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CLINICAL REVIEW 138

Anabolic-Androgenic Steroid Therapy in the Treatment of Chronic Diseases

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The purpose of this study was to review the preclinical and clinical literature relevant to the efficacy and safety of anabolic androgen steroid therapy for palliative treatment of severe weight loss associated with chronic diseases. Data sources were published literature identified from the Medline database from January 1966 to December 2000, bibliographic references, and textbooks. Reports from preclinical and clinical trials were selected. Study designs and results were extracted from trial reports. Statistical evaluation or meta-analysis of combined results was not attempted.

Androgenic anabolic steroids (AAS) are widely prescribed for the treatment of male hypogonadism; however, they may play a significant role in the treatment of other conditions as well, such as cachexia associated with human immunodeficiency virus, cancer, burns, renal and hepatic failure, and anemia associated with leukemia or kidney failure. A review of the anabolic effects of androgens and their efficacy in the treatment of these conditions is provided. In addition, the numerous and sometimes serious side effects that have been known to occur with androgen use are reviewed.

Although the threat of various side effects is present, AAS therapy appears to have a favorable anabolic effect on patients with chronic diseases and muscle catabolism. We recommend that AAS can be used for the treatment of patients with acquired immunodeficiency syndrome wasting and in severely catabolic patients with severe burns. Preliminary data in renal failure-associated wasting are also positive. Advantages and disadvantages should be weighed carefully when comparing AAS therapy to other weight-gaining measures. Although a conservative approach to the use of AAS in patients with chronic diseases is still recommended, the utility of AAS therapy in the attenuation of severe weight loss associated with disease states such as cancer, postoperative recovery, and wasting due to pulmonary and hepatic disease should be more thoroughly investigated. (*J Clin Endocrinol Metab* 86: 5108–5117, 2001)

ANDROGENIC STEROIDS such as T and its derivatives have a wide range of uses in clinical medicine and were initially recognized for their anabolic effects. In 1889, French physiologist Charles Edouard Brown-Sequard announced that an extract of dog and guinea pig testicles given iv results in an increase in physical strength, improvement in intellectual energy, relief of constipation, and lengthening of the arc of his urine. In the late 1930s the anabolic agent responsible for these effects, the androgens, were isolated. In the 1940s, scientists confirmed Brown-Sequard's claim that androgens, particularly T, could facilitate muscle growth. With the publication in 1945 of Paul de Kruif's widely read book, *The Male Hormone*, T use among athletes became more common. Although initially used by body builders, the positive results encouraged AAS use in other strength-intensive sports, including football, track and field, hockey, swimming, soccer, cycling, volleyball, and wrestling.

Anabolic-androgenic steroids (AAS) have also been used in clinical practice since the 1940s in the treatment of chronic debilitating illnesses, trauma, burns, surgery, and radiation therapy (1–4). The effects on hematological parameters were recognized as early as 1942, and before bone marrow transplantation and the use of synthetic erythropoietin became common, AAS were often used to treat various types of anemias (5). Norethandrolone and methandrostenolone [Dianabol (discontinued in 1993); CIBA, New Jersey] also became available on the market during the 1950s. The psychoactive effects of AAS broadened its use to treat depression and melancholia.

Recent studies demonstrating positive effects of AAS on body composition have prompted further research in their use in treating the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS)-associated wasting syndrome. Since 1995, the use of AAS is estimated to have increased 400%, mostly attributable to treatment of AIDS-associated wasting. However, cachexia is prevalent in a wide spectrum of chronic diseases, including chronic renal failure, hepatic cirrhosis, cancer, and pulmonary disease. Although increased caloric intake and an exercise regimen are of paramount importance in the maintenance of body weight, treatment with anabolic agents may enhance the effects of these measures.

AAS therapy does have several clinical uses other than androgen replacement. These compounds are used in the treatment of short stature (as in Turner's syndrome or constitutionally delayed growth and puberty), breast cancer (as an anti-estrogen), and the treatment of hereditary angioedema. These applications are not discussed in this review. Instead, we focus primarily on the anabolic properties of these agents in patients with debilitating conditions.

Abbreviations: AAS, Androgenic anabolic steroids; AIDS, acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease; HDL, high density lipoprotein; HIV, human immunodeficiency virus; LBM, lean body mass.

AAS chemistry

Synthesis. T is a steroid hormone synthesized primarily in the Leydig cells of the testes in men; however, it is also present in women, in whom it is synthesized in the ovaries and adrenal glands. Its synthesis is stimulated by the action of LH, which in men, targets testicular Leydig cells resulting in an increase in cAMP production. This, in turn, enhances the activity of the enzymes needed for T synthesis and increases the availability of their primary substrate, cholesterol. This is followed by a cascade of enzymatic reactions that yields T as the final product.

Healthy adult men produce between 2.5–11 mg T/d, with plasma concentrations ranging between 300-1000 ng/dl (1). About 44% of the secreted T is bound to SHBG, whereas about 2% is in free form. The remaining T (54%) is known as bioavailable T, which is loosely bound to albumin and can dissociate within capillary beds (2). In target tissues such as the prostate, seminal vesicles, and pubic skin, T is irreversibly converted to DHT by 5α-reductase. DHT has a relatively higher receptor binding affinity of 0.46 compared with 0.23 of T (3). Estimates of the relative potency of DHT to T have ranged from 2:1 to 10:1. Likewise, the dissociation constant for DHT is 0.25–0.50 nM, while the K_d of T is 0.4–1.0 nM, indicating that DHT is a much stronger androgen.

In women, T is secreted by the ovaries and adrenal glands. About 50% of the secreted T (0.25 mg/d) is synthesized extraglandularly, where androstenedione produced by the adrenals is converted to T. Plasma concentrations range from 15–65 ng/dl. The majority of T produced in women is converted to E2 in adipocytes by the enzyme aromatase.

Classification. Since T in its native form is rapidly absorbed and degraded regardless of the route used, the use of modified analogs has become a favored method of androgen administration. There are three main classes of androgen analogs. Class A is made up of those analogs produced via esterification of the 17β-hydroxyl group with any of the several carboxylic acid groups. Longer carbon chains in these groups yield androgen derivatives that are more soluble in lipid vehicles, such as those used for im injection. T, when injected as a solution in oil, is rapidly absorbed, metabolized, and excreted. T esters are less polar and are absorbed slowly when injected im in oil. Different esters have variable durations of action, and therefore the frequency of T administration depends on the type of ester being used. T propionate is given two or three times weekly, T cypionate and enanthate are effective when given at 2- to 4-wk intervals, and T buciclate can be administered at 12-wk intervals (6). Class B analogs are those that have been alkylated at the 17α position, such as methyltestosterone. Class C analogs are those that are produced via modification of the A, B, or C rings, such as mesterolone. These analogs often exist in conjunction with those of class A as AC analogs (Table 1). As alkylated analogs and those with a modified ring structure are not metabolized by the liver as quickly as T and its 17β-esterified derivatives, therefore, class B and C analogs are available for oral use (4).

Metabolism. T is inactivated primarily by the cytochrome P450 family of hepatic isoenzymes. Therapeutic preparations of T have been developed to circumvent this immediate metabolism. Class A derivatives have long alkyl side-chains, rendering them less polar than T and hence retarding their hepatic metabolism and increasing their half-life in the peripheral tissues. They are, however, eventually hydrolyzed and metabolized by the same pathway as endogenous T. The modification in the class B and C derivatives alters their metabolic pathway, yielding a longer half-life. They are variably excreted either unaltered or as metabolites and conjugates in the urine or feces (5).

Is there a pure anabolic or androgenic agent?

For decades researchers have known the anabolic potential of androgens. This made the use of androgens popular

TABLE 1. T analogs approved in the U.S.

Drug class	Generic name	Trade name	Route	Indications	Dosage
A	T propionate	Testex	im	T replacement	10–25 mg 2–3 ×/wk
	T enanthate	Delatestryl, Everone, Durathate	im	T replacement	50–400 mg every 2–4 wk
	T cypionate	Virilon im, Depotest, Andro-Cyp	im	T replacement	50–400 mg q 2–4 wk
	T patches	Androderm, Testoderm TTS	Top	T replacement	5 mg/day
	T Gel	Androgel	Top	T replacement	5 g/day
AC	Nandrolone decanoate	Deca-Durabolin	im	Renal insufficiency-associated anemia	50–200 mg/wk
	Nandrolone, phenpropionate	Durabolin	im	Renal insufficiency-associated anemia	50–200 mg/wk
B	Methyltestosterone	Testred, Android, Virilon	PO	T replacement; endometriosis	10–50 mg/d 800 mg/d initially
BC	Danazol	Danocrine	PO	HAE	400–600 mg/d initially
	Fluoxymesterone	Halotestin	PO	T replacement	5–20 mg/d
	Methandrostenolone	Methandienone	PO		
	Oxandrolone	Anavar, Oxandrin	PO	Wt loss	5–10 mg/d
	Oxymetholone	Anadrol	PO	Anemia	1–5 mg/kg·d
	Stanozolol	Winstrol	PO	HAE attack prevention	6 mg/d

HAE, Hereditary angioedema; PO, taken orally.

among athletes. However, it was soon noted that these agents along with being anabolic, also result in androgenic side effects such as acne and increased sebum production in men and hirsutism and even virilization in women. For years, scientists have labored to dissociate anabolic from androgenic effects with the hope of producing a purely anabolic agent that is free from any androgenic side effects. Unfortunately, to date no such compound exists.

Androgens are a group of biologically diverse compounds with a variety of effects (anabolic and androgenic) in different body tissues (7). The androgenic effects of AAS include induction of male phenotype starting from sexual differentiation *in utero*, growth of sexual organs (genitals and prostate), development of secondary sexual characteristics, maintenance of sexual function, and fertility. The anabolic effects of AAS include nitrogen retention and increases in muscle mass and strength.

Although androgens mediate a broad range of developmental and homeostatic function, all of the androgens induce their response via a single AR despite this diversity. The receptor is a 120-kDa cytosolic protein encoded on the X chromosome, and to date only one AR cDNA has been identified (8). As there is only one AR, how do AAS mediate these diverse actions? Attempts in the past have failed to isolate a pure anabolic or a pure androgenic receptor (9). One explanation in the case of T is that it is a prohormone, and many of its actions in different tissues are mediated by its metabolites. T is converted by 5α-reductase to DHT (the main androgen in the prostate) and by aromatase to E2. It is known that skeletal muscle is almost devoid of 5α-reductase activity, and therefore T is the major hormone in the skeletal muscle promoting anabolism (9). Furthermore, the relative binding affinity of DHT to AR in muscle is much lower than that to AR in the prostate. On the other hand, prostate tissue is rich in 5α-reductase activity, and almost whatever T enters the prostate is converted to DHT, which maintains its growth along with that of seminal vesicles and vas deferens, hence exerting its androgenic action. These analogs interact with the AR directly. These data show that the conversion of AAS in various tissues into different metabolites and the relative binding affinity of these metabolites to AR in these tissues are responsible for its diverse actions. However, in a recent animal study, Hsiao *et al.* (10) found two different kinds of androgen response elements that could respond differentially to T and DHT. Therefore, it is possible that a selective androgen response element sequence may play a role in differential T *vs.* DHT AR *trans*-activation.

Mechanism of anabolic action of AAS

Many studies have shown that administration of androgens to hypogonadal young and elderly men results in an increase in lean body mass (LBM) (11, 12). However, interestingly, supraphysiological doses of T result in an increase in muscle mass and strength even in eugonadal men (13). The positive response observed in these men (even though the majority of ARs are likely to be saturated) suggests that androgens also mediate anabolic effects indirectly, *i.e.* not via AR. Therefore, one can divide the anabolic actions of AAS into direct and indirect mechanisms.

Direct mechanism

Administration of T to hypogonadal men results in an increase in both contractile and noncontractile skeletal muscle proteins. Increased incorporation of leucine into the skeletal muscle was observed in six hypogonadal men after 6 months of treatment with T cypionate (14). There was a 56% increase in the fractional synthetic rate of mixed muscle proteins from the baseline, including a 46% increase in the synthesis of myosin heavy chain, the main contractile protein (14). All men had an increase in muscle mass from the baseline. Similarly, short-term administration of oxandrolone (a synthetic analog of T) to normal young men resulted in a 44% increase in the fractional synthesis of muscle proteins (15). Furthermore, oxandrolone administration significantly increased mRNA levels of skeletal muscle AR. Similarly, a single injection of 200 mg T enanthate results in increased skeletal muscle protein synthesis and efficient utilization of amino acids (16). In summary, androgens increase muscle mass and strength by increasing efficient utilization of amino acids and, at least in case of oxandrolone, by increasing AR expression in skeletal muscle.

Indirect mechanism

Antiglucocorticoid action. Indirect evidence exists that the anabolic effects of androgens on skeletal muscle may be mediated by the antiglucocorticoid action of androgens. *In vitro* experiments have shown that T has a high affinity for GR (17). The same group has also shown that T acts as an antagonist to endogenous circulating glucocorticoids (18). These observations are appealing because there is a great degree of homology between AR and GR (19). These observations are further supported by the fact that antagonism of glucocorticoids prevents muscle atrophy in men who have undergone orchidectomy (20). Furthermore, administration of large doses of AAS to these men result in an increase in urinary free cortisol (20). Men with androgen insensitivity syndrome also show nitrogen retention when given large doses of AAS despite having nonfunctional ARs (21). Similarly, T administration to patients with severe burns (a state of hypercortisolism and hypogonadism) shows a significant decrease in protein breakdown (22). Although the majority of the reports suggest GR antagonism as the main mode of androgen action, some have proposed that AAS interfere with glucocorticoid action at the gene level by interfering with hormone response elements (23).

Interaction with IGF-I system. Intravenous infusion of IGF-I results in stimulation of skeletal muscle protein synthesis (24). It has been shown that androgens are necessary for the local production of IGF-I within the skeletal muscle regardless of the systemic IGF-I levels and rate of GH production. This is supported by the observation that induction of hypogonadism in normal young men results in a reduction in IGF-I mRNA levels in skeletal muscle (25). Indeed, when hypogonadal elderly men are treated with T, there is an increase in IGF-I mRNA levels in muscle biopsy specimens (26). These reports show that T-IGF-I interaction is also important for the anabolic process.

Regulation of myostatin gene. The effects of AAS at the genetic level are currently poorly understood. Recently, the human myostatin gene was cloned. This gene is located on chromosome 2 and is a negative regulator of muscle growth. Inactivating mutations of this gene in mice and cattle are associated with double muscling in these animals (27). The myostatin protein is secreted into the serum and can be measured in the circulation. In a recent study, myostatin levels were elevated in the serum and skeletal muscle biopsy specimens of patients with AIDS associated sarcopenia compared with those in AIDS patients without any weight loss and normal controls (28). Furthermore, high levels of circulating myostatin have produced muscle atrophy in the rat (29). Preliminary research suggests that the myostatin protein may play a role in age-associated sarcopenia (30). This is further supported by the fact that low gravity-induced muscle wasting accompanies an increase in myostatin mRNA (31). As androgen levels decline with aging, it is possible that myostatin levels may rise as a result of andropause. Therefore, it is possible that androgens may exert their anabolic effects by either directly or indirectly suppressing the expression of myostatin. However, the role of myostatin in humans is not extensively defined, and these hypotheses should be tested by well designed clinical research.

Therapies currently in use for treatment of cachexia

Therapies that are currently available include AAS, megestrol acetate (Megace; Bristol-Myers Squibb, Princeton, NJ), GH, high calorie supplements, parenteral nutrition, and exercise. Therapy with Megace typically results in an increase in fat mass. GH use is associated with high cost and some untoward side effects. For this reason, other methods of treatment are in demand. Table 2 provides a summary of the conditions in which AAS therapy has been tested. These conditions are described below.

AIDS. Cachexia/anorexia resulting from an imbalance between nutritional intake and resting energy expenditure is a common problem in HIV patients. Weight loss of greater than 10% baseline body weight (HIV-associated wasting) is a strong predictor of mortality in HIV-infected men (32). The use of T and its analogs in the treatment of chronic disease-associated catabolism is best studied in HIV/AIDS patients, because a significant proportion of this population has hypogonadism (33). Furthermore, the degree of weight loss in male HIV patients correlates with reductions in circulating T levels (34). This shows that androgen depletion may play a role in HIV-associated wasting.

Androgen replacement therapy for the treatment of HIV-associated wasting has met with varying degrees of success depending on the preparation, route of administration, and dosage used (35). Many studies using im T preparations to treat HIV-associated wasting have been performed to examine its effects on body composition. In an uncontrolled, open label study of T cypionate (400 mg every 2 wk), an average weight gain of 2.3 kg over a period of 12 wk was observed (36). Grinspoon *et al.* (37) have also shown an increase in LBM and muscle mass using 300 mg T cypionate every 3 wk. Bhasin *et al.* (38) recently completed a randomized, double blind, placebo-controlled 16-wk trial of T enanthate (100 mg/wk) and exercise (alone and in combination) compared with placebo in HIV-infected men with hypogonadism (total T, $<$350 ng/dl) and 5% weight loss. T-treated patients experienced a total weight gain of 2.6 kg and an increase in LBM of 2.3 kg. There was also a significant increase in muscle strength. The patients in the exercise-only group also showed an increase in total weight and LBM, whereas the placebo group lost weight. Interestingly, T and exercise in combination did not result in greater gains than either intervention alone. However, one trial with T enanthate did not produce any significant weight gain (39).

Transdermal T patches have also been used in HIV patients. The transscrotal T patch, Testoderm (Alza Corp., Mountain View, CA), at a dose of 5 mg daily did not result in weight gain or increase in LBM in HIV patients (40). On the other hand, Androderm (TheraTech, Inc., Salt Lake City, UT), a nonscrotal T patch, has been shown to increase LBM when applied at the same dose of 5 mg/d (41). It is important to remember that the difference in efficacy between different products could relate to the level of T achieved in the serum. Preparations achieving lower T levels demonstrated less significant benefit. Recently, Miller *et al.* (42) for the first time showed that therapy with T patches in women with HIV results in a significant improvement in weight and overall

TABLE 2. Efficacy of AAS therapy in chronic diseases associated with catabolic states

Condition	Wt gain efficacy	Disease-specific efficacy	Safety comments
HIV	Yes	No	
Pulmonary	Yes	Conflicting[a]	
Liver failure	Yes	Yes[b]	Hepatic dysfunction associated with 17α-alkylated analogs
Postoperative recovery	Yes	Yes	
Burns	Yes	Yes[c]	
Cancer	Not studied[d]	Yes[e]	
Renal failure	Yes	Yes[f]	Sodium retention may exacerbate edema

[a] Studies examining AAS effects on maximal inspiratory pressure (Pmax) have yielded conflicting results.
[b] Oxandrolone treatment in alcoholic hepatitis has yielded significant improvement in liver function.
[c] AAS has beneficial effects in preliminary studies.
[d] The efficacy of AAS therapy for weight gain in cancer patients has not yet been examined in a clinical trial.
[e] AAS therapy has been shown to have positive effects on remission rates in leukemia patients.
[f] In addition to increasing lean body mass in dialysis patients, AAS also improves erythropoietin synthesis.

quality of life compared with placebo. Furthermore, no adverse effects of T patches were seen in women.

Oral preparations of T are seldom used because of rapid metabolism and inactivation in the case of class A analogs, and liver toxicity in the case of class B and C analogs. However, oxandrolone, an orally active T derivative, may be suitable for treatment of HIV-associated wasting. Significant increases in weight and LBM in patients treated with oxandrolone have been demonstrated. In a 4-month randomized, placebo-controlled study of oxandrolone (15 mg/d) in 63 AIDS patients with more than 10% body weight loss, oxandrolone resulted in significant weight gain, increase in appetite, and improvement in physical activity (43). At wk 16, patients taking oxandrolone had an increase of 0.6 kg in mean body weight, whereas the placebo patients lost 1.1 kg. In another study eugonadal HIV patients with weight loss were given T therapy at a dose of 100 mg/wk and randomized to oxandrolone (20 mg/d) or placebo (44). The patients in the oxandrolone group experienced increase in nitrogen retention, LBM, and muscle strength. Similarly, the use of nandrolone decanoate in this patient population also resulted in a significant increase in weight and LBM (45, 46). Oxymetholone is another oral preparation that has been used to treat HIV wasting with positive effects on total body weight (47). At a dose of 50 mg three times a day, oxymethalone resulted in an increase of 8.2 kg over a 30-wk period, whereas the subjects on placebo lost 1.8 kg. There was also a significant improvement in the quality of life variables in subjects taking oxymethalone.

In summary, these studies suggest that T and its analogs, regardless of the route of administration, result in an increase in weight and LBM. However, further studies would be welcomed to determine the exact nature of the relationship between factors such as dosage, route, and preparation used and the resultant changes in body composition in HIV patients, including women.

Pulmonary disorders. As in HIV, weight loss in patients with chronic obstructive pulmonary disease (COPD) is associated with mortality (48). Recent studies indicate a potential use for AAS therapy in COPD-associated wasting. A regimen of exercise, 250 mg im T administration at the baseline visit, and then 12 mg/d oral stanozolol for 27 wk showed significant improvement in weight, body mass index, LBM, and muscle size compared with exercise alone in patients with COPD (49). However, there was no increase in maximum inspiratory pressure or measures of physical endurance. Schols *et al.* (50) studied 217 patients with COPD and randomized them to either nandrolone decanoate plus nutrition and exercise or nutrition and exercise alone for a period of 8 wk. There was a significant increase in fat-free mass and an improvement in maximum inspiratory pressure in the nandrolone group. Similarly, oxandrolone therapy (20 mg/d) in tetraplegic patients produced significant improvement in weight and respiratory parameters (51). Caution is recommended when treating COPD patients with androgens due to the risk of developing polycythemia. Further research in a large number of patients is needed before the use of AAS becomes routine in this patient population.

Liver disease. AAS also have a role in treating patients with hepatitis-related malnutrition. In a study of 271 patients with alcoholic hepatitis, oxandrolone along with a high calorie supplement was compared with placebo and a low calorie supplement. Significant improvement in liver function and overall survival was observed in the oxandrolone and high calorie supplement group (52). Similarly, oxandrolone therapy has been shown to result in a reduction in 6-month mortality in patients with alcoholic hepatitis (53). In a V.A. cooperative study of 273 patients with moderate protein calorie malnutrition secondary to alcoholic hepatitis, 80 mg/d oxandrolone along with an enteral food supplement resulted in improved 6-month survival, decrease in liver injury, and improvement in malnutrition compared with the placebo group (54). However, no significant improvement was observed in patients with severe malnutrition. Although this dose of oxandrolone was very high, especially in a population with established liver disease, no hepatotoxicity was reported in subjects taking oxandrolone. In summary, although the preliminary studies hold promise, the use of AAS in these patients is not considered a standard of care and may be potentially dangerous. Further studies are necessary to fully characterize the effects of AAS, especially 17α-alkylated agents such as oxandrolone, in this patient population.

Wound healing and postoperative recovery. The anabolic effects of T may also have a place in the process of wound healing and surgical recovery. The 17α-alkylated agent stanozolol has been shown *in vitro* to significantly enhance collagen synthesis when applied to human dermal fibroblasts (55). Animals with full thickness wounds when treated with oxandrolone show early closure and increased tensile strength of the wound (56). A positive effect of AAS on wound healing in patients with nonhealing wounds has also been demonstrated (57). In this study patients with weight loss and nonhealing wounds for more than 1 yr who had failed to respond to nutritional supplements showed significant weight gain while taking oxandrolone. As they restored their body weights, there was significant improvement in the rate of wound healing, as measured by wound diameter. Amory *et al.* (58) have recently shown that the positive effects of AAS on muscle strength lead to early mobilization and, hence, alleviates the postoperative debilitation associated with knee replacement surgery. In their placebo-controlled trial of T enanthate (600 mg weekly for 3 wk before surgery), there was a significantly shorter in-patient stay and a higher degree of functional independence in patients receiving T. Although the data on wound healing appear promising, the process of wound healing may be due to general recovery and early mobilization of these patients rather than to direct effects of AAS on the wounds itself. Therefore, until more research is available AAS should not be used on a routine basis to expedite the process of wound healing.

Burns. There is a significant decrease in T levels in patients with severe burn injuries (59). As these patients are catabolic, the anabolic effects of AAS may play an important role in weight gain in these patients. The efficacy of AAS was tested in a prospective randomized study of 13 burn patients, 7 of whom received oxandrolone (10 mg twice daily) along with

a high protein diet, whereas the remaining 6 were treated with diet alone (60). There was no difference in daily caloric intake between the two groups. Patients taking oxandrolone experienced significantly greater increases in average weight gain and physical therapy index than patients treated with diet alone. This efficacy of oxandrolone in burn patients is not age dependent (61). Recently, oxandrolone (20 mg/d) administered during the immediate postburn period to patients with burns covering 40–70% of their body surface area produced a decrease in net weight loss, an increase in nitrogen retention, and a decrease in healing time compared with placebo (62). Furthermore, oxandrolone has an equal anabolic potential as human GH and is, in fact, safer (63). In summary, the use of oxandrolone in this patient population has shown positive results. Therefore, we recommend judicious use of AAS in patients who have major burn injuries and are severely catabolic.

Cancer. Anorexia and weight loss are common occurrences in patients with cancer. Cachexia is a state of increased resting energy expenditure that continues despite decreased host reserves. Furthermore, weight loss in cancer is different from that in starvation. During starvation, the body adapts to use fat as the major source of fuel while conserving protein. In cancer-associated wasting, weight loss ensues due to equal losses of protein and fat. Increased utilization of amino acids for gluconeogenesis is responsible for muscle catabolism (64). The cachexic/anorexic effects of cancer lead to malnutrition and contribute to androgen deficiency (65). Therefore, AAS may have a role to play in the treatment of cancer cachexia. However, only a few controlled trials have been performed to ascertain whether this represents an influence of hormones on nutritional intake or *vice versa*. Preclinical trials with nandrolone decanoate in rats did not support the former hypothesis (66). In 1988, Todd (65) reported that malnutrition and the resulting weight loss in patients with pancreatic cancer are responsible for hypogonadism, rather than hypogonadism being the culprit. In either case, depressed serum T could result in decreased anabolic activity and loss of LBM.

Androgen therapy may also have other benefits in patients with cancer. Patients with cancer are anemic due to either malnutrition or the effect of chronic disease. Androgen therapy results in increases in hemoglobin levels (1–5 g/dl) and red blood cell volume (325–350 ml) (67, 68). Before the availability of recombinant erythropoietin, refractory anemia, especially secondary to bone marrow failure, was treated successfully with androgen therapy (69).

The erythropoietic effects of androgens have been known for many years in patients with leukemia. Clinical studies show that the treatment with stanozolol during the induction phase of chemotherapy results in a positive effect on the duration of remission (70, 71). However, with the advent and wide availability of recombinant erythropoietin, androgen use has become rare. It may be appropriate in certain circumstances, however, when wasting accompanies anemia or when cost is an issue.

Renal failure. Malnutrition and sarcopenia are commonly seen in patients with end-stage renal disease receiving dialysis (72). As parenteral nutrition has proven to be ineffective in improving the nutritional status of these patients, AAS therapy appears to be an exciting alternative. In a recent double blind, placebo-controlled trial, 29 patients were randomized to either placebo or nandrolone decanoate (100 mg/wk, im) for 6 months (73). Serum creatinine and LBM were significantly greater in the nandrolone group. The results of functional tests such as timed walking and stair-climbing also significantly improved in the nandrolone group, whereas they worsened in the placebo group.

In addition to the increase in LBM, patients with chronic renal failure benefit from the stimulation of erythropoiesis resulting from the administration of AAS (74, 75). A recent study of 25 male anemic patients with normal serum iron levels showed an increase in erythropoietin synthesis in 15 patients treated with nandrolone decanoate (200 mg/wk, im) for 6 months (76). Although erythropoietin levels returned to baseline 6 wk after the final dose of nandrolone, the hemoglobin concentration remained in the normal range up until 16 wk after discontinuation of nandrolone. Clinical trials have shown that nandrolone decanoate therapy in combination with recombinant human erythropoietin result in a greater increase in hematocrit compared with erythropoietin alone (77). Based on these positive data, the role of AAS should be further studied in patients with renal failure, especially evaluation of functional status and quality of life.

Safety

At this point little is known about the complications of AAS therapy in patients with cachexia. The safety information that is available is mainly from the use of AAS in athletes. A 1997 survey of 97 body builders using AAS reported various side effects, including testicular atrophy, gynecomastia, hypertension, fluid retention, tendon injuries, nosebleeds, frequent colds, hepatic and renal dysfunction, and sleep irregularities (78). Studies examining these effects are described below in further detail.

Effects on gonads. A reduction in fertility associated with anabolic steroid use results due to gonadotropin suppression, which, in turn, results in azoospermia, abnormalities in sperm motility and morphology, and testicular atrophy (79–81). The reversibility of these effects is variable. Some have suggested that restoration of hormonal balance after discontinuation of AAS use allows testicular function to return to normal (82, 83), whereas other studies have shown the persistence of hormonal abnormalities even after discontinuation of AAS (84, 85).

Muscular-skeletal injury. Despite the apparent positive effects of AAS on bone and muscle strength, alterations in connective tissue structure induced by AAS therapy have been associated with deleterious effects on tendon strength. Evidence suggests that anabolic steroid use leads to dysplasia of collagen fibrils, resulting in a decrease in overall tendon tensile strength (86). The risk of triceps tendon rupture, a relatively uncommon injury, is also increased in association with AAS use (87). Further research focusing on the risk of tendon injury in both athletic and nonathletic populations should be conducted.

Lipoproteins. Fluctuations in lipid profile are often seen in patients receiving AAS therapy. Palatini *et al.* (88) compared

10 body builders using AAS to 14 body builders who did not receive any anabolic agent. At the completion of the study, subjects taking AAS had lower high density lipoprotein (HDL) cholesterol and elevated low density lipoprotein concentrations. Similarly, weekly im administration of nandrolone decanoate (200 mg/wk) to 14 hemodialysis patients resulted in a significant decrease in HDL-2 cholesterol and apolipoprotein A-I levels (89). An increase in the concentrations of apolipoprotein B and triglycerides was also seen. The use of 17β-esterified derivatives have less adverse effects on serum lipids than oral 17α-alkylated analogs (90–92). Interestingly, T has been shown to be less deleterious to the lipid profile compared with other AAS. Thompson *et al.* (93) in their 6-wk cross-over trial of 11 male weight lifters showed that administration of oral stanozolol at a dose of 6 mg/d resulted in a more adverse lipid profile than im injection of supraphysiological dose of T (200 mg/wk). Serum HDL levels decreased by 33% during stanozolol treatment compared with a decline of 9% during T administration. The reason for this difference may be due to an increase in the activity of hepatic triglyceride lipase (the enzyme responsible for HDL catabolism) in response to oral agents (93). In the future, more comparative studies between T and other AAS concerning their effects on lipid profile would be helpful.

Cardiovascular. For more than 6 decades, T has been known to induce hypertension in animals (94). Animal studies have shown that AAS inhibit 11β-hydroxylation of 11-deoxycorticosterone to corticosterone, which results in hypertension in rats (95). Fluid retention may also contribute to hypertension. The human heart expresses the AR and hence is a target organ for androgens (96). Cardiomegaly has been reported in the preclinical studies of AAS (97, 98), and electron microscopy shows disintegration of intercalated discs, mitochondriolysis, myofibrillolysis, and intracellular edema when AAS is given in conjunction with physical training (99). The risk of atherosclerosis may also be increased with AAS use, as shown by an increase in aortic elastin and collagen content with T administration to male rats. A study of male athletes found significantly greater cardiovascular risk factors in AAS users than nonusers (100). Subjects using AAS had a high total cholesterol/HDL ratio, higher low density lipoprotein levels, and lower HDL levels compared with nonusers.

The incidence of cardiovascular morbidity associated with AAS use, however, has been difficult to determine, partially because of the clandestine nature of steroid use in athletes. In patients undergoing therapeutic AAS treatment, there were only 16 reported cases of morbid circulatory events between 1976 and 1993 (101). No clinical study has yet demonstrated a conclusive link between AAS use and fatal cardiovascular events. However, patients with COPD should be followed more carefully, because the use of AAS may aggravate their polycythemia, thus predisposing them to myocardial ischemia and congestive heart failure.

Hepatic. Studies have linked various abnormal liver function tests (elevated plasma alkaline phosphatase, aminotransferases, conjugated bilirubin, and plasma proteins) with the use of AAS (102–104). Jaundice occasionally occurs in patients with a previously normal functioning liver due to a hypersensitivity-type reaction. Cholestatic hepatitis has also been reported with the use of 17α-alkylated agents due to the accumulation of bile in the biliary canalicules without any obstruction in the larger ducts (105). If jaundice occurs, it generally develops after 2–5 months of therapy. In the majority of the patients, elevation in transaminases is transient, with levels normalizing within a few weeks of discontinuation (106). In athletes, particular care should be exercised when interpreting liver function tests, because breakdown of skeletal muscle during intense training can result in elevation of transaminases (107). There has been some concern over the use of AAS in patients with AIDS, as many of these patients have subclinical hepatic disease. As protease inhibitors and oxandrolone are metabolized by cytochrome P450 3A4 enzyme system, combined use of these drugs may result in elevation of the oxandrolone concentration to harmful levels. We recommend further pharmacological study in this regard. Peliosis hepatis has also been reported with the use of AAS (108–111). Lastly, there have also been isolated reports of AAS use resulting in carcinomas of the liver (112–115). An exhaustive review of the literature by the authors failed to show any clear increase in the incidence of liver cancer associated with AAS use, and virtually all clinical studies of AAS-associated hepatoma have been isolated case reports. Furthermore, the majority of these patients were taking these compounds for approximately 1–7 yr. AAS may play a role in the development of hepatocellular hyperplasia and hepatocellular adenoma; however, these effects usually occur in patients taking high doses of AAS or untraditional combinations of 17α-alkylated AAS (116, 117). Although *in vitro* analysis does show some evidence for altered liver function with the use of 17α-alkylated steroids (118), therapeutic doses have not been decisively proven to cause hepatocellular carcinomas. Furthermore, in the isolated cases in which cancers were reported to develop subsequent to the use of AAS, detailed evaluation found them to be hyperplastic lesions that regressed upon withdrawal of the drug. Supporting this observation, a long-term study of patients treated with stanozolol or danazol and followed for 15–47 months did not show any harmful effect on the liver (119).

Psychiatric. The effects of T on human aggression are controversial. Anecdotal evidence supports the claim that anabolic steroid use results in a typical "roid rage" phenomenon, during which athletes experience an increase in aggression and irritability while using AAS. The validity of this assertion is questionable in consideration of the fact that virtually all evidence supporting this behavior is based on either case reports or correlational studies (120). A few well controlled studies have demonstrated an association between AAS use and feelings of aggression, alertness, irritability, anxiety, suspiciousness, and other mood extremes (121–123). However, these results have been contradicted by other studies that found no evidence of aggressive behavior even when supraphysiological doses of T were administered (124). Wang *et al.* (125) recently reported that T administration to hypogonadal men resulted in a significant decrease in anger, sadness, irritability, and nervousness along with an increased sense of well-being, energy, and friendliness.

Additional safety considerations

Traditionally, physicians have been concerned about the effects of T administration on the prostate. However, recent reviews suggest that the incidence of prostate cancer is not increased by T administration (126). Furthermore, there is no clear evidence that androgen administration results in the development of benign prostatic hypertrophy. Recently, Snyder *et al.* (127) completed the longest (3-yr) study of T administration to hypogonadal elderly men. During the study period, there was no significant difference in major prostate events between the T and the placebo groups; however, the androgen group did demonstrate a small increase in prostate-specific antigen levels. Furthermore, there was no difference between the two groups in urinary flow rate, urinary symptom score, or residual postvoid urine volume (127). Although these data suggest that T has a good safety profile, many more studies are required before a firm conclusion can be made. Androgen administration remains an absolute contraindication in patients with a history of prostate cancer.

Clinical applications

In this review we have attempted to make endocrinologists aware of the fact that AAS may have a wide range of use in clinical medicine. Although the basic chemistry of the compounds is well characterized, the absolute safety and efficacy of AAS use under any circumstance other than androgen replacement for male hypogonadism have remained in question. Conventional wisdom has dictated that the use of AAS is not warranted due to possible safety hazards. However, recent clinical studies investigating these issues more thoroughly are beginning to demonstrate a possible usefulness for AAS therapy. Although patient safety remains a primary concern, the devastating cachexic effects of disease states such as HIV/AIDS require specific treatment.

Currently, the AAS therapies used in the U.S. for the treatment of severe weight loss include T esters (200 mg im every 2 wk), oxymetholone (50–150 mg/d), and oxandrolone (20 mg/d). Adequate nutrition must always be the first line of therapy for weight loss. However, AAS may have a role in patients in whom nutrition and standard care have been ineffective. We think that there are sufficient positive data available to recommend AAS for the treatment of cachexia associated with the AIDS wasting syndrome. Although data from patients with burn injury-related cachexia are scant, the available data are positive, and therefore, we recommend judicious use of AAS in patients with major burns who are severely catabolic. We propose further research in exploring the role of AAS in the treatment of wasting due to renal failure, cancer, COPD, and postoperative recovery.

We suggest the following plan for the treatment of patients with cachexia associated with chronic diseases. As many of these chronic disease states are associated with hypogonadism, patients who are found to be hypogonadal should be started on physiological T replacement therapy with either a patch or im injection (until further studies are available, we do not recommend supraphysiological doses of T in these patients). However, if these patients are eugonadal (normal T) despite being catabolic, we do not recommend therapy with AAS at this time. Even though recent evidence suggests that administration of AAS such as oxandrolone to eugonadal men results in an increase in LBM (44), we believe that more research is needed to further evaluate the role of AAS such as nandrolone and oxandrolone in eugonadal catabolic patients.

Because of possible side effects associated with AAS therapy, several precautions should be taken before administrating AAS. The possibility of altered liver function, especially with 17α-alkylated anabolic steroids, warrants serial liver function testing. The androgenic nature of all anabolic steroids necessitates the testing of PSA levels in men before therapy is initiated. Additionally, serum lipids should be checked, as AAS therapy may be detrimental to patients at high risk for cardiovascular complications, especially those with low serum HDL levels.

The goal of AAS therapy, along with appropriate nutrition, would be to increase weight and LBM, which would translate into an improvement in functional status and reductions in mortality. Unfortunately, the number of studies evaluating these outcomes are limited. Moreover, there is a great need to evaluate the role of AAS in women with wasting syndromes. Although at this time we can recommend AAS in a limited number of conditions, further research is needed on the use of AAS in multiple diseases and their impact on quality of life and survival.

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