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Mini Review

Adverse effects of anabolic steroids in athletes A constant threat

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Abstract

Anabolic-androgenic steroids (AAS) are used as ergogenic aids by athletes and non-athletes to enhance performance by augmenting muscular development and strength. AAS administration is often associated with various adverse effects that are generally dose related. High and multi-doses of AAS used for athletic enhancement can lead to serious and irreversible organ damage. Among the most common adverse effects of AAS are some degree of reduced fertility and gynecomastia in males and masculinization in women and children. Other adverse effects include hypertension and atherosclerosis, blood clotting, jaundice, hepatic neoplasms and carcinoma, tendon damage, psychiatric and behavioral disorders. More specifically, this article reviews the reproductive, hepatic, cardiovascular, hematological, cerebrovascular, musculoskeletal, endocrine, renal, immunologic and psychologic effects. Drug-prevention counseling to athletes is highlighted and the use of anabolic steroids is must be avoided, emphasizing that sports goals may be met within the framework of honest competition, free of doping substances.

Keywords: Anabolic-androgenic steroids (AAS); Testosterone; Adverse effects; Athletes; Doping

Contents

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1. Introduction

Since the discovery of testosterone in 1935, numerous derivatives of testosterone have been synthesized and studied in order to prolong the metabolic half-life of the parent molecule and its efficacy. Testosterone has been found to exert its effects; designated as androgenic and anabolic, on both reproductive and non-reproductive target tissues. Androgenic effects are responsible for growth of the male reproductive system and development of secondary sexual characteristics, whereas anabolic effects stimulate nitrogen fixation and increased protein synthesis (Kuhn, 2002).

The potential therapeutic value of testosterone's anabolic activity in various catabolic situations has led to synthesis of many derivatives, more appropriately called, anabolic-androgenic steroids (AAS) with the goals of prolonging the biological activity of the parent molecule in vivo, producing orally active androgens, and developing products that are less androgenic and more anabolic. Although complete dissociation of testosterone's androgenic and anabolic effects have not been achieved, the AAS have shown significant anabolic activity with somewhat reduced androgenicity (Shahidi, 2001).

The anabolic activity of testosterone and its derivatives is primarily manifested in its myotrophic action, which results in greater muscle mass and strength. This, in conjunction to the stimulatory effects of androgens on the brain, which frequently result in a feeling of euphoria and increased aggressiveness, has led to the widespread use of AAS by athletes at all levels, as well as by "recreational" drug users. Such use is not limited to professional and Olympic athletes. Studies focusing on anabolic steroids have shown a continuing and significant increase of use among adolescent athletes and non-athletes alike (Wagner, 1989; Windsor and Dumitru, 1989). In response to the alarming high rate of use of anabolic steroids and the attendant medical risks, policy statements have been published by many medical and athletic organizations as well as by individual scientists (American Academy of Pediatrics, 1997). These statements condemn the use of anabolic steroids but confirm that they enhance strength very definitively (Bhasin et al., 1996a,b). It has become evident that prohibitions against anabolic steroid use and claims that steroids lack efficacy or produce harm have been insufficient to curtail their use (Marshall, 1988; Goldberg et al., 1990). In addition, anabolic steroids have long ago been available on the black market and they are easy to obtain in many gyms or health clubs (Duchaine, 1989).

It is an unfortunate fact that most athletes use more than one steroid at one single time. This state is often referred to as "stacking". The stack or array of drugs often includes at least one oral and one injectable agent. The drugs may be taken at low doses initially, increased gradually, and then tapered. Some of the common orally administered anabolic steroids include oxymetholone, oxandrolone, methandrostenolone and stanozolol. Some of the injectable steroids include nandrolone decanoate, nandrolone phenpropionate,

Table 1
Anabolic steroids generally used by athletes

Oral anabolic steroids (generic name)	Injectable anabolic steroids (generic name)
Oxymetholone[a]	Nandrolone decanoate[b]
Oxandrolone[a]	Nandrolone phenpropionate[b]
Methandrostenolone[a]	Testosterone cypionate[c]
Ethylestrenol[a]	Testosterone enanthate[c]
Stanozolol[a]	Testosterone propionate[c]
Fluoxymesterone[a]	Methenolone enanthate
Norethandrolone	Boldenone undecyclenate
Methenolone acetate	Trenbolone acetate[d]
Mesterolone	Trenbolone[d]
Testosterone undecanoate	Stanozolol

[a] 17-Alpha alkylated steroids.
[b] 19-Nortestosterone esters.
[c] Testosterone esters.
[d] Veterinary steroids.

testosterone cypionate, and boldenone undecylenate (Table 1).

The fact remains that the abuse of androgenic anabolic steroids (AAS) is a remarkably prevalent problem in competitive and non-competitive athletes. The goal of this is to summarize the clinically relevant issues regarding AAS abuse, including prevalence, mechanism of action, efficacy and adverse effects. This information will therefore enable physicians and pharmacists to adequately educate and guide athletes, teenagers, parents, teachers and coaches to stay away from any doping process.

2. Mechanism of action

Studies performed to determine the effects of anabolic steroids on muscle strength and size have been controversial, with approximately half of them finding an increase with steroid use and the other half finding no increase (Johnson, 1990). Differences in study protocols, as well as uncontrolled dosages and number of drugs taken by athletes, who participate in the studies, could explain discrepancies in the results (Haupt and Rovere, 1984). Nevertheless, anabolic steroids seem to be effective in three ways:

1. They convert a negative nitrogen balance to a positive one by improving the use of ingested protein and increasing nitrogen retention. They also have the ability to induce protein synthesis in skeletal muscle cells). Anabolic steroids are believed to exert their effects by binding to androgen receptors at the cellular level, which translocate to binding sites on chromatin, promoting gene transcription, stimulating production of mRNA, and ultimately increasing protein synthesis (Bahrke and Yesalis, 2004). The various clinical effects are determined by the type and concentrations of androgen receptors and enzymes controlling steroid metabolism in a given organ. The structure of androgen receptors appears to be identical in muscle and other organs (Wilson and Griffin, 1980; Snyder, 2001).
2. Steroids compete for glucocorticosteroid receptors, causing an anti-catabolic effect by blocking the glucocorticosteroid effects of depressed protein synthesis during stressful training (Haupt and Rovere, 1984).
3. Athletes often experience a state of euphoria, increased aggressive behavior, and diminished fatigue during steroid use (Wilson and Griffin, 1980). They report that they recover more rapidly from workouts and they can train more frequently and intensively while using the drugs (Haupt and Rovere, 1984). A placebo effect has also been suggested (Ariel and Saville, 1972).

Table 2
Desired effects of anabolic steroids as perceived by sports competitors[a]

Increased muscle mass
Increased strength
Decreased recovery time
Increased aggression
Promote healing of injuries
Maintain same “advantage” as one’s opponent
Obtaining a winning edge

[a] Adapted from Hough (1990).

A summary of the desired effects of anabolic steroids in sports competitors appears in Table 2.

3. Adverse effects of AAS

It is a well known fact that the clinical-therapeutic trials of the main AAS often used by physicians are not free of adverse effects. These adverse effects are dose- and type of steroid-related and include elevated levels of liver enzymes, cholestatic jaundice, peliosis hepatis and various neoplastic lesions. An overview of these effects is outlined in Table 3 (Landry and Primos, 1990). In addition, deep IM injections of AAS may lead to bacterial and fungal abscesses and exuberant local tissue reactions (Shahidi, 2001).

Although many excellent reviews on the adverse effects of anabolic steroids are available, due to the fact that clinical trials are not feasible, much of the information on adverse reactions is anecdotal, or is assumed from known problems associated with therapeutic use of these agents (Lamb, 1984; Yesalis and Bahrke, 1995; Hickson et al., 1989; Sullivan et al., 1999; Mottram and George, 2000; Kuhn, 2002; Kutscher et al., 2002; Parssinen and Seppala, 2002; Juhn, 2003; Bahrke and Yesalis, 2004). Nevertheless, one has to pay attention not to confound these health consequences of AAS with those provoked by other performance enhancing and

Table 3
Possible adverse effects of anabolic steroids[a]

Reproductive
Male
Decreased reproductive hormones
Testicular atrophy
Oligospermia/azoospermia
Impotence
Prostatic hypertrophy
Prostatic carcinoma
Gynecomastia
Priapism
Female
Menstrual irregularities
Clitoral hypertrophy
Uterine atrophy
Breast atrophy
Teratogenicity
Liver
Hepatocellular damage
Cholestasis
Peliosis hepatis
Hepatoadenoma
Hepatocarcinoma
Cardiovascular and hematologic effects
Increased cholesterol
Decreased HDL cholesterol
Hypertension
Thrombosis
Musculoskeletal
Early epiphyseal closure in children
Increased rate of muscle strains/ruptures
Increased risk of musckulotendinous
Endocrine (other than reproductive)
Decreased glucose tolerance
Larynx
Deepening of the voice
Integument
Acne
Alopecia
Hirsutism
Male pattern baldness
Edema
Urinary
Elevated BUN, creatinine
Wilm's tumor
Immunologic and Infectious effects
Decreased IgA levels
Hepatitis B or C; HIV infection
Psychologic
Mood swings
Aggressive behavior
Depression
Psychosis
Addiction
Withdrawal and Dependency Disorders

[a] Adapted from Landry and Primos (1990).

illicit drugs co-administered with AAS (Bahrke and Yesalis, 2004).

3.1. Reproductive effects

Use of steroids in men decreases levels of luteinizing hormone and follicle-stimulating hormones, which leads to decreased endogenous testosterone production, decreased spermatogenesis, and testicular atrophy. The testicular atrophy and the oligospermia or azoospermia usually resolve after discontinuation of the drugs, but the count and morphology of the sperm may be abnormal for up to 6 months (Boyadjiev et al., 2000; Dohle et al., 2003; Eklof et al., 2003). Prostatic hypertrophy, priapism, and, rarely, carcinoma of the prostate can be associated with steroid use (Wemyss-Holden et al., 1994). Gynecomastia may result from the peripheral conversion of androgens to estradiol and estrone. This side effect can be pronounced in persons with liver disease, probably because of decreased hepatic clearance of the parent steroid or estrogenic metabolites. The breast tissue becomes softer and less prominent after steroid use stops. Use of anabolic steroids in women, is not only associated with menstrual abnormalities but with masculinizing effects as well. These effects of AAS in women include hirsutism, acne, deepening of the voice, clitoral hypertrophy, and male-pattern baldness. Some of these androgenic effects may be irreversible (American Academy of Pediatrics, 1997; Elliot and Goldberg, 2000).

3.2. Hepatic effects

Elevations in levels of liver enzymes (aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase) are also common in athletes who use steroids. Nevertheless, these enzymes can often be elevated in weightlifters who are not using steroids (Hough, 1990). Hepatic dysfunction is most commonly associated with the 17-alpha alkylated steroids (Friedl, 2000; Snyder, 2001). Cholestatic jaundice occurs occasionally with steroid use and typically resolves within 3 months of discontinuing the drugs. Liver tumors, both benign and malignant, have been linked to the administration of steroids (Watanabe and Kobayashi, 1993; Soe et al., 1994; Friedl, 2000; Velazquez and Alter, 2004). Several athletes with extensive histories of steroid use have died of hepatocellular carcinoma or of

hepatic tumor rupture. Hepatocellular carcinomas were more often associated with oxymetholone and methyl testosterone (Velazquez and Alter, 2004). There is an increased risk of peliosis hepatis with steroid use. This is a rare form of hepatitis characterized by formation of multiple blood-filled cysts within the liver, which can be fatal (Lamb, 1984; Dourakis and Tolis, 1998; Pavlatos et al., 2001).

3.3. Cardiovascular, cerebrovascular and hematological effects

Anabolic steroids may adversely affect the serum lipid profile, but their long-term effects on the development of coronary artery disease have not been determined. Thrombotic phenomena associated with anabolic steroid use include strokes, myocardial infarctions and limb loss (Ferenchick, 1990; Ferenchick and Adelman, 1992).

A significant decrease in high-density lipoprotein (HDL) cholesterol and, often, an increase in low-density lipoprotein (LDL) cholesterol occur with steroid use, placing the user at increased risk for atherosclerotic heart disease. Cholesterol levels may return or not to normal following cessation of steroid use and normalization depends on the duration of AAS abuse (Cohen et al., 1988; Glazer, 1991; Shahidi, 2001; Hartgens et al., 2004).

Hypertension is associated with anabolic steroid use and myocardial infarction has been reported in several athletes who used steroids for a prolonged period of time (Ferenchick, 1990). These case reports reveal that the actual frequency of myocardial infarction and sudden death among users of AAS is presumably underreported in medical literature and although a causal relationship has not yet been established, a pathogenic effect is plausible (Ferenchick and Adelman, 1992; Rockhold, 1993; Ansell et al., 1993; Halvorsen et al., 2004). Moreover, anabolic use has been related to irreversible changes to myocardium, such as concentric left ventricular hypertrophy (Urhausen et al., 2004).

Anabolic steroids increase red blood cell (RBC) mass, hematocrit and RBC count (Snyder, 2001). Increased fibrinolytic activity and an increase in clotting factors have been associated with the use of specific steroids. Cerebrovascular accidents have been reported in two steroid-using athletes (Mochizuki and Richter, 1988; Kledal et al., 2000; Shahidi, 2001). A case of lethal cerebral oedema has been associated with massive abuse of AAS in a previously healthy 21-year-old man (Kledal et al., 2000).

3.4. Musculoskeletal effects

Of particular concern is the premature epiphyseal closure in any child/adolescent, which results in a decrease in adult height after prolonged exposure to androgens (Al-Ismail et al., 2002). Some scientists believe that there is an increased risk of musculotendious injuries with steroid use. Tendons may not increase in strength as muscles do and, when subject to increased intensity and frequency of training, may be at higher risk for rupture according to a small number of published reports (Shahidi, 2001; Battista et al., 2003). Although experimental data from animal models suggest that steroids alter the biomechanical properties of tendon, ultrastructural analysis of tendons has not shown collagen changes that might predispose to tendon rupture in humans (Evans et al., 1998).

3.5. Endocrine effects

In the prepubertal or pubertal male, prolonged steroid use will result in accelerated maturation with subsequent changes in physique and development of secondary sexual characteristics.

Altered glucose tolerance with increased insulin resistance, as well as, decreases of thyroid hormones have also been reported with anabolic steroid use in male power lifters (Cohen and Hickman, 1987; Shahidi, 2001; Snyder, 2001).

Acne is a common side effect of steroid use and it is a result of the androgenic stimulation of the sebaceous glands. Lesions, most often located on the back and chest, do not always respond to routine acne therapy (Kiraly et al., 1987).

Temporal hair recession and alopecia can be seen in men and women using anabolic steroids for extended lengths of time.

In women using anabolic steroids for a prolonged period of time, masculinization may be manifested as hirsutism, deepening of the voice, and menstrual irregularities that are caused by steroid use, but which may be irreversible once the drugs are discontinued (Bahrke and Yesalis, 2004).

3.6. Renal effects

Weightlifters not using anabolic steroids may experience a rise in serum creatinine as a result of increased skeletal muscle mass. Steroid use may also cause an elevation in serum creatinine, blood urine nitrogen (BUN), and uric acid. These values often return to normal once the drugs are discontinued (Mochizuki and Richter, 1988; Juhn, 2003).

Acute renal failure as a complication of rhabdomyolysis in a body builder using AAS has been reported (Hageloch et al., 1988). The combination of AAS and creatinine supplement that has been currently abused by body builders may cause renal damage. A case of diffuse membranoproliferative glomerulonephritis has been reported (Revai et al., 2003).

Wilm's tumor, uncommon in adults, has been reported in several athletes using anabolic steroids (Joyce, 1991). There is evidence suggesting that steroids are weak carcinogens that can initiate tumor growth or promote such growth in the presence of other carcinogens (Lamb, 1984; Watanabe and Kobayashi, 1993).

3.7. Immunologic and infectious effects

There have been cases of hepatitis B or C and HIV infections reported in bodybuilders who were sharing needles for steroid injections in some cases. Increased risks of infections from improper handling of syringes and needles and from use of impure substances have also been reported (Rogol and Yesalis, 1992; Wu, 1997; Shahidi, 2001).

3.8. Psychologic effects

Some individuals may experience mental status and behavioral changes with anabolic steroid use, including irritability, aggressiveness, euphoria, depression, mood swings, altered libido, and even psychosis (Kashkin and Kleber, 1989; Bahrke et al., 1990; Middleman and DuRant, 1996; Clark and Henderson, 2003).

A recent study of health club athletes revealed that 90% of users reported episodes of over aggressiveness and violent behavior which were believed to be induced by steroids (Tamir et al., 2004), whereas other studies do not support any association between AAS and aggressive behavior (Bhasin et al., 1996a,b; Yates et al., 1999).

Anabolic steroid withdrawal and dependency disorders have also been reported (Foley and Schydlower, 1993; Bahrke, 2000). Acute anabolic steroid withdrawal may produce symptoms of central nonadrenergic hyperactivity including anxiety, irritability, insomnia, hot flashes, sweats, chills, anorexia, myalgia, nausea, vomiting, piloerection, tachycardia, and hypertension. Depression and anabolic steroid craving may also occur with withdrawal. Nevertheless, high risk psychological behaviors may also be the primary problem of those who take anabolic steroids although relative psychiatric disorders may be observed on these users prior to use (Middleman and DuRant, 1996).

Steroids may be psychologically addicting, even meeting the DSM-IV criteria for psychoactive substance dependence in some cases. Electroencephalogram changes similar to those seen with psychostimulant drugs have been reported with steroid use (Frankle et al., 1988). Physical withdrawal symptoms, similar to those seen in opiate withdrawal, have occurred upon cessation of extremely high doses of steroids. Moreover, the developing nervous system of children may be especially vulnerable to the psychological effects of steroids. Adolescents may lack the maturity to cope with possible drug-induced mood changes. In addition, the development of appropriate social skills and controls necessary to deal with pubertal changes may be made difficult if changes occur more rapidly than expected (Snyder, 2001).

There have also been reports stating that there is a relationship between hormone levels (gonadotropins, gonadal steroid hormones, and adrenal androgens) and the emotional dispositions and aggressive behaviors of adolescents. The results indicate that high hormone levels were related to potentially adverse psychological consequences for boys and girls (Clark and Henderson, 2003). Nevertheless, more sophisticated longitudinal studies (probably placebo and training regimen controlled) are required to dissect the role of anabolic-androgenic steroids in behavioral disturbances.

4. Conclusions

Potential anabolic steroid users have been and will continue to be involved in sports where strength and

muscle mass are at a premium. Endurance athletes and non-athletes at any age, seeking to add strength, bulk, muscle definition, or to improve their self-image must also be considered to be at risk.

Anabolic steroid users and potential users should be aware that many of the adverse effects of anabolic steroids might be present without obvious warning signs. Nevertheless, one should present youth with both the risks and the benefits of anabolic steroids use, hoping that this will be more effective in convincing adolescence about steroids negative effects. A more sophisticated approach might be methods that have been used in international programs, such as ATLAS, where participants, apart from being informed on the potential effects of anabolic steroids, they are also informed how strength training and proper nutrition can help them to meet their goals (Landry and Prinos, 1990, Rogol and Yesalis, 1992). In addition, proper weightlifting techniques can be offered by trainers as an alternative to drug use (Goldberg et al., 1996, 2000).

Drug-prevention counseling should be provided preferably at early adolescence which hopefully lead to a healthy alternative to drug use. Most athletes will find a way to meet their sports goals without using anabolic steroids. Athletes may need to be reminded that the health, fitness and social benefits of sports participation can be readily met without use of performance-enhancing substances. For the athlete who is convinced that steroids are essential for success, it may be helpful to point out role models in the sports community whose success did not depend on the use of drugs.

With the appropriate knowledge about the effects and side effects of anabolic steroids, physicians and pharmacists can adequately educate and guide athletes, teenagers, parents, teachers and coaches to stay away from doping and help towards the ultimate goal of the society to accomplish not only totally drug-free athletic competitions, but also a drug-free youth. Physicians and pharmacists play a key role in doping control programs in a number of ways and they have also the obligation when counseling, advising and treating athletes to help them avoid banned substances. Moreover, the challenge of developing a global anti-doping program requires acceptance of doping as a problem by sport organizations, athletes and public authorities. All parties involved in this type of programs must fight for drug free sports, particularly emphasizing the need to keep away from any doping substance or any other methods known in the long run of sports history.

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