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Limits of Anabolic Steroids

Application in Sport and Exercise

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1. Introduction

Androgens are the group of hormones that promotes the development and maintenance of male sex characteristics and are largely responsible for the developmental changes that occur during puberty and adolescence. The most important androgen secreted is testosterone. It is both an active hormone and a prohormone for the formation of a more active androgen, the 5 α -reduced steroid dihydrotestosterone (DHT), which acts in the cell nucleus of target tissues, such as skin, male accessory glands, and the prostate, exerting predominantly androgenic, but also anabolic, effects. [75]. Testosterone is 19-carbon steroid formed from cholesterol via a series of enzymatic reactions in the Leydig cells of the testes and adrenal cortex in men, while in woman the primary site is the adrenal cortex [33]. Testosterone secretion is under the control of luteinizing hormone (LH) which is produced by the pituitary gland. Synthesis and release of LH is under control of the hypothalamus through gonadotropin-releasing hormone (GnRH) and inhibited by testosterone via a negative feedback mechanism [43]. Testosterone basic structure is composed of 3 cyclohexane rings and 1 cyclopentane ring with a methyl group at positions 10 and 13 [67]. Healthy men produce approximately 4.0–9.0 mg of testosterone per day with blood concentrations ranging from 300 to 1,000 ng/dL-1 (10.4–34.7 nmol/L-1), while blood concentrations for females range from 15 to 65 ng/dL-1 (0.5–2.3 nmol/L-1) [43]. Testosterone is carried to target cells through the bloodstream either free (only about 1–3% of circulating testosterone) or bound to a carrier protein. Most of the circulating testosterone (~50–60%) is bound with high affinity to sex hormone-binding globulin (SHBG), while a smaller fraction (40–50%) is bound loosely to albumin [49]. After reaching target cell, testosterone passes the membrane by simple diffusion because of its small molecular weight and lipophilic nature, [8]. Once entering the cell, the effects of testosterone in males and females occur by the way of two main mechanisms: genomic action

by activation of the androgen receptor (directly or as DHT - 5 alpha dihydrotestosterone), and nongenomic action by conversion to estradiol and activation of certain estrogen receptors [19]. In nutshell, the binding of the testosterone to its receptor produces conformational changes that result in the formation of a "transformed" or activated receptor with high affinity for specific DNA-binding site. This consequently recruits co-activators or co-repressors of gene expression [4]. Several non-genomic mechanisms appear to be involved regarding testosterone, including mediation by the membrane-bound sex hormone-binding globulin receptor and also a putative G-protein-coupled receptor that androgens directly bind with, as well as through stimulation of nonreceptor tyrosine kinase c-SRC. In addition, testosterone administration has been shown to rapidly increase intramuscular calcium and extracellular signal-regulated kinase 1/2 (ERK 1/2) phosphorylation, involved in muscle hypertrophy [26]. Testosterone is metabolically inactivated in the liver and excreted in urine thru conjugation reactions, act to couple the anabolic steroid or its metabolite with glucuronic acid or sulfate [65].

Testosterone effects on body tissue are far more complicated than its production and secretion, directly or indirectly through its metabolites influencing the development and function of practically every organ in the body [51, 52]. Its complex biological actions regulates the development of the male phenotype, secondary sexual characteristics that transforms boys into men during embryonic life and at puberty respectively and regulates many physiological processes in the adult male including protein metabolism, sexual and cognitive functions, erythropoiesis, plasma lipids and bone metabolism [11, 74]. In general, testosterone has masculinizing (growth of the male reproductive tract and development of secondary sexual characteristics) and anabolic effects (nitrogen fixation and increased protein synthesis with consequent increase in skeletal muscle mass and strength). Anabolism is defined as any state in which nitrogen is differentially retained in lean body mass through the stimulation of protein synthesis and/or a reduction in protein breakdown [54].

Medical interest in testosterone started in the mid-1930s after the chemical structure was published, and was largely based on its anabolical effect. Shortly after its synthesis, oral and injectable testosterone preparations become available to the medical community [77], with early studies mainly exploring its effects for treating hypogonadism and impotency [43]. However, it has been shown early that testosterone itself is relatively ineffective when taken orally or injected in an aqueous solution because it is susceptible to relatively rapid breakdown by the liver before it can act on the target organ. About 90% of the hormone is already metabolized before it reaches the bloodstream. Testosterone has a short free-circulating half-life due to its rapid metabolism by the cytochrome P450 family of hepatic isoenzymes [3]. In addition, it has a therapeutic index of 1 meaning there is similarity in the proportion between the anabolic and androgenic effects. Consequently, the chemical structure of testosterone has been modified to circumvent this problem. It should be noted, however, that no synthetic steroid has completely eliminated the androgenic effect, which is partly due to the fact that the androgenic and anabolic effects differ only in location and not in the mechanism of the steroid hormone action. Since its discovery, numerous derivatives of testosterone have been synthesized, in order to delay the degradation of steroids, to maintain blood levels of

the drug for prolonged time periods, to intensify the overall effects of the compound while limiting androgenic effects and overpower the catabolic pathways by supplying the drug in mass quantity. Slight biochemical modifications has been proved to alter biological activity by modifying presystemic metabolism, half-life, AR binding affinity, AR stabilization, coactivator recruitment, nuclear translocation, DNA binding affinity, and tissue selectivity. One of the first changes made to the testosterone molecule was the addition of a methyl or ethyl group to the 17-alpha- carbon position (called alkylation), which inhibits the presystemic metabolism of the molecule, substantially extending its half-life and making it active when administered orally [43]. Beyond alkylation, one more major modifications can be distinguished, esterification of testosterone and nortestosterone at the 17-beta- position makes the molecule more soluble in lipid vehicles used for injection and slows the release of the injected steroid into the circulation [6]. Those synthetic compounds, which are similar in chemical structure to testosterone, are collectively called anabolic steroids.

The effect of testosterone and its derivatives on muscle mass gains has not been lost on the medical community. The therapeutic importance of anabolic steroids in treatment of catabolic conditions was recognized as early as in the 1950s, after which an enormous number of steroids were synthesized and tested for potency. For example, metandienone and stanozolol, two of the most frequently used anabolic steroids, were synthesized in 1955 and 1959, respectively [65]. Today, there are more than 100 varieties of anabolic steroids that have been developed, but only a limited number have been approved for human use. The common anabolic steroids are shown in Table 1.

Oral Agents 17- alpha-alkyl derivatives	Injectable Agents 17 beta-ester derivatives
Methandrostenolone (dianabol)	Testosterone esters: blend, cypionate, enanthate, heptylate, propionate
Methyltestosterone (android)	Nandrolone esters: decanoate (deca-durabolin) , phenpropionate
Oxandrolone (anavar)	Boldenone
Oxymetholone (anadrol)	Methenolone
Stanozolol (winstrol)	Trenbolone
Fluoxymesterone (halotestin)	Stanozolol
Danazol	Dromostanolone
Ethylestrenol (maxibolin, oraboline)	

Table 1. Anabolic Steroids in Common Use

As can be seen in Table 1., there are two major classes of AS used, based on the route of administration: Oral and parenteral AS preparations. Oral preparations are synthesized in order to offer protection to the molecule when it becomes exposed to the strong acid solutions

found in the stomach, and when it contacts the enzymic mechanisms of the liver. Protection is conferred by the substitution of a methyl (CH₃) or ethyl (C₂H₅) group for the H attached to the carbon atom (C) on the cyclopentane ring structure, in position 17. The 17 α -alkylated steroids prevent deactivation by the first-pass metabolism by sterically hindering oxidation of the 17 β -hydroxyl group. The effectiveness of 17-alkylated AS is due to a slower hepatic inactivation that occurs with unmodified hormone. Oral activity can also be obtained through attachment of a methyl group at C-1, but these anabolic steroids are considered to be relatively weak in pharmacological activity. Oral preparations are proved to have a short half-life so, in order to maintain the appropriate blood concentration the drug must be taken several times a day. Parenteral preparations do not require a 17 α -alkyl group, but the 17 β -hydroxyl group is esterified with an acid moiety to prevent rapid absorption from the oily vehicle. Once an AS-ester hits the bloodstream, enzymes called esterases rapidly split off the fatty acid. A long fatty acid makes the AS more lipid-soluble and it will disperse from the injected oil depot more slowly (days to weeks). The duration of action of the parenteral steroids depends upon the chain length of the acid moiety and the formulation, with general tendency that the longer the chain length, the more slowly the preparation is released into circulation. Generally, parenteral AS dosing require intramuscular dosing once every 2 to 12 weeks, depending on the carboxylic acid groups added [9].

Pharmaceutical companies initially developed these synthetic analogues of testosterone in order to treat catabolic medical conditions. A number of clinical studies have shown that the potent anabolic effects of anabolic steroids could be used to: restore hormone levels in hypogonadal men, thereby increasing fat-free mass, muscle size and strength, and bone density; improve mood and alleviate depression; increase body weight, muscle mass, and strength in eugonadal patients with secondary wasting syndromes, such as infection with HIV when maintaining lean body mass may be beneficial for long-term survival; and augment muscle mass in older men and prevent age-related sarcopenia that contributes to frailty and falls [28]. The anabolic activity of testosterone derivatives is primarily manifested in its myotrophic action, which results in greater muscle mass and increased strength. This, in addition to the stimulatory effects of androgens on the brain, which frequently result in a feeling of euphoria, increased aggressive behavior, and diminished fatigue, has led to the widespread use of anabolic steroids by both professional and recreational athletes. Athletes use them to enhance performance, driven by the potential financial and other rewards that may come with sporting success. In addition, recreational users of anabolic steroids are the most rapidly growing group, and their aim is to combat ageing and obesity as well as to improve physical appearance in order to receive the admiration that modern society give to a 'perfectly toned' body. However, anabolic steroids have been associated with a range of transient side effects, which can be divided into several categories, including cardiovascular, hepatic, endocrine/reproductive, behavioral, dermatologic, and injection related. Data from larger observational studies suggest that the majority (88%-96%) of anabolic steroid users experience at least 1 minor subjective side effect [14]. Studies on the benefits and risks of testosterone are ongoing, but seem to consistently produce mixed results. As therapeutic use becomes more common, its controversy in the sports world has lead to considerable public outcry against its use. In this chapter we will consider available data on anabolic steroid applica-

tion in sport & exercise with special attention on three distinct aspects of AS usage by professional and recreational athletes: effects on sport performance, adverse effects and legislative considering its usage.

2. Anabolic steroids and sport performance

Soon after the development of synthetic steroids, these drugs were discovered by athletes for their muscle building and performance enhancing properties. According to anecdotal reports, it has been rumored, but never documented, that some German athletes were given testosterone in preparation for the 1936 Berlin Olympics. West Coast bodybuilders began experimenting with testosterone preparations in the late 1940s and early 1950s. It appears that the use of testosterone and its synthetic derivatives began to infiltrate sports during the 1950s, with even government instituted-top secret program implementation that provided for the administration of androgens and other doping products to male and female athletes during later period [43]. In the early 1950s, the first suspicion that anabolic steroids were actually administered in order to improve sporting performance came with allegation that soviet weightlifters were administering AS to gain strength [71]. News of the efficacy of these drugs apparently spread during the early 1960s to other strength-intensive sports, from the throwing events of track and field to football. Throughout the 1960s, the use of anabolic steroids increased so dramatically that In 1969 John Hendershott, the editor of Track & Field News, called these drugs the "breakfast of champions" [40]. Although the International Olympic Committee banned use of anabolic agents in 1964, the practice spread and probably reached its pinnacle in the athletic programs in Germany during the 1970s [78]. Their use nowadays is most common among weight lifters and heavy throwers, nevertheless almost all types of athletes whose event requires explosive strength, including football players, swimmers and track and field athletes, have been known to use steroids. The level of steroid use appears to have increased significantly over the past three decades [46], and is no longer limited to elite athletes or to men. Although competitive athletes report higher rates of steroid use, a significant number of recreational athletes and non-athletes appear to be using these drugs, probably to "improve" their appearance.

The effects of testosterone and its derivatives on human performance have been extensively studied. As early as 1889, Brown-Sequard, reported increases in muscular strength, mental abilities, and appetite as a consequence of self-injections of testicular extracts from guinea pigs and dogs [22]. Largely based on this work, two of the Austrian physiologist Oskar Zoth and Fritz Pregl began to investigate the effects of injections of testicular extracts on muscle strength and athletic performance [42]. Zoth and Pregl injected themselves with extracts from bull testicles and reported increased strength of their middle fingers. Although it is likely that these results were placebo effects, Zoth may be the first person to suggest injecting steroids in an attempt to increase performance [41].

Since the 1960s many researchers have investigated performance-enhancing effects of anabolic steroid administration in professional and recreational athletes. The strength gains and

other purported performance-enhancing benefits commonly attributed to anabolic steroid use in professional and recreational athletes were challenged and often discounted by early medical studies. Upon further examination of initial studies it became apparent that most of them had major flaws in design, such as lack of control groups and a double-blind procedure, the presence of confounding factors (e.g., differences in level of exercise and in motivation), and inappropriate statistical techniques [12, 34]. In addition, most of them have used steroid doses 5–20 times lower than those used by many athletes. As it has been proved that anabolic steroid administration increases lean body mass, muscle mass, and maximal voluntary strength in a concentration-dependent manner [13], it is no surprise that early investigations were usually unable to determine any substantial effect of AS administration on human performance.

Considerable amount of research investigating ergogenic effects of anabolic steroid administration were conducted before and during 1980s, with conflicting findings presented. Several studies did not report ergogenic effects of anabolic steroids on muscle strength or performance. Fowler and coworkers [31] examined the intake of 20 mg/day for 16 weeks of methyl androstenediol acetate to 47 men (10 rugby players and 37 untrained students) who either did not exercise or exercised 30 min/day, 5 days a week and reported no significant difference between groups in muscle size, body weight, or isometric strength. Weiss and Muller [72] examined the intake of 10 mg of Metandienone for 17 days in 32 high school students and did not report any enhancement of strength measured during arm extension. Casner and coworkers [18] examined the intake of 6 mg/day of Stanozolol in 27 young men conducting the weight training 3 d/wk and reported no ergogenic effects of anabolic steroid on leg, arm and trunk isometric strength. Golding and coworkers [35] administered 10 mg/day of Metandienone in three consecutive 4-week cycles interspersed with 1 week of no administration in 40 experienced weightlifters and reported no significant improvements in strength parameters. Stromme and coworkers [67] examined the intake 75 mg/day of mesterolone for 4 weeks and 150 mg/day for the subsequent 4-week period in 21 students engaged in weight training sessions and reported that anabolic steroids did not enhance strength parameters measured during different flexion and extension exercises. Crist and coworkers [21] administered 100 mg/week of testosterone cypionate or placebo (3 weeks each) and reported no significant difference was observed in several isokinetic flexion/extension exercises between anabolic steroid and placebo conditions. Loughton and Ruhling [55] examined the intake of 10 mg/day of Metandienone for 3 weeks and 5 mg/day for 3 more weeks concomitant with weight training and running program and reported greater weight gains in the androgen group but nonsignificant interactions in strength performance.

Considerable amount of research during this period did report significant ergogenic effects of anabolic steroid administration in professional or recreational athletes. Johnson and O'Shea [45] examined administration of 10 mg/day of Metandienone during the last 3 weeks of 6 week training programme to half of the 24 subjects. They reported significantly greater gains in isometric strength and 1 repetition maximum (1RM) squat in the steroid group. Next year, O'Shea and Winkler [60] reported enhanced muscle strength after 6 weeks of strength training with concomitant use of 10mg/day of Oxandrolone in well-trained

weightlifters. Finally, O'Shea [61] administered 10 mg/day of Dianabol for 4 weeks to half of the sample consisted of 18 weightlifters and reported significantly higher increase in squat and bench press strength in the steroid group. Several other authors reported similar results obtained on the sample of professional or recreational athletes administering Metandienone in the same quantity as O'Shea in previously mentioned study with a similar duration of studies [15, 44, 12]. Moreover, although most research has focused on absolute strength determined by one repetition maximum or isokinetic strength, one study tested the effects of anabolic steroid use on sport performance. Rademacher and coworkers [64] reported that in male canoeists, 6 weeks of Oral-Turinabol administration improved strength and performance measured by canoe ergometry with 6% and 9%, respectively.

Although study designs improved during 1970s and 1980s and in some cases were more realistic than previously, it could be speculated that the first rigorous study of the performance-enhancing effects of anabolic steroids was not carried out until 1996. In this seminal study by Bhasin and coworkers [11] supraphysiological dosages of anabolic steroid (testosterone enanthate- 600mg/week) were administered to forty eugonadal men between 19 and 40 years old (within 15% of their ideal body weight) who were or were not engaged in strength training programme. Subjects sample was randomly assigned to one of four groups: placebo but no exercise; testosterone but no exercise; placebo plus exercise; testosterone plus exercise. The subjects who were administered both anabolic steroid and strength training were found to gained significantly greater muscle mass (+6 kg), fat free mass (6,1 kg), quadriceps and biceps area (+1174 mm² and +501mm², respectively) as well as 1-RM bench and press squats (+22kg and +38 kg, respectively) when compared to other groups. Moreover, injectable steroid has been shown to improve strength even without a concomitant resistance-training programme! The investigation suggests that supraphysiological doses of anabolic steroids stimulate significant alterations in muscle size and muscle strength, especially when taken in conjunction with a progressive resistance training programme. Several other studies during and after this period further examined anabolic steroid use in professional or recreational athletes, with continuous reports that anabolic steroid users had greater mass than nonusers and that longitudinally anabolic steroids increased lean body mass, muscle strength and performance. Subsequent work showed that increases in fat-free mass, muscle size, and strength are highly dose-dependent and correlated with serum testosterone concentrations [12, 76] It has been shown that improvements in body physique were greatest at higher doses, for example, at least 125 mg/week¹ [43]. It appears that the most common benefit of anabolic steroid use is an increase in muscle mass and/or strength. It also appears that this effect may demonstrate a dose-response relationship, i.e. the more anabolic steroid used, the greater the effect on muscle mass and strength [13]. However, higher dosages are correlated with higher incidence of adverse effects of anabolic steroid use in humans, which we will discuss further in the next section.

Information on doses and modes of administration of AS used by athletes to increase their performance is relatively sparse. It is known that steroid regimens favored by professional and recreational athletes differ markedly from those used clinically. Athletes use suprapharmacological doses that range from 10–100-fold above normal levels [75]. Steroids are usually

used in the off-season, when athletes are strength trained and when use is least likely to be detected. Typically, they take androgens in cycles of 4-12 weeks, with a period of abstinence, known as a “drug-free holiday” period of varying duration. The purpose for the holiday is to minimize side effects, promote recuperation of various hormonal systems, and avoid detection during competition. Although the length of each cycle is quite variable (ranges from 1 to 728 weeks), the median cycle length is reported to be 11 weeks [43]. After this period, athletes often reported a plateau in subjective benefits, which might be explained by steroid receptor saturation and downregulation. In addition, most athletes use “stacking” regimens that involve taking multiple agents simultaneously, and/or a pyramid doses in cycles of 6 to 12 weeks. At the beginning of a cycle, one starts with low doses of the drugs being stacked and then slowly increases the doses. In the second half of the cycle, the doses are slowly decreased to zero. Athletes tend to use both oral and parenteral (injectable) compounds, with typical regimen of 3 agents being reported [43].

3. Adverse effects of anabolic steroids

For clinical purposes, the administration of anabolic steroids can be of therapeutic benefit and reasonably safe. By contrast, for the purposes of enhancing performance in sport or for cosmetic purposes, usually because it is a clandestine activity, the athletes and bodybuilders are making subjective decisions regarding the effect these steroids are having on their health. The incidence of complications associated with the nonmedical use of anabolic steroids as performance-enhancing drugs is unclear because the denominator of drug use in athletes is not well defined. Data from larger observational studies [27] suggest that the majority (88%-96%) of anabolic steroid users experience at least 1 subjective side effect. Since anabolic steroids have effects on several organ systems, a myriad of side effects can be found. Consequently, the undesirable effects arising from anabolic steroid administration have been extensively studied and reviewed [37, 66, 50]. However, it should be recognized that giving super high doses of anabolic steroids to induce side effects for ethical reasons cannot be studied in laboratory settings, with data defining cumulative effects caused by stacking remains speculative and derived from case reports and medical literature from lower level doses. Nevertheless, summarising the literature, it can be concluded that the potential adverse effects of anabolic steroid use can be divided into several categories, including cardiovascular, hepatic, endocrine/reproductive, psychological, musculoskeletal and dermatologic related.

In both the medical and lay literature one of the principal adverse effects generally associated with anabolic steroid use is the increased risk for myocardial infarction. Several case reports document myocardial infarction and stroke in 20- to 30-year-old weightlifters that used anabolic steroids, which can be attributed to the increased platelet count and platelet aggregation that occurs in people who abuse anabolic steroids [30]. Steroids also cause hypertrophy of the myocardium, which also increases the likelihood of arrhythmias, sudden death, systolic and diastolic hypertension [44]. Anabolic steroid abuse cause harmful changes in lipoprotein profile with increased LDL levels (by 40-50%) and decreased HDL

level (40-70%). The decline in HDL are most evident with the use of oral administration anabolic steroids with drugs such as stanozolol, oxymetholone and metandienone and can often be seen in a few days after the initiation of anabolic steroid use [70]. High doses of AS may increase the risk of atherosclerosis and thrombosis through their effects on clotting factors and platelets and induce vasospasm or myocardial injury because of effects on myocardial cells [56]. Finally, high dose AS use is found to induce systemic hypertension, with magnitude and incidence of hypertension likely related to dosage and to the type of AS used [17]

Cardiovascular	Myocardial infarction; Myocardium hypertrophy; Increased LDL and decreased HDL levels; Thrombosis; Elevated blood pressure
Hepatic	Increased risk of liver tumors and liver damage
Endocrine/reproductive	Male: Testicular atrophy; Oligospermia; Gynecomastia; Prostatic hypertrophy Female: Alterations of pubic hair growth, Clitoral hypertrophy, Menstrual irregularities; Breast atrophy
Psychological	Mood swings; Aggressive behavior; Depression; Psychosis
Musculoskeletal	Increased risk of musculotendinous injuries
Dermatological	Acne; Alopecia

Table 2. Adverse effects of anabolic steroid use.

Liver function disturbances and diseases in AS-abusing athletes have been of great concern since animal studies have clearly shown the deleterious effects of AS on the liver. In addition, liver cancer occurrence in non-athletic populations being treated with testosterone for aplastic anemia has been reported [58]. Elevations in levels of liver enzymes (aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase) are regularly reported in athletes who use steroids. Several case reports have associated the occurrence of liver disorders such as subcellular changes of hepatocytes, impaired excretion function, cholestasis, peliosis hepatis and hepatocellular hyperplasia, and carcinomas in with the abuse of AS in young, healthy athletes. Hepatic dysfunction is most commonly associated with the 17-alpha alkylated steroids, with no cysts or tumors have been reported in athletes using 17β-alkylated steroids. Thus, evidence appears to indicate that the risk for hepatic disease from anabolic steroid use may not be as high as the medical community had originally thought although a risk does exist especially with oral anabolic steroid use or abuse.

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 usually resolve after discontinuation of the drugs, but the count and morphology of the sperm may be abnormal for up to 6 months [23]. Prostatic hypertrophy, priapism, and, rarely, carcinoma of the prostate can be associated with steroid use [72]. When AS levels are elevated, they undergo aromatization, being converted to estrogens and consequently can produce (i)reversible gynecomastia. Use of anabolic steroids in women, is not only associated with menstrual

abnormalities but with masculinizing effects as well. Female athletes reported the development of acne vulgaris, changes in libido and alterations of the voice as the most pronounced acute effects, with long-term AS administration proved to induce loss of hair, alterations of pubic hair growth, clitoral hypertrophy, menstrual irregularities and a reduction of the breasts [43].

Historically, low doses of AS have been used to treat depression and melancholia either as monotherapy or as adjunct to standard treatment, but misuse of these agents has added a new term to the drug lexicon "roids rage" Anecdotal reports of "roid rage," have attracted a great deal of attention in scientific community. Pope and Katz [63] noted that anabolic steroids produce clear psychiatric effects, particularly in individuals using excessive doses (more than 1,000 mg/wk) of these compounds and stacking the drugs. Some individuals may experience mental status and behavioral changes with anabolic steroid use including irritability, aggressivity, euphoria, grandiose beliefs, hyperactivity, and reckless or dangerous behavior [20]. Other presentations have included the development of acute psychoses, exacerbation of tics, and the development of acute confusional states [38]. Kouri and coworkers [53] reported that administration of supraphysiological doses (600 mg weekly) of testosterone enanthate to healthy young men was associated with a significant increase in aggressive responses than placebo administration. A high proportion of women athletes using high doses of androgens report symptoms of hypomania and depression, rigid dietary practices, and dissatisfaction and preoccupation with their physique [36].

Some scientists believe that there is an increased risk of musculotendinous injuries with steroid use in humans. It has been speculated that 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 [7, 66]. However, although the studies in mice and rats have suggested that anabolic steroids may lead to degeneration of collagen and/or decrease in collagen synthesis [48, 57], the response in humans has been less clear. Ultrastructural analysis on ruptured tendons from anabolic steroid users have shown that anabolic steroids did not induce any ultrastructural collagen changes that would increase the risk of tendon ruptures [29].

Acne is one of the more common side effects associated with anabolic steroid administration, and it is a result of the androgenic stimulation of the sebaceous glands. One study reported that 43% of users experienced acne as a consequence from androgen use [62]. They appear to disappear upon cessation of anabolic steroids administration. Finally, temporal hair recession and alopecia can be seen in men and women using anabolic steroids for extended periods of time.

Summarising the literature, it can be concluded that anabolic steroid users and potential users should be aware that many of the adverse effects of anabolic steroids are present and may exert profound effects on their health. More so, studies have been able to link anabolic steroids to many of the serious adverse effects listed. It would seem logical that the axiom, particularly among professional and recreational athletes who can use excessively large amounts of steroids, that the 'more you take, the more you grow' should be accompanied with 'the more you may damage your health'.

4. Anabolic steroids and doping regulations

The use of substances to enhance performance in sports is a long standing phenomenon. In 1928, the International Amateur Athletics Federation (IAAF), became the first International Sport Federation to ban the use of stimulating substances. Many other federations followed suit, but restrictions remained ineffective because no tests were made. Meanwhile the problem was made worse by synthetic substances developed in the 1930s and in growing use for doping purposes by the 1950s. The death of a Danish cyclist at the 1960 Olympic Games in Rome put pressure on sports authorities to work more aggressively to deter doping following the confirmation of amphetamine in biologic fluids collected at autopsy on this athlete [32]. The death of cyclist Tom Simpson, during the Tour de France, following the use of amphetamines, further catalysed the situation and in 1966, the first doping tests were introduced for international cycling and football. With the increasing use of performance-enhancing drugs and several high-profile deaths of athletes from various sports, the International Olympic Committee (IOC) established a medical commission in 1967 with its primary goal to create a list of prohibited substances and methods [32]. The initial goal of putting in place an antidoping structure was rapidly widened to encompass the following three fundamental principles: (1) protection of the health of athletes, (2) respect for both medical and sports ethics, and (3) equality for all competing athletes. In the same year, the International Olympic Committee drew up its first list of prohibited substances, and drug tests were first introduced at the 1968 Olympic Games in Mexico. At that time, many sports governing bodies such as UCI (cycling) and FIFA (football) based in Europe established rules regarding the use of drugs in sports.

At the 1988 Olympic games in Seoul, Canadian sprinter and then current world's fastest man Ben Johnson tested positive for stanozolol [16]. This positive test sent shock waves through the sporting community, resulting in the U.S. government passing the Anti-Drug Abuse Act, which made it illegal to distribute or possess androgens. Additionally, the IOC expanded the banned substance list to include diuretics, such as probenecid, and other products typically used to mask androgens use. In 1990, the U.S. government went a step farther when it passed the first Anabolic Steroid Control Act and inserted 27 steroids, along with their muscle building salts, esters, and isomers as class III drugs and simple possession could result in prison time [43]. Today, under the US Federal Controlled Substances Act, anabolic steroids are classified as Schedule III substances, which places them in the same category as amphetamines, methamphetamines, opium and morphine. Possession of any Schedule I substance is a felony offense with punishment up to five years in prison. If one sells steroids, or possesses enough to evidence an intent to sell, he/she faces up to five years in prison and a \$250,000 fine.

During a raid at 1988 Tour de France, police found a large number of prohibited medical substances. This highly publicized scandal highlighted the need for an independent international agency that would establish unified standards for antidoping work and coordinate the efforts of sports organizations and public authorities. The IOC took the initiative and convened the World Conference on Doping in Sport held in Lausanne, Switzerland in Feb-

ruary 1999. Following the proposal of the Conference, the World Anti-Doping Agency (WADA) was established on November 10, 1999.

According to surveys and media reports, the illegal use of AS to increase muscle size and strength is widespread [28]. Current estimates indicate that there are as many as three million AS users in the United States alone and that 2.7–2.9% of young American adults have taken AS at least once in their lives [59]. Interviews of high-school students in several European countries reveal that 1–5% have used AAS [69], with similar figures found for high-school-aged students from Canada, Australia and South Africa [5]. Anabolic steroids are used for performance enhancement across the spectrum of athletes, from the elite to rising young men and women in youth programs and high school. Increasing numbers of athletes are nowadays relying on anabolic steroids to enhance their strength, endurance, and performance, despite the knowledge of the potentially serious adverse consequences these agents can have. According to the WADA statistics, AS are the most frequent adverse analytical findings for Olympic sport athletes, in-and out-of- competition. In 2003, the Worldwide Out-of-Competition Testing Program conducted by the World Anti-Doping Agency detected 23 positive cases among a total of 5004 samples obtained (4229 urine, and 775 blood samples), with three refusals to provide a sample. The prevalence values for AS use among other groups of exercisers and athletes range between 6.2 and 38.4%. However, the reported response rates were at best 66%, rendering these findings highly unreliable [69]. In 2006, the 33 WADA accredited laboratories in 29 countries reported 1 966 (45.4%) of the 4 332 adverse analytical findings were anabolic steroids. It is likely that the AS use among athletes from high school to Olympics caliber is on the rise and gaining momentum, according to individuals closest to the issue [10].

Nowadays, many countries are on the way to strengthening the laws against possession and use of AS and now consider these drugs as equivalent to narcotics. An important concern is the ease with which banned substances can be obtained by athletes and the public. The results of studies by Eriksson [24,25] show the effect of AS on muscle fibres lasts much longer than believed, which suggests that athletes using anabolic agents should be disqualified for longer than 2 years. His histological observations is highly in accordance to an old observation in East Germany that “androgenic initiation” has long-lasting effects. Anabolic steroids are controlled substances and are illegal to possess or sell without a prescription for a legitimate medical condition by the prescribing physician. Androstenedione, norandrostenedione and other similar prohormones, at one time available over the counter as dietary supplements, are now defined as controlled anabolic steroids. Due to serious health risks, non-medical use of anabolic steroids is nowadays banned by most major sports organizations. International Olympic Committee banned the use of anabolic steroids in 1976. In addition, anabolic steroids are on the WADA (World Anti-Doping Agency) prohibited list, the annual publication of all illegal performance-enhancing substances.

Acknowledgments

The chapter is dedicated to Z. Djindjic (1952-2003).

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