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Emerging Issues in Androgen Replacement Therapy*

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THE LAST FEW years in the androgen field can only be described in the words of Charles Dickens, as ". . . the age of wisdom, (and) . . . the age of foolishness." Some of the recent advances in the androgen field have been truly spectacular. Our understanding of androgen action and the pathophysiology of androgen insensitivity syndromes has been greatly enhanced by the characterization of the androgen receptor and the 5-α reductase genes. The development of 5-α reductase inhibitors has made available a new class of therapeutic agents for the treatment of a number of androgen-dependent clinical disorders including benign prostatic hyperplasia. Several attractive testosterone delivery systems have been approved, and many more are under development (1–6). Clinical trials have established the effectiveness of testosterone-induced azoospermia and/or severe oligozoospermia in inducing reversible contraception in healthy men (7–9). The rationale for anabolic applications of replacement and supraphysiological doses of testosterone has been strengthened by well-controlled clinical trials (10, 11).

On the other hand, several recent trends in androgen use are alarming. Because a substantial portion of the androgen market is underground, exact estimates of androgen use in the United States are not available. However, audits of direct and indirect sales indicate that the androgen sales in this country are growing 20–30% each year. There is reason to believe that a substantial part of the overall androgen market involves the illicit use of testosterone for unapproved indications, particularly for muscle building by athletes and recreational body builders. The use of testosterone in human immunodeficiency virus (HIV)-infected men is growing, although clinical trials to examine the effectiveness of testosterone in reversing HIV-wasting syndrome are still in progress. It is distressing that a significant proportion of hypogonadal men continue to be undiagnosed, diagnosed late, or inappropriately treated. Thus a paradoxical situation has developed in which testosterone replacement therapy continues to be underutilized or inappropriately used for legitimate indications, while its use for unapproved indications continues to expand.

The objective of this review is to highlight the new androgen formulations, and suggest pragmatic regimens for the institution and monitoring of testosterone replacement therapy. In addition, the review will also discuss the rationale for the proposed anabolic applications of androgen therapy in wasting states.

Testosterone delivery systems

Testosterone is well absorbed after its oral administration but is quickly degraded during its passage through the liver. Therefore, it is not possible to achieve sustained blood levels of testosterone after oral administration of crystalline testosterone. 17-α alkylated derivatives of testosterone are relatively resistant to hepatic degradation and can be given orally; however, because of the potential for hepatotoxicity, these formulations are not recommended for clinical use.

The esterification of the testosterone molecule at the 17-β-hydroxy position makes the molecule hydrophobic and extends its duration of action. Deesterification of testosterone is not a limiting factor in determining its duration of action; the plasma half-lives and clearance rates for testosterone and testosterone enanthate are similar. It is the slow release of the hydrophobic testosterone ester from its oily depot in the muscle that accounts for its extended duration. The longer the side chain, the greater the hydrophobicity of the ester and the greater the duration of action. Thus testosterone enanthate and cypionate with longer side chains have longer duration of action than testosterone propionate.

After intramuscular administration of 200 mg testosterone enanthate, serum testosterone levels rise rapidly into the high normal or even the supraphysiological range within 24 h and then gradually decline into the hypogonadal range over the next 2 weeks (12, 13). Therefore, a bimonthly regimen of testosterone enanthate or cypionate results in highs and lows in serum testosterone levels that are attended by similar changes in the patient's mood, sexual desire and

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activity, and energy level. The kinetics of testosterone enanthate and cypionate are identical. Serum levels of estradiol and dihydrotestosterone (metabolites that are derived by conversion from testosterone) are normal if testosterone replacement is physiological.

Two transdermal testosterone systems are now commercially available: a scrotal testosterone patch (Testoderm, ALZA Corporation, Palo Alto, CA) and a permeation-enhanced nongenital patch (Androderm, SmithKline Beecham Pharmaceuticals, Collegeville, PA). The scrotal transdermal system, when applied daily on the scrotal skin, can produce mid-normal serum testosterone levels in hypogonadal men 4–8 h after application of the patch followed by gradual decrease in serum testosterone levels over the next 24 h (2). Serum estradiol levels are normal but dihydrotestosterone levels are high relative to testosterone levels in hypogonadal men treated with the scrotal testosterone patch, presumably because of the high rates of 5-α reduction of testosterone to dihydrotestosterone during its passage through the scrotal skin. It is not known whether long-term exposure to high serum dihydrotestosterone levels have any deleterious effects on the prostate and whether intraprostatic dihydrotestosterone levels are elevated. Also, to promote good adhesion of the patch, the scrotal skin must be shaved.

A permeation-enhanced nongenital patch can be applied on the nonscrotal skin (3). After nightly application of two patches, serum testosterone and estradiol levels are in the mid-normal range 8–12 h after application of the patch. Unlike the scrotal patch, the nongenital patch produces physiological levels of serum dihydrotestosterone and normal dihydrotestosterone to testosterone ratios. Sexual function and sense of well being is restored. The two transdermal systems are substantially more expensive than testosterone esters (approximate monthly cost: testosterone esters $8, scrotal patch $80, and nongenital patch $100). The expense of testosterone esters is increased greatly if injections are given in a medical office; however, nearly all patients or a close family member will accept the responsibility of administering the injections.

Testosterone undecanoate, when administered orally in oleic acid, is absorbed preferentially through the lymphatics into the blood stream and is thus spared the first-pass degradation in the liver. This compound needs to be administered two or three times a day for clinical effects (14). The circulating levels of testosterone tend to vary among subjects receiving the same dose of this formulation. This formulation is not approved for use in the United States, but is being used in Europe, Canada, and elsewhere.

Testosterone pellets have been around for more than four decades. When implanted by a trocar under the skin through an incision, three 200-mg pellets or six 100-mg pellets can provide normal testosterone levels as well as physiological levels of estradiol and dihydrotestosterone for as long as 6 months (15). However, because of the need for a skin incision and occasional spontaneous extrusion of the pellets, this formulation is rarely used in the United States.

Because of the potential applications of testosterone as an anabolic agent and for male contraceptive regimens, there has been a resurgence of interest in developing more physiological, sustained-release testosterone formulations. A single intramuscular injection of a biodegradable testosterone microsphere formulation provides eugonadal levels of testosterone in hypogonadal men for up to 11 weeks (5); serum estradiol and dihydrotestosterone levels are maintained in the normal male range. A long-acting testosterone ester, testosterone buciclate, which has a 12- to 16-week duration of action, is also under investigation. A cyclodextrin-complexed testosterone sublingual formulation is absorbed rapidly from the sublingual mucosa into the blood stream, where testosterone is released from the cyclodextrin shell (6). Testosterone undecanoate, when administered intramuscularly in a hydrophobic suspension has a more extended duration of action than testosterone enanthate (16).

Monitoring androgen therapy

Measurement of serum testosterone levels is the most cost-effective way of monitoring testosterone replacement therapy (Table 1). In patients being treated with testosterone enanthate or cypionate, serum testosterone levels should be in the mid-normal range 1 week after the injection. If nadir levels 14 days after the injection are low, the interval between injections may be shortened. In men on chronic scrotal transdermal therapy, serum testosterone levels 4 h after the patch application should be at least mid-normal. In men using the nongenital patch, serum testosterone levels 8–12 h after the nightly application of the patch should be mid-normal.

It is uncommon for serum LH levels to be normalized by physiological replacement doses of testosterone in men with hypergonadotropic hypogonadism, particularly those with Klinefelter's syndrome. Relative resistance of the gonadotrope in men with Klinefelter's syndrome to testosterone suppression has been reported. In men with hypergonadotropic hypogonadism receiving the transdermal scrotal or nongenital testosterone patch, serum LH and FSH are usually not normalized by serum testosterone levels that are in the normal range and that restore sexual function. Therefore,

TABLE 1. Testosterone replacement regimens and guidelines for monitoring the adequacy of replacement

Preparation	Usual regimens	Monitoring
Testosterone enanthate or cypionate	200 mg im every 10–16 days **or** 100 mg im every week	Serum testosterone levels 1 week after injection should be in mid-normal range
Scrotal testosterone patch	1 patch on scrotal skin every morning	Serum testosterone levels 4 h after patch application should be mid-normal
Nongenital testosterone patch	2 patches on nongenital skin nightly	Serum testosterone levels 8–12 h after application of patches should be mid-normal

the usefulness of LH and FSH levels to assess the adequacy of testosterone replacement remains questionable.

Restoration and maintenance of sexual function and secondary sex characteristics are important objectives of androgen replacement therapy. Assessment of sexual function is hampered by the uncertainty about the validity of instruments used to assess sexual function. Some hypogonadal men continue to complain of sexual dysfunction even after testosterone replacement has been instituted; these patients can benefit from counseling. Hypogonadal men with prepubertal onset of androgen deficiency who are started on testosterone in their late 20s or 30s may find it difficult to cope with their new-found sexuality and need counseling before and during testosterone replacement therapy. If the patient has a sexual partner, it is crucial to include the partner in counseling because of the dramatic physical and sexual changes that occur with androgen treatment. The facial hair growth in response to androgen replacement is variable and dependent on the ethnic background.

Testosterone replacement increases body weight, fat-free mass, muscle size, and strength in hypogonadal men, presumably by increasing fractional muscle protein synthesis (11). However, the methods for quantitating protein metabolism are too complicated to be useful as clinical markers.

Hypogonadal men experience accelerated bone loss after the onset of hypogonadism. Androgen treatment of hypogonadal men prevents further bone loss and may increase bone mass in some patients (17). However, bone mass may not necessarily be normalized or completely restored. Therefore, it is unclear whether measurement of bone density by dual energy x-ray absorptiometry should be a part of the initial or follow-up evaluation. There is insufficient experience with biochemical markers of bone formation and resorption to recommend them for clinical use at this time.

The systemic side effects, including abnormalities of liver functions, development of liver tumors, and peliosis hepatis, are extremely rare with the replacement doses given by the injectable esters and the two transdermal formulations. More frequent side effects include acne, oiliness of skin, breast enlargement and/or tenderness, and leg edema. Breast tenderness is often transient and abates with continued treatment. Body weight and hemoglobin levels show modest increases. Clinically significant polycythemia is uncommon but can occur in men with sleep apnea, significant smoking history, or chronic obstructive lung disease; in such patients, hemoglobin levels should be closely monitored after institution of testosterone replacement. Testosterone can exacerbate sleep apnea in some individuals.

Testosterone effects on plasma lipids remain controversial. Plasma high-density lipoprotein (HDL) levels decrease during testosterone replacement therapy; nonaromatizable androgens produce a greater decrease in plasma HDL levels than aromatizable androgens. Short-term testosterone treatment of older men with low testosterone levels has not been associated with significant changes in plasma lipids. On the other hand, epidemiological studies have reported direct correlation of endogenous testosterone levels with plasma HDL levels and an inverse correlation with abdominal obesity in middle-aged men. Testosterone increases platelet aggregation and thrombogenicity; however, thrombotic events and changes in hemostasis and platelet function reported with supraphysiological doses of anabolic steroids have not been observed in hypogonadal men receiving replacement doses of testosterone.

Testosterone replacement therapy increases prostate volumes to those seen in age-matched controls, but continued androgen treatment does not further increase prostate volume in to the supraphysiological range (18). Serum prostate specific antigen levels are lower in testosterone-deficient men and are restored to normal following testosterone replacement (19). Routine monitoring of serum prostate specific antigen levels is not recommended in young hypogonadal men. Whether long-term testosterone administration to older men will unmask microscopic foci of prostate cancer remains an issue of concern.

Local skin reactions including erythema and induration can occur at the site of patch application in 5–10% of patients receiving the nongenital patch. Blister formation is relatively rare. Local skin reactions are less common with the scrotal patch.

Indications for testosterone replacement therapy

Although there is agreement that hypogonadal men need testosterone replacement, there are problems in diagnosing the hypogonadal state. Few would quibble with the proposition that patients with sexual dysfunction and low testosterone levels caused by Klinefelter's syndrome or hypothalamic-pituitary dysfunction are hypogonadal. The uncertainty pertains to whether men with chronic illness and low testosterone levels or those with sexual dysfunction and low normal testosterone levels need androgen replacement. Because of the paucity of good biological markers of androgen action, the complexities of circadian and pulsatile rhythms, and the binding proteins, it is difficult to interpret serum total testosterone levels in the low-normal range. In men with mild to moderate obesity, serum sex-hormone binding globulin levels are decreased, resulting in lower total testosterone levels, but free testosterone levels are usually normal. Hypogonadism is an uncommon cause of impotence; however, it is important to exclude it because it is treatable. In older men, some experts recommend measurement of bioavailable testosterone; serum bioavailable testosterone levels of less than 70 ng/dL, especially if associated with sexual dysfunction, should warrant an empirical trial of testosterone therapy.

In children with micropenis, judicious use of testosterone for a short period can enhance penile growth. In boys with constitutional delay of puberty, especially when there are significant psychosocial consequences of the delayed sexual development, careful testosterone administration for a finite period can induce virilization and augment growth (20). There is evidence that constitutional delay of growth and development in boys may have a significant long-term impact. Bone densities and fat-free mass are lower in boys with constitutional delay of puberty than in those without after both groups of boys have reached adulthood. Some children with GH deficiency may also suffer from delayed pubertal development. In these boys, testosterone administration can induce sexual development and enhance the growth-pro-

moting effects of GH. In hereditary angioneurotic edema, androgens stimulate the hepatic production of C1-esterase inhibitor. In this instance, the therapeutic use of orally administered, 17-α-alkylated steroid compounds can be justified; these compounds, after absorption into the portal circulation, produce a greater stimulation of the hepatic C1-esterase inhibitor.

Slightly supraphysiological doses of testosterone esters when administered to normal men can suppress LH and FSH levels and sperm production (7). Azoospermia and severe oligozoospermia (sperm density <3 million/mL) induced by 200 mg testosterone enanthate weekly causes reversible infertility in healthy men (8). Combined administration of replacement doses of testosterone with a GnRH antagonist or a progestational agent can achieve high rates of azoospermia (7, 9). The clinical application of this concept for male contraception awaits development of more user-friendly formulations for both testosterone and GnRH antagonists.

Anabolic applications of androgens

The idea that androgen administration can promote accretion of fat-free mass in catabolic states is not new (21, 22). Androgens increase muscle mass and nitrogen retention in castrated males of other species, in prepubertal boys, women, and hypogonadal men given replacement doses of testosterone (11, 21, 22). However, considerable controversy persisted until recently with regard to the effects of supraphysiological doses of androgens on muscle size and strength in eugonadal men. Some of the studies that examined this issue were not randomized; most failed to control energy and protein intake. The exercise stimulus was not standardized so that the effects of exercise and testosterone could not be evaluated independently. Inclusion of competitive athletes was another confounding factor in some of the studies. In a recent study, Bhasin *et al.* (10) demonstrated that a supraphysiological dose of testosterone (600 mg testosterone enanthate im weekly), especially when administered in association with a standardized program of resistance exercise, increases fat-free mass, muscle size, and strength in healthy young men. A number of clinical states that are attended by loss of lean body mass, such as aging, wasting syndromes associated with HIV infection, and cancer are characterized by a high prevalence of low testosterone levels (23–26). However, it remains to be demonstrated whether replacement or supraphysiological doses of testosterone can prevent or reverse sarcopenia in these wasting disorders.

Of the various metabolic abnormalities that attend the course of HIV infection, hypogonadism is the most frequent (23, 24). A third of the HIV-infected men in our HIV clinic have serum testosterone levels less than 300 ng/dL. There is a high prevalence of sexual dysfunction among homosexual men. Low testosterone levels correlate with weight loss and disease progression. Cross-sectional studies have shown that serum testosterone levels are lower in men with acquired immune deficiency syndrome (AIDS) than in asymptomatic HIV-infected or normal men. Longitudinal studies reveal that serum testosterone levels are lower in HIV-infected men who progress to AIDS than in those who do not. The etiology of hypogonadism in HIV infection is complex. Potential pathogenic mechanisms include malnutrition, cytokines, the host's immune response to infection, drugs, secondary illnesses, and virus replication. Autopsy studies reveal a high prevalence of testicular atrophy in men dying of AIDS. Histological changes include interstitial inflammation, fibrosis, thickening of basement membrane, and hypospermatogenesis. Regardless of the mechanism, HIV infection has emerged as a leading cause of testicular failure and hypogonadism. Low serum testosterone levels may contribute to weight loss and muscle wasting. Several studies are in progress to examine whether androgen replacement in HIV-infected men with low testosterone levels may prevent or reverse weight loss and augment lean body mass.

There is general agreement that total and free testosterone levels and testosterone production rates are lower in older men compared with young healthy men (25, 26). Some studies that exclusively recruited healthy, well-educated, middle-income older men failed to detect significant differences in serum testosterone levels between old and young men. Recent studies with more representative population samples have reconfirmed the age-related decrease in serum testosterone levels. Interpretation of serum testosterone levels in the older men in these studies has been complicated by several confounding factors: the cross-sectional nature of these studies, the loss of diurnal variation in serum testosterone levels in the elderly so that studies that obtain samples in the afternoon underestimate the age-related changes in testosterone levels, and the higher sex-hormone binding globulin levels in older men so that total testosterone levels underestimate the greater decline in free testosterone levels (both dialysable and bioavailable). A meta-analysis of 44 studies of testosterone levels in older men demonstrated an unequivocal decrease in morning testosterone levels. Recent longitudinal studies of normal men have verified the age-related decline in serum testosterone levels. Lower testosterone levels are the result of changes at multiple levels of the hypothalamic-pituitary-gonadal axis. Testicular response to gonadotropins is diminished in older men, gonadotrope responsiveness to androgen suppression is attenuated, and the pulsatility of the hypothalamic GnRH pulse generator is altered. Coexisting diseases, malnutrition, and concomitant medications can also affect serum testosterone levels. A number of clinical problems prevalent in older men may be related to androgen deficiency, including sexual dysfunction, muscle weakness and wasting, changes in body composition, osteopenia and increased prevalence of hip and vertebral fractures, decreased body hair, decreased hematopoiesis, and memory loss. Although all of these disorders are multifactorial, it has been speculated that age-related androgen deficiency or insensitivity plays a role in their pathophysiology in the elderly, and that androgen replacement may help prevent or reverse these disorders. However, most older men free of disease do not have testosterone levels in the hypogonadal range. Whether older men are relatively insensitive to the anabolic effects of testosterone remains to be established. Several published studies (22, 23) have provided preliminary evidence of modest gains in muscle strength and lean body mass with replacement doses of testosterone, and long-term clinical studies to test this hypothesis are now in progress.

There is a substantial prevalence of low testosterone levels in men with cancer. The etiology of hypogonadism in men with cancer is complex. Both hypogonadotropic and hypergonadotropic hypogonadism have been reported. Although in some patients, testicular dysfunction is a direct consequence of the cancer chemotherapy, in others the cause of hypogonadism is not readily apparent. Malnutrition, drugs, and as yet unidentified factors related to the host immune response play a role in the pathogenesis of hypogonadism. The speculation that low testosterone levels contribute to the multifactorial etiology of weight loss in patients with cancer remains to be tested.

Patients suffer a striking loss of lean body mass during immobilization following major trauma, space travel, the postoperative state, and extensive burns. It is not known if a short-term, carefully supervised, trial of supraphysiological doses of testosterone can promote wound healing and prevent muscle wasting in such patients.

A substantial proportion of men with chronic obstructive lung disease have low total and free testosterone levels. Consistent with trends observed in other wasting syndromes, both hypogonadotropic and hypergonadotropic hypogonadism have been observed. Many of the patients with chronic obstructive lung disease have substantial muscle wasting that limits rehabilitation. The potential of anabolic agents such as testosterone and GH to augment respiratory muscle mass and enhance response to rehabilitation therapy is being explored.

Many autoimmune rheumatological diseases, with or without glucocorticoid therapy, are associated with low testosterone levels. Most autoimmune diseases are more common in women and men with Klinefelter's syndrome than in normal men. Remission of the underlying autoimmune disease has been reported in men with Klinefelter's syndrome following institution of testosterone treatment. Pharmacological doses of glucocorticoids, regardless of the indication for their use, suppress serum testosterone levels. Some of the complications of glucocorticoid therapy such as muscle wasting and bone loss may be caused by or aggravated by the attendant androgen deficiency.

Androgenic steroids improve nitrogen balance following surgery in otherwise healthy individuals. However, androgen treatment has not been shown to increase body weight or strength in debilitated and cachectic individuals, in acute illness, or chronic catabolic illness (3). Androgens induce positive nitrogen balance in patients with end stage renal disease, but this effect is transient and has not been demonstrated to alter disease outcomes. Therefore, although the high prevalence of low testosterone levels in wasting states and the demonstrable anabolic effects of testosterone in replacement and supraphysiological doses provide rationale for exploring these anabolic applications in diseases characterized by sarcopenia, the evidence to support these anabolic applications has yet to be presented.

Androgen replacement in women

The ovaries secrete on average 150 μg of testosterone each day in premenopausal women; however, the physiological role of testosterone in women remains unclear. The changes in serum testosterone levels after menopause are variable. Women who have undergone hysterectomy and bilateral oophorectomy and have been treated with combined estrogen and testosterone therapy report higher rates of sexual desire, arousal and number of fantasies than those who are given either estradiol alone or left untreated (27, 28). Sherwin (28) has proposed that testosterone may be important for the maintenance of sexual function in postmenopausal women. Postmenopausal women treated with estrogen plus methyl testosterone have lower rates of bone resorption over a 3-month treatment period than those treated with estrogen alone. Most of the published androgen studies in postmenopausal women have used relatively large doses of testosterone. It is not surprising that supraphysiological doses of testosterone increase muscle size and strength in pre- and postmenopausal women. We do not know, however, whether addition of physiological replacement doses of testosterone to a regimen of estrogen replacement can augment fat-free mass, muscle strength, sexual function, and bone density in postmenopausal women. The critical question is whether these beneficial anabolic effects can be achieved by testosterone doses that do not result in virilization.

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