REVIEW ARTICLE

DRUG THERAPY

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ANDROGENS IN MEN — USES AND ABUSES

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THE female steroid hormones, estrogen and progesterone, are prescribed widely by physicians, and their risks and benefits have been studied extensively. Although androgen preparations have been available for many years, most clinicians are less familiar with these hormones, and their risks and benefits have received less attention. The most common indication for androgen therapy is hypogonadism in men, but other potential uses of androgens are being explored. In addition, androgen abuse has become common among athletes and bodybuilders. It is therefore important that physicians be aware of the physiology, pharmacology, clinical indications, and adverse effects of androgens.

PHYSIOLOGY

The hypothalamus secretes gonadotropin-releasing hormone, which stimulates the pituitary to secrete luteinizing hormone and follicle-stimulating hormone[1,2] (Fig. 1). In men luteinizing hormone stimulates Leydig cells to produce testosterone.[1] Follicle-stimulating hormone acts on Sertoli cells, thereby stimulating spermatogenesis.[2,3] Approximately 7 mg of testosterone is produced daily in men.[4]

Testosterone can act directly on target cells, or it can be converted to dihydrotestosterone by the 5α-reductase enzymes or to estradiol by the aromatase enzyme complex. Both testosterone and dihydrotestosterone bind to the androgen receptor, but dihydrotestosterone has a higher affinity for the receptor and is therefore a more potent androgen.[4] The 5α-reductase enzymes are most abundant in prostate, skin, and reproductive tissues. Two forms have been identified that vary in terms of their distribution in tissues and susceptibility to inhibition.[5] The aromatase enzyme complex is most abundant in adipose tissue, liver, and certain central nervous system nuclei.[6]

Testosterone circulates primarily in bound form, mostly to sex hormone–binding globulin; only 1 to 2 percent is unbound.[7] Testosterone bound to sex hormone–binding globulin is generally not available to tissues.[8] For nearly all clinical purposes, serum testosterone can be measured as total testosterone, which includes the fractions bound to sex hormone–binding globulin and other serum proteins together with testosterone circulating in the unbound state. Alternatively, free (unbound) testosterone can be measured, which may be useful in a few clinical settings (e.g., obesity) in which serum sex hormone–binding globulin concentrations are low, making serum total testosterone concentrations inappropriately low.

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BIOLOGIC EFFECTS

Reproductive Tissues

Androgens stimulate prenatal differentiation and pubertal development of the testes, penis, epididymis, seminal vesicles, and prostate.[6] In adults, androgens are required for the maintenance of these tissues. Testosterone is also necessary for the initiation and maintenance of spermatogenesis.[9,10]

Sexual Function and Behavior

Androgens have a key role in stimulating and maintaining sexual function in men.[11,12] Testosterone replacement in men with hypogonadism induces greater interest in sexual activity and improvement in other aspects of sexual behavior.[13-16] The role of androgens in increasing the frequency and quality of erections is unclear.[11,13-16] Administration of androgens in men with erectile dysfunction but normal gonadal function is usually not beneficial.[17] In normal young men, suppression of serum testosterone concentrations to the range associated with castration reduces sexual desire, sexual fantasies, and spontaneous erections.[12] Several reports suggest that there is a threshold (which varies considerably from person to person) below which sexual function is impaired.[12,18,19]

Studies of nonhuman primates have shown that aggressive behavior is directly correlated with serum testosterone concentrations,[20] but in studies of men, self-assessments of aggressive behavior are not reliably correlated with serum testosterone concentrations.[12,16] Although short-term administration of methyltestosterone may increase hostility, violent feelings, and irritability in normal men,[21] moderately supraphysiologic doses of testosterone enanthate given for several months do not increase aggressive behavior or irritability.[22,23]

Muscle

Androgens increase nitrogen retention, lean body mass, and body weight.[6,24-26] Although some athletes and bodybuilders use androgens solely to increase muscle mass, the nitrogen-retaining (anabolic) properties of androgens cannot be dissociated from their ability to stimulate male phenotypic and secondary sexual characteristics (androgenic properties). In other words, no pure anabolic steroid exists.[24] Testosterone acts through

the androgen receptor to increase the size of muscle cells, with little effect on their number.[6]

Skin and Hair

Sebum production is an androgen-dependent process, and acne is a well-recognized concomitant of puberty. Dihydrotestosterone is believed to be the active hormone in sebaceous glands. Most men with severe acne, however, do not have elevated serum androgen concentrations. Local conversion of precursors may increase androgen concentrations in the skin.[6]

Axillary hair and hair on the lower pubic area respond to low concentrations of androgens, but hair on the face, chest, and upper pubic area requires higher concentrations. Hair follicles can metabolize testosterone to dihydrotestosterone, and temporal balding may be a consequence of dihydrotestosterone production.[6]

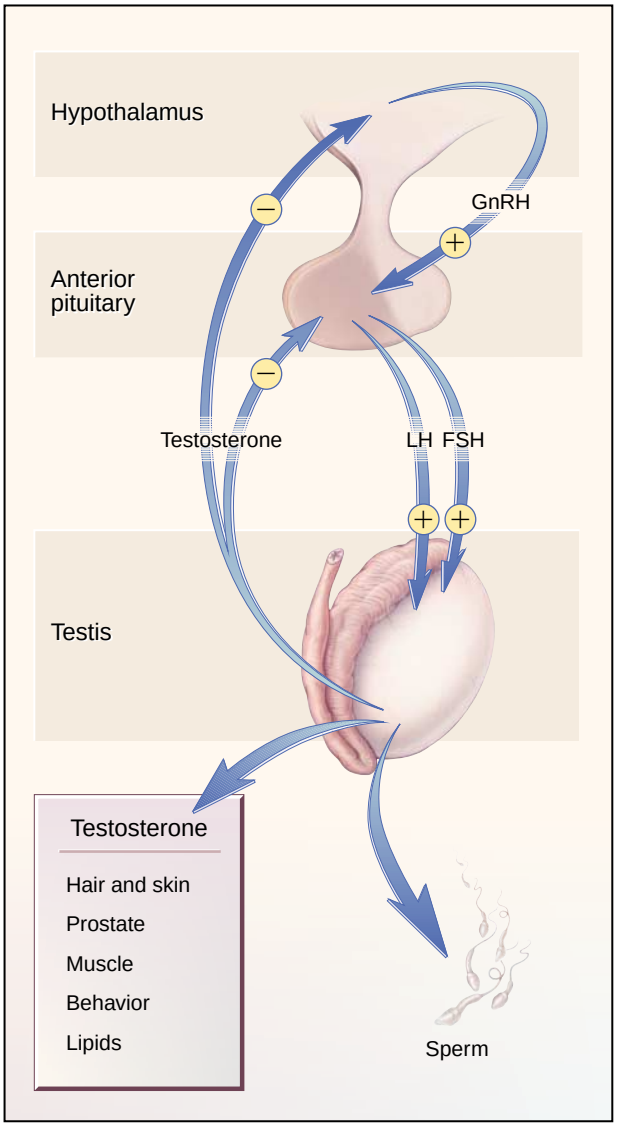


Figure 1. The Hypothalamic–Pituitary–Gonadal Axis in Men. GnRH denotes gonadotropin-releasing hormone, LH luteinizing hormone, and FSH follicle-stimulating hormone. The plus signs indicate stimulatory effects, and the minus signs inhibitory effects.

Liver

Androgens increase the synthesis of clotting factors, hepatic triglyceride lipase, sialic acid, α_1-antitrypsin, and haptoglobin.[27] Conversely, androgens decrease the production of sex hormone–binding globulin, other hormone-binding proteins, transferrin, and fibrinogen.

Lipids

Men generally have lower plasma concentrations of high-density lipoprotein (HDL) cholesterol and higher concentrations of triglyceride, low-density lipoprotein (LDL) cholesterol, and very-low-density lipoprotein cholesterol than do premenopausal women.[28] The administration of androgens decreases plasma HDL cholesterol concentrations in adolescent boys with delayed puberty[29] and in men with hypogonadism.[30] Exogenous androgens, especially those that cannot be metabolized to estrogen (i.e., nonaromatizable androgens), decrease plasma HDL cholesterol concentrations.[22,31-35]

Bone

Bone density increases during puberty in boys, and peak bone mass is achieved in the mid-20s.[36] Bone mass in men declines linearly with age thereafter, and the decrease in trabecular mass is greater than that in cortical mass.[37] Hypogonadism is an important risk factor for osteoporosis in men.[37-39] Androgens stimulate the proliferation of bone cells in vitro.[40,41] Little is known about the amount of androgen required to maintain bone mass in men, however, nor is it known whether the beneficial effect of androgen is due to the androgen itself or to the estrogen produced from it.

Hematologic and Immunologic Effects

Androgens stimulate the production of erythropoietin in the kidneys,[42,43] thereby increasing hemoglobin concentrations,[44,45] which decline when androgen secretion is inhibited.[46] Alkylated androgens (but not testosterone or testosterone esters) stimulate the production of C1 esterase inhibitor.[45]

The incidence of many types of autoimmune disease is higher in women than in men. Women have greater cell-mediated and humoral immunity than men.[47] Men with Klinefelter's syndrome have a higher incidence of autoimmune disease than do men with normal gonadal function, and the symptoms of autoimmune disease may remit when men with Klinefelter's syndrome are treated with testosterone.[48]

Androgen Preparations

Currently Available Preparations

Since it is degraded quickly by the liver,[49] testosterone must be altered chemically to produce clinically useful preparations. Testosterone is commonly esterified at the 17-hydroxy position. The resultant compounds are hydrophobic and are released gradually from oily vehicles. After injection, testosterone is hydro-

lyzed from the ester at the site of injection and is metabolically identical to endogenous testosterone. However, hydrolysis is not constant; serum testosterone concentrations are high for the first few days after an injection but often fall to base-line levels (or lower) before the next injection. The testosterone esters currently available are listed in Figure 2 and Table 1. Because of extensive first-pass hepatic metabolism, esters other than testosterone undecanoate must be injected intramuscularly. It is usually possible to train the patient or a family member to administer the injections.

Testosterone may be alkylated at the 17-hydroxy position, giving rise to androgens that are more resistant to hepatic metabolism (Fig. 2 and Table 1). 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 (see Complications and Side Effects).

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.[50] Some men prefer patches to injections. For the patch to be used successfully, the scrotum must be of adequate size, which may be a problem in some men, particularly those with pubertal hypogonadism. Shaving of the hair on the scrotum is occasionally required for good skin contact.

A patch that can be used on nonscrotal skin has recently become available.[51] 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.[52] This formulation is rarely used in the United States. Testosterone undecanoate, which is available for oral use in several other countries, must be taken more than once daily for an optimal effect.

Experimental Delivery Systems

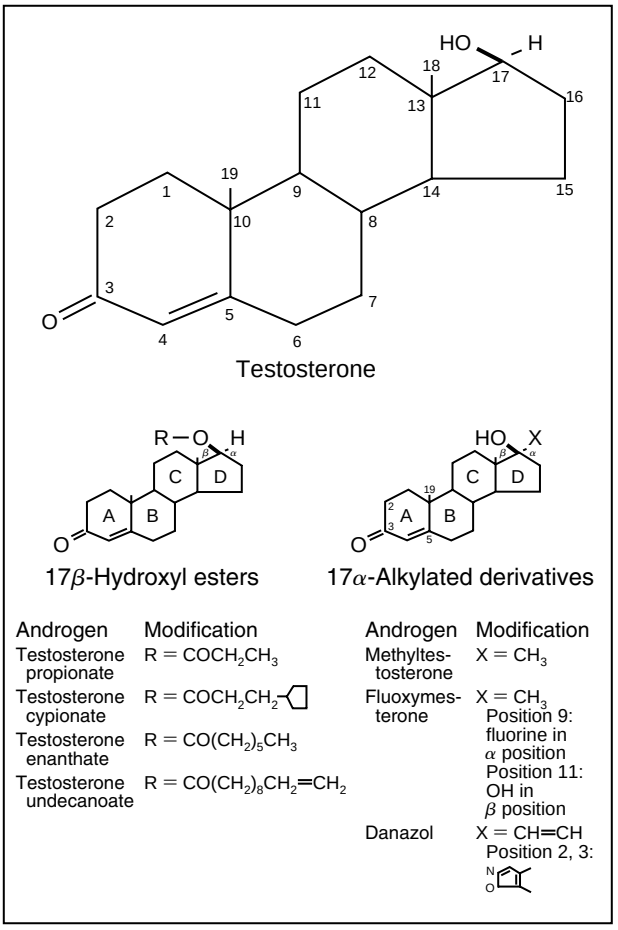
Testosterone buciclate has a duration of action of 12 to 16 weeks and is currently being evaluated in clinical trials. Preliminary studies suggest that the formulation is safe and effective in men with hypogonadism.[53] Injectable, long-acting microcapsules of testosterone are also under investigation.[54]

Clinical Indications

Hypogonadism in Adults

Men with documented testosterone deficiency are candidates for androgen-replacement therapy. It is important, however, to distinguish between primary hypogonadism (low serum testosterone concentrations and elevated serum luteinizing hormone and follicle-stimulating hormone concentrations) and secondary hypogonadism (low serum testosterone concentrations and serum luteinizing hormone and follicle-stimulating hormone concentrations that are low or at the low end of the normal range) before initiating therapy (Table 2). Men with primary hypogonadism are unable to synthesize normal quantities of androgens, and androgen-dependent processes are stimulated and maintained only by exogenous hormone replacement. In these men, fertility cannot be induced by hormonal therapy. In contrast, men with secondary hypogonadism are potentially fertile and can be treated with exogenous androgen to stimulate and maintain androgen-dependent processes. In addition, endogenous androgen secretion and often spermatogenesis can be stimulated by treatment with gonadotropins.

The goals of androgen replacement in men are to induce or maintain secondary sexual characteristics, sexual behavior, muscle development, and male habitus. Because of testosterone's negative feedback on gonadotropin secretion, any persisting spermatogenesis is sup-



Androgen	Modification
Testosterone propionate	R = $COCH_2CH_3$
Testosterone cypionate	R = $COCH_2CH_2$-cyclopentyl
Testosterone enanthate	R = $CO(CH_2)_5CH_3$
Testosterone undecanoate	R = $CO(CH_2)_8CH_2{=}CH_2$

Androgen	Modification
Methyltestosterone	X = CH_3
Fluoxymesterone	X = CH_3 Position 9: fluorine in α position Position 11: OH in β position
Danazol	X = CH=CH Position 2, 3: isoxazole

Figure 2. The Structures of Testosterone and Its Modifications in Clinical Use.

Table 1. Androgen-Replacement Regimens Used in the Treatment of Hypogonadism.

PREPARATION	DOSE
Testosterone enanthate	200 mg given intramuscularly every 10 to 14 days
Testosterone cypionate	200 mg given intramuscularly every 10 to 14 days
Testosterone propionate	25–50 mg given intramuscularly three times a week
Testosterone patches	1 patch (4 or 6 mg) applied daily
Fluoxymesterone	10–20 mg given orally each day
Methyltestosterone	10–40 mg given orally each day

pressed, and men with hypogonadism cannot expect to attain or regain fertility while they are receiving androgens.

Because they are long-acting and do not have toxic effects on the liver, testosterone enanthate and testosterone cypionate (Table 1) are the preparations of choice for the treatment of hypogonadism. A regimen of 200 mg given intramuscularly every 10 to 14 days is frequently used. With this regimen, serum testosterone concentrations are usually supranormal for the first few days after an injection,[55] then decline to the lower end of the normal range before the next injection. In some men these oscillations in serum concentrations cause troublesome fluctuations in behavior or physical functioning. A dose of 100 to 150 mg given every 7 to 10 days may prevent such problems. Elderly men with hypogonadism and symptoms of prostatic hypertrophy or bladder-outlet obstruction should be treated initially with a lower dose — for example, 50 mg of testosterone enanthate or testosterone cypionate every 14 days. Prostatic enlargement or bladder obstruction rarely progresses with this approach.

The patient's clinical status is the best indication of the effectiveness of androgen therapy. Most men notice increased libido, energy, and strength within days to weeks after the start of therapy. Changes in physical appearance usually evolve over a period of six months. Men who have not previously undergone full puberty will have profound physical and psychological changes, and it is important that the men, their families, and their sexual partners receive appropriate counseling about these changes and their effects. In older men, the prostate should be examined carefully before androgen therapy is initiated, as well as during treatment, and they should be questioned about symptoms of obstruction. Serum prostate-specific androgen concentrations should be measured before the start of therapy and after the first three to six months; the concentration may double with androgen-replacement therapy.[56] The same criteria for evaluating serum prostate-specific androgen values in normal men can be used in men receiving long-term replacement therapy with the doses recommended above. There is rarely a need to measure serum testosterone or gonadotropin concentrations repeatedly after androgen replacement has been initiated.

Delayed Puberty

Normal puberty in boys begins before the age of 15 years. Boys who do not have any signs of puberty by this age may have true hypogonadism or a constitutional delay of puberty. Many cases of primary hypogonadism and some cases of secondary hypogonadism can be diagnosed on the basis of the personal or family history, physical examination, growth curve, and laboratory evaluation. In some cases, however, the history, physical examination, and laboratory tests suggest no underlying disorder. Moreover, there are no diagnostic tests that can reliably distinguish secondary hypogonadism from a constitutional delay of puberty. Although a six-month period of watchful waiting may be justified, in most circumstances psychological factors dictate intervention, and a short course of testosterone can be initiated to stimulate pubertal development.

Testosterone esters (50 to 100 mg given intramuscularly every two to four weeks) can be administered for six months in boys suspected of having delayed puberty. Doses in this range do not accelerate bone age inappropriately or interfere with potential adult height, but they do stimulate linear growth and secondary sexual development and may have long-lasting psychological benefits.[57] After six months, the injections should be discontinued, and the patient evaluated three to six months later. In many boys puberty starts spontaneously after treatment has been stopped; the regimen may be repeated, however, if there is no evidence of maturation.

In boys who have physical or laboratory evidence of hypogonadism, long-term androgen replacement is appropriate beginning at the age of 13 or 14 years. A testosterone ester should be administered at a dose of 50 to 100 mg every 2 to 4 weeks for 6 to 12 months. The dose should be gradually increased during the next three to five years until the full adult dose of 200 mg every two weeks has been reached.

Hematologic Disorders

Androgen therapy can be beneficial in patients with aplastic anemia or Fanconi's anemia, although response rates vary considerably.[43] Androgens have also been reported to be beneficial in patients with myelofibrosis, hemolytic anemias, sickle-cell anemia, or idiopathic thrombocytopenia purpura.[43] With the availability of recombinant erythropoietin, androgens are now used infrequently in the treatment of anemia associated with chronic renal failure.

Hereditary Angioedema

Alkylated androgens stimulate the production of C1 esterase inhibitor and can therefore be used prophylactically in the treatment of hereditary angioedema. To minimize the virilizing effects, danazol, a weak androgen, is used in women.[58]

Endometriosis

Danazol inhibits ovulation and estradiol and progesterone secretion; it also has direct antiprogestational effects on the endometrium.[59] Because of these properties, danazol is used in the treatment of endometriosis. Although effective, it cannot be taken indefinitely because of the hypogonadal state it induces, and recurrences are common when it is stopped.[59] In addition,

many women have symptoms of hypoestrogenism or hyperandrogenism,[59] and decreases in serum HDL cholesterol concentrations and increases in serum LDL cholesterol concentrations are common during treatment with danazol.[60,61]

Experimental Uses

Aging

Serum testosterone concentrations decline in men as they age.[62,63] This decline may contribute to decreases in libido, muscle strength, and mass that often occur in aging men. Preliminary studies suggest that androgen replacement in elderly men may restore body weight and lean body mass, increase the hematocrit, and decrease biochemical indexes of bone turnover.[64,65] These results are encouraging, and larger and longer trials are under way.

Male Contraception

Exogenously administered androgens inhibit gonadotropin secretion, secondarily inhibiting spermatogenesis, and are therefore potential contraceptive agents in men, alone or in combination with other agents. Among 157 couples in which sperm counts in the male partners were suppressed to zero by weekly injections of testosterone enanthate, there was only one pregnancy.[66] However, only 50 to 70 percent of white men have azoospermia with this regimen. Whether the suppression of sperm counts to very low levels is sufficient to prevent pregnancy is now being studied. Regimens of testosterone combined with progestagens or gonadotropin-releasing hormone antagonists are also being investigated.[67-70]

Abuse of Androgens

Epidemiology and Patterns of Use

The observation that androgens promote nitrogen retention and muscle mass led to their use to improve physical performance as early as the 1940s, and by the 1950s they were being used by weight lifters.[71] Androgens are now widely used by professional and recreational athletes, weight lifters and bodybuilders, and nonathletes wishing to enhance their appearance. In a recent survey of over 30,000 randomly selected persons, among those over 12 years of age, 0.9 percent of the male respondents and 0.1 percent of the female respondents had taken anabolic steroids at some time.[72] The authors estimated that there are more than 1 million current or former steroid users in the United States and that more than 300,000 persons used these steroids in the year of the survey. In addition, the use of androgens has become popular among adolescents. In another survey,[73] 7 percent of male high-school seniors reported having used anabolic steroids, and the majority of these boys started at or before the age of 16. Clearly, misuse of androgens has become a problem of extensive proportions.

Although the exact compounds and the pattern of administration vary among geographic regions and activities, typical androgen-containing regimens among athletes differ markedly from the regimens used clinically. Whereas the clinical regimens consist of a fixed dose of an androgen compound given at regular intervals on a continuous basis, regimens that are popular among athletes usually consist of several androgens taken intermittently and in progressively higher doses. Androgens may be taken for periods of 4 to 18 weeks at a time, followed by a drug-free period as short as a month or as long as a year.[74] Often, several agents are used at once ("stacking"); they are frequently initiated at low doses, which are progressively increased over a period of several weeks.[75,76] The regimens may include testosterone esters, as well as androgens with very limited clinical indications (e.g., stanozolol and nandrolone) and those approved only for veterinary use.[75] These androgens are almost invariably taken in large doses, up to 100 times the doses used for replacement therapy.[74,76] Because of the increased use of urine testing at athletic events, androgens that are difficult to detect in urine or are metabolized and excreted in a few days (particularly stanozolol and testosterone) have become popular among athletes.[75]

When urine is tested for androgen use, the ratio of testosterone to epitestosterone (an inactive metabolite of testosterone secreted largely from the gonads, with little production from the peripheral metabolism of testosterone) is often measured. The normal ratio is ap-

Table 2. Causes of Hypogonadism.

Primary (hypergonadotropic) hypogonadism
Gonadal defects
Genetic defect
Klinefelter's syndrome
Myotonic dystrophy
Polyglandular autoimmune disease
Other genetic syndromes
Anatomical defect (including castration)
Defect caused by toxins
Drugs (cytotoxins and spironolactone)
Radiation
Alcohol
Viral orchitis (mumps most common)
Hormone resistance
Androgen insensitivity
Luteinizing hormone insensitivity
Secondary (hypogonadotropic) hypogonadism
Organic causes
Panhypopituitarism
Idiopathic
Pituitary or hypothalamic tumor
Miscellaneous
Granulomatous disease
Vasculitis
Hemochromatosis
Infarction
Trauma
Hyperprolactinemia
Isolated gonadotropin deficiency
Kallmann's syndrome and variants
Idiopathic hypothalamic hypogonadism
Isolated deficiency of luteinizing hormone or follicle-stimulating hormone
Genetic disorder
Prader–Willi syndrome
Laurence–Moon–Biedl syndrome
Systemic disorder
Chronic disease
Nutritional deficiency or starvation
Massive obesity
Drugs
Glucocorticoids
Constitutional cause (delayed puberty)

proximately 1:1 in men and women.[77] When exogenous testosterone is administered, however, the testosterone: epitestosterone ratio increases, and a ratio of more than 6:1 is often considered indicative of steroid abuse.[77]

Effects on Strength and Performance

The secrecy that surrounds the use of androgens to enhance performance makes it difficult to investigate their effects on strength and performance in an objective and controlled manner. Many of the published studies are flawed because of small numbers of subjects, lack of control groups, wide variations in the base-line characteristics of the subjects, variations in the training regimens, or differences in the measures used to assess the outcome. Even studies that control for as many variables as possible are hampered by the difficulties of conducting a blinded trial and designing a measure of the outcome that is independent of individual effort.

In a review of this subject, Elashoff et al.[78] concluded that previously trained athletes had a slightly greater increase in muscle strength after a trial of androgens than did previously untrained persons. However, the investigators were unable to draw conclusions about the effects of androgens on performance itself. Because simple steroid regimens were used in the studies analyzed, the conclusions cannot be extrapolated to the complex regimens used by many athletes. These findings are in accordance with the conclusion of the American College of Sports Medicine that in some athletes, the use of androgens can increase the "gains in muscular strength achieved through high-intensity exercise and proper diet" but that androgens do not increase aerobic capacity.[79]

Complications and Side Effects

The undesired effects of androgens depend on both the type and dose administered. In general, replacement doses and the use of testosterone esters are associated with fewer complications than is the use of alkylated androgens, particularly at the high doses of alkylated androgens that are used by many athletes and bodybuilders.

Side Effects during Androgen Replacement

The side effects of androgen replacement are essentially the physiologic androgenic and estrogenic actions of androgens. The accumulation of lean body mass and fluid retention generally cause weight gain. Acne is common in adolescents and young men. Since testosterone can be aromatized to estradiol in peripheral tissues, it occasionally induces mild gynecomastia, most commonly in adolescents. Other than reassurance, no specific intervention is required for gynecomastia in pubertal adolescents or in older men undergoing pubertal maturation for the first time.

Sleep apnea occasionally develops or worsens during androgen-replacement therapy,[80] and erythrocytosis may also occur. Asking about symptoms of sleep apnea and checking the hematocrit annually are appropriate in treating middle-aged and older men. Because all alkylated androgens lower plasma HDL cholesterol concentrations,[31-34] plasma lipid concentrations should be monitored in men receiving these agents as replacement therapy. The importance of the small decrease in plasma HDL cholesterol concentrations associated with testosterone ester replacement is unknown.

Peliosis hepatis (hemorrhagic liver cysts) can occur during treatment with alkylated androgens.[81] This very serious complication appears to be unrelated to the dose or the duration of treatment.[81-83] In some patients the lesions regress when the androgen is discontinued, but in others the disorder progresses to liver failure.[83] For unknown reasons, patients with Fanconi's anemia seem to be at increased risk for hepatic tumors during treatment with alkylated androgens.[83] In contrast, testosterone ester replacement rarely causes these lesions or other hepatic disorders.

Complications and Side Effects of Supraphysiologic Doses of Androgens

Because of the secrecy surrounding the use of high doses of androgens, few data are available on the relation of adverse effects to the doses or compounds used. In addition, whereas some effects are due to androgenic or estrogenic actions, others may be due to the toxic (nonhormonal) effects of the androgen or its metabolite (or metabolites), especially when the dose is very large.

Acne, decreased testicular size, and azoospermia are common in men who take supraphysiologic doses of androgens; these effects may persist for months after the use of the agents has ceased.[74] In women, high doses of androgens can induce changes ranging from acne and hirsutism to amenorrhea and frank virilization.

Alkylated androgens at high doses can cause hepatocellular and intrahepatic cholestasis that occasionally results in severe jaundice and hepatic failure.[81,82] Peliosis hepatis, hepatocellular adenoma, and carcinoma may also result from the use of these compounds.[83]

Supraphysiologic doses of androgens may have adverse effects on the vascular system. Alkylated androgens lower plasma HDL cholesterol concentrations substantially, particularly HDL_2,[31-34] and may increase plasma LDL cholesterol concentrations.[31,32] Low plasma HDL cholesterol concentrations may increase the risk of cardiovascular disease[84]; one weight lifter using androgens, who was 22 years old, had a myocardial infarction,[85] and another, who was 34 years old, had a stroke.[86] In addition, platelet counts and platelet aggregation may be increased in weight lifters taking androgens, especially in men older than 22 years.[87]

The behavioral effects of anabolic–androgenic steroids have received much attention. Increased or decreased libido, increased aggression, and a variety of psychotic symptoms have been described.[88,89] Physical and psychological dependence on these steroids, as well as withdrawal syndromes, has also been reported.[90,91] It is not possible to determine whether these behavioral symptoms result from the types or doses of compounds used or from underlying behavioral disturbances unrelated to steroid abuse.

Conclusions

Androgens are required for normal sexual differentiation, growth and development, and the maintenance

of secondary sexual characteristics in men. Androgen deficiency may have serious consequences in men, and this condition requires diagnosis and appropriate treatment. When administered properly, androgens are safe. When administered inappropriately or abused, however, they may cause considerable harm. These compounds are commonly used in our society, and physicians should be aware of their physiologic effects.

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CORRECTION

Androgens in Men — Uses and Abuses

Androgens in Men — Uses and Abuses . On page 710, in the left-hand column, in lines 9 and 13 from the bottom, the term should have been, ``serum prostate-specific antigen,'' not ``serum prostate-specific androgen,'' as printed.