further studies are needed to assess whether testosterone supplementation can produce clinically meaningful changes in muscle function and disease outcome in HIV-infected men.

Testosterone Therapy in Women

Women may experience symptoms secondary to androgen deficiency. There is also substantial evidence that androgen replacement can be effective in relieving both the physical and psychological symptoms of androgen insufficiency, and is indicated for clinically affected women[23,24]. Doses are restricted to the 'therapeutic' window for androgen replacement in women, such that the beneficial effects on wellbeing and quality of life are achieved without incurring undesirable virilizing side effects. The predominant symptom of women with androgen deficiency is loss of sexual desire[24,25].There is increasing interest in other uses of testosterone replacement in women that include premenopausal iatrogenic androgen deficiency states, glucocorticosteroid-induced bone loss, management of wasting syndromes and possibly premenopausal bone loss, premenopausal loss of libido and the treatment of the premenstrual syndrome[23]. If plasma levels of bioavailable testosterone are low, these symptoms will mostly be relieved by judicious administration of testosterone.

Sarcopenia in Old Age

Decreased muscle mass and function characterizes fragility of old age and may benefit from testosterone treatment. However, most of the ongoing studies of testosterone replacement, have preferentially recruited relatively healthy, older men[6]. Therefore, it still remains to be determined whether androgen replacement in older men with chronic diseases and frailty will improve muscle mass and function.

The feasibility and relative safety of administering replacement doses of testosterone to older men over a

1-year period has been demonstrated. However, several critical issues with respect to the usefulness and long-term safety of androgen-substitution for reversing or preventing sarcopenia and frailty in older men remain unresolved[6].

Male Osteoporosis

In males testosterone deficiency accounts for nearly half the patients with osteoporosis. These patients could benefit from testosterone replacement. Intramuscular testosterone has been shown to moderately increase lumbar bone density in men; the results on femoral neck bone density are inconclusive[8,12]. Without bone fracture data, the available trials offer weak and indirect inferences about the clinical efficacy of testosterone on osteoporosis prevention and treatment in men[12,17].

Stimulation of Erythropoiesis

Testosterone and other androgens are known to stimulate erythropoiesis and have been used in refractory anemias and anemia of renal failure with some success[2]. Generally, testosterone is not used for the purpose and other androgens are used.

Side Effects

The adverse effects of testosterone are shown in Table 4. These could be due to inappropriate physiological actions like virilization in the female and feminizing in the male. Virilization includes coarsening of voice, hirsutism, and menstrual irregularities. If untreated these may lead to male pattern baldness, and hypertrophy of the clitoris[18]. Feminization in the male is due to aromatization of excessive testosterone and estradiol production that results in gynecomastia[18]. This is usually seen in adolescents along with acne Toxic effects are generally more common with oral alkylated testosterone – liver dysfunction, hemorrhagic liver cysts and hepatoma. A list of possible adverse effects is given in Table 4. Sleep apnea and elevated hematocrit are more important in middle aged and older patients[26].

Table 4: Adverse effects of testosterone

- Virilization (female)
- Feminizing side effects (male)
- Precocious puberty and stunted growth
- Cholestatic jaundice
- Enlargement of prostate
- Unmasking of prostate cancer
- Atherosclerosis
- Hepatic dysfunction (17 alpha alkylated androgens only)
- Hepatic carcinoma
- Edema and weight gain
- Elevated hematocrit and hyperviscosity
- Decrease HDL-C levels
- Sleep apnea
- Priapism

Monitoring Patients on Testosterone

Because of the uncertain safety of testosterone, monitoring patients during therapy is recommended[18]. The AACE guidelines suggest routine monitoring of male patients by history and physical examination including a digital rectal examination and measuring prostate-specific antigen levels, testosterone levels in patients receiving injections, hematocrit, and lipid profiles[7]. Generally, women are watched for side effects rather than checking testosterone levels. It is recommended that physicians monitor women taking testosterone for virilization and do baseline and semiannual breast examinations, complete blood cell count, lipid levels, annual mammography, and endometrial ultrasonography[4].

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