Abuse of Anabolic Androgenic Steroids (AAS) for Doping

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Contents

Abstract

Anabolic androgenic steroids (AAS) are the preferred drugs used in competitive and recreational sports and by bodybuilders to improve appearance and performance (Appearance and Performance-Enhancing Drugs, APED), commonly known as doping. Many AAS, often obtained via the Internet and from dubious sources, are not properly tested, and are consumed in extremely high doses and in irrational combinations with other drugs. Controlled clinical trials examining adverse effects are lacking because ethical restrictions prevent study subjects from being exposed to potentially toxic therapies, obscuring a causal relationship between AAS abuse and potential consequences. This chapter summarizes the side effects of AAS abuse, particularly the impact on reproductive system functions, based on detailed case reports and small clinical trials.

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37.1 Dimension of the Problem/ Epidemiology

Although doping has been practiced since ancient times, often with placebo or toxic effects, truly effective Appearance and Performance-Enhancing Drugs (APEDs) became available only with the rise of modern pharmacology, particularly after the isolation and synthesis of testosterone and anabolic androgenic steroids (AAS). Testosterone was used clinically shortly after its synthesis in 1935 (Nieschlag and Nieschlag 2019), and its first documented use for doping was by

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German rowers in 1952 (ostensibly to maintain their marital duties during strenuous training); Russian weightlifters soon followed in 1954 to improve their strength.

After various approaches to curb doping, a global anti-doping control network, the **World Antidoping Agency (WADA)**, was established in 1999. Under the motto "Play true," the World Antidoping Code strives to keep sports "clean" and protect each athlete (www.wada-ama.org). The **WADA Prohibited List,** renewed annually, summarizes all pharmacological substances and medical procedures that are prohibited in training and competition. Since then, AAS have been detected most frequently in positive samples by the 30 WADA-accredited laboratories worldwide (Handelsman 2020) or among black market substances seized by customs and police (Krug et al. 2014). By a rigorously administered **Therapeutic Use Exemption (TUE),** WADA may allow the use of testosterone in therapeutic doses for athletes suffering from *organic*, but not from *functional* hypogonadism.

Since all approved testosterone and AAS preparations are only available by prescription, the drug sources remain unclear. In some cases, these substances are no longer or have never been on the official market. There have been cases of physicians prescribing AAS, especially under pressure from bodybuilders who risk becoming champions by doping with AAS. Surveys of fitness center customers found that up to half of AAS users received the drugs with or without a prescription from physicians or pharmacies (Striegel et al. 2006; Raschka et al. 2013). Laboratories in Eastern Europe, Asia, and South America that manufacture a variety of AAS offer them for sale on the Internet, which, along with gyms, have become the main source of AAS. The **black and internet market for AAS** appears to be growing. In December 2011, there were 328,000 results on the Internet generated by the search term "steroids for sale" (Brennan et al. 2013) through the Google search engine; in December 2020, there were 4,130,000 for English-language sources (own research)! A qualitative analysis of the products provided to 100 subjects in the HAARLEM study showed that only about half of the samples did not contain the AAS declared on the package (De Ronde and Smit 2020).

In addition, AAS can be added **undeclared to dietary supplements** (Van Thuyne et al. 2006; Geyer et al. 2008; Rahnema et al. 2015) or are contained in **natural medicine** preparations made from **animal organ extracts**. For example, musk glands used in traditional Chinese medicine contain 16 different AAS, as detected in doping tests (Thevis et al. 2013).

Finally, secret but official **programs of sports organizations or states** can provide their athletes with AAS and other APEDs, as shown by the systematic doping program of the former German Democratic Republic (GDR) in the 1970s and 1980s, which became public knowledge after its regime collapsed in 1989 (Franke and Berendonk 1997). Nonetheless, state-organized doping in high-performance sports continues to flourish as shown by the example of Russia, where large-scale doping fraud was uncovered by WADA at the 2014 Winter Olympics in Sochi (Makarychev and Medvedev 2019).

AAS, like all other APEDs, can have **adverse side effects** in addition to the desired ones, resulting from the combination of various AAS in extremely high doses with other drugs and from the duration of administration over a period of months to many years. Due to the clandestine nature of this drug abuse, dosage and duration are largely unknown and there are understandably **no properly controlled clinical trials.** Therefore, scientific evaluation of the consequences of AAS abuse relies on case reports and some retrospective research, making a review of this area extremely difficult and frustrating in the age of evidence-based medicine. Nevertheless, this chapter aims to provide information on symptoms and diseases caused by AAS that can be misinterpreted without specific knowledge when searching for their origin. Proper diagnosis is further hampered by patient reluctance to admit to AAS use and ignorance of their potential serious side effects.

37.2 Chemistry and Detection

Testosterone and AAS (including designer steroids) are collectively referred to as AAS, although both the chemical structure and biological profiles of each differ (Fig. 37.1).

In general, both effects and side effects of specific AAS depend on their chemical structure. The full spectrum of biological effects requires that the androgen can be aromatized to estradiol and reduced to 5-alpha-dihydrotestosterone. As indicated in Table 37.1, the most commonly used AAS, testosterone, boldenone, Metandienone, and nortestosterone can be aromatized as well as 5-alpha-reduced, whereas fluoxymesterone and formebolone can be 5-alpha-reduced but not aromatized. Some AAS can neither be aromatized nor 5-alpha-reduced; in particular, the dihydrotestosterone derivatives are among them (Fig. 37.1 and Table 37.1). In addition, the genetic disposition of the individual athlete may modify the response to androgenic substances, as exemplified by the androgen receptor polymorphism that modulates testosterone activity (Zitzmann and Nieschlag 2007).

However, distinguishing them is difficult due to the different combinations and doses of additional commonly practiced doping polypharmacy (Skarberg et al. 2009; Dodge and Hoagland 2010), including erythropoietin, insulin, IGF-1, L-thyroxine, clenbuterol, amphetamines, diuretics, and so on. The characteristic of alkylation in the 17α-position of the androgen molecule should be noted, as these AAS may be

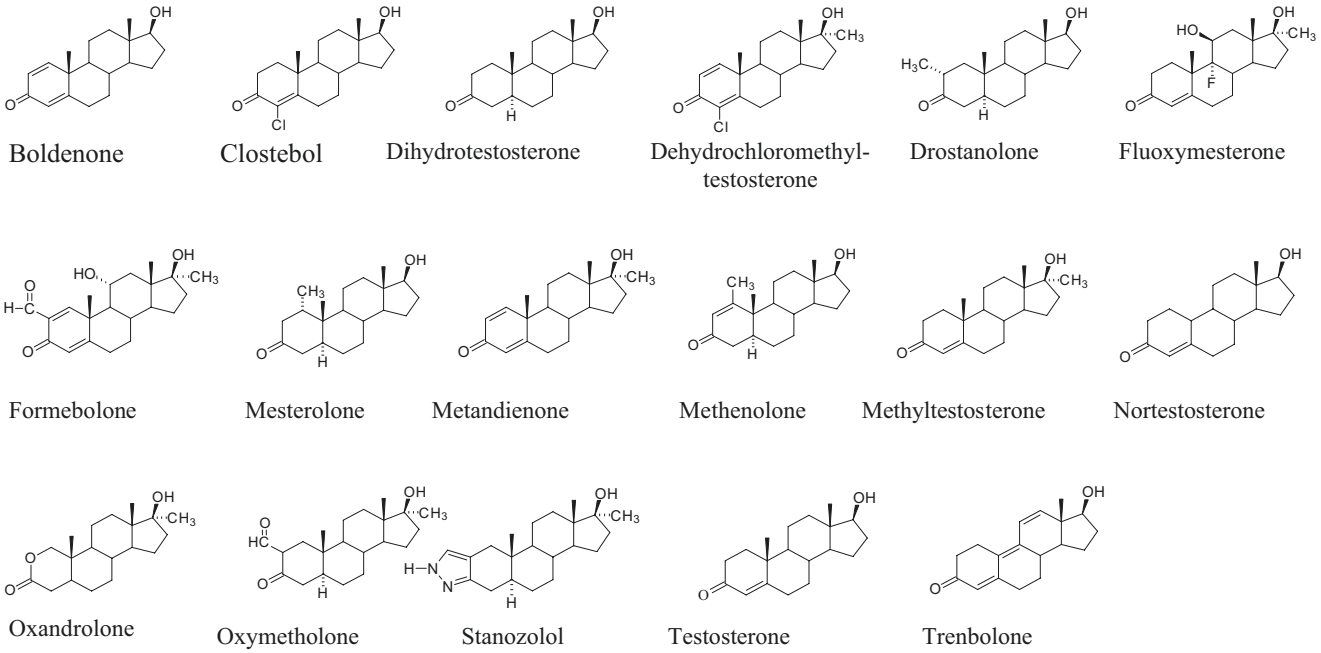

Fig. 37.1 Structural formulae of anabolic androgenic steroids (AAS) frequently detected in doping control samples (modified from Schänzer and Thevis 2012)

Table 37.1 Androgen anabolic steroids (AAS), metabolism, and hepatotoxicity

	Aromatization	5α-reduction	17α-alkylation (hepatotoxic)
Testosterone	x	x	–
19-nortestosterone	x	x	–
Boldenone	x	x	–
Dihydrotestosterone	–	x	–
Mesterolone	–	x	–
Methenolone	–	x	–
Trenbolone	–	x	–
17α-methyltestosterone	–	x	x
Fluoxymesterone	–	x	x
Dehydrochloromethyl testosterone	–	x	x
Formebolone	–	x	x
Oxandrolone	–	x	x
Oxymetholone	–	x	x
Stanozolol			
Metandienone	x	x	x
Closteboll	–	–	–
Drostanolone	–	–	–

highly toxic to the liver (Table 37.1). AAS abuse is also characterized by "stacking and cycling," i.e., increasing doses over time and changing preparations and their combinations in alternation with AAS-free periods to maximize desired effects and minimize side effects. Whether these therapies actually serve their purpose cannot be judged because they are based on trial and error and no evidence-based studies are available.

37.3 Side Effects on Reproductive Functions (Table 37.2)

Table 37.2 Side effects of high-dose steroids on reproductive and sexual functions/organs

Male reproductive functions
Decreased testicular volume
Reduced spermatogenesis
Infertility
Loss of libido
Erectile dysfunction
Gynecomastia
AAS-induced hypogonadism (ASIH)
Female reproductive functions
Anovulation
Amenorrhea
Dysmenorrhea
Infertility
Breast atrophy
Clitoral hypertrophy
Dysphonia
Deepening of the voice

37.3.1 Specific Side Effects in Men

Due to negative feedback regulation of the hypothalamic-pituitary-gonadal axis, AAS can cause reversible **suppression of spermatogenesis**, including azoospermia (Nieschlag and Vorona 2015;, Rolf and Nieschlag 1998). Since sperm-producing tissue accounts for up to 80% of the testes, its

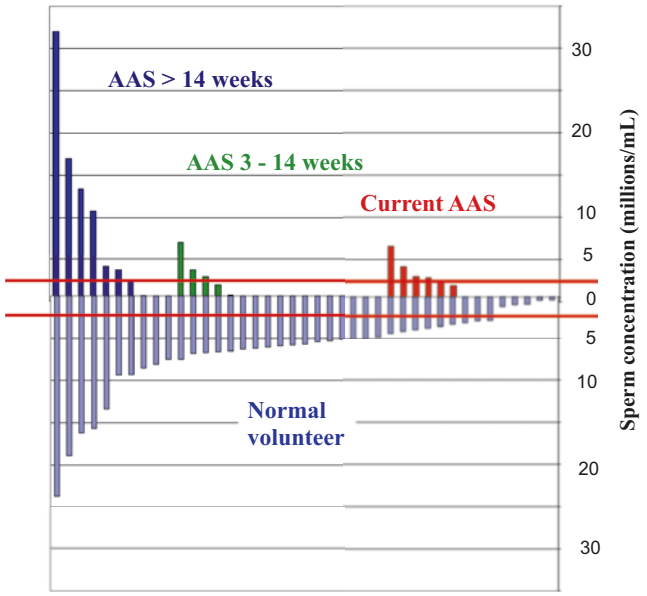

Fig. 37.2 Sperm concentrations in 41 bodybuilders currently using anabolic steroids, 3–14 weeks ago or more than 14 weeks ago (upper part) and in 41 drug-free volunteers (lower part). The bars represent sperm concentrations from individual bodybuilders (upper panel) and from normal volunteers (lower panel). The horizontal lines indicate a concentration of 20 million/mL as lower limit of normal (modified from Knuth et al. 1989)

functional impairment is followed by **atrophy of the testes**, which correlates with the dose and duration of AAS abuse (Rasmussen et al. 2016). After cessation of AAS intake, spermatogenesis and testicular volume recover within months (Fig. 37.2).

During intake, users may be infertile to varying degrees and are often unaware of the causal relationship. Proper diagnosis may be hampered by the fact that these men may not want to admit abuse to either their physician or their partner, and persistent follow-up is required. Low LH, FSH, and testosterone (in cases where endogenous testosterone is not used as an AAS) indicate suppression of the pituitary-testicular axis (Fronczak et al. 2012). The time required to **restore spermatogenesis** is significantly longer (10–14 months on average) than that required to normalize testicular steroidogenesis (7–9 months) (Shankara-Narayana et al. 2020). If spermatogenesis does not recover after cessation of use, a preexisting fertility disorder is more likely than AAS-induced damage. To accelerate recovery, hCG is sometimes prescribed without evidence of efficacy. It should be mentioned here that the suppression of the pituitary gland and spermatogenesis by testosterone is exploited in approaches to male hormonal contraception, with the complete recovery period taking an average of 3 months (see Chap. 48).

Given the large number of **teenagers using AAS**, the question arises whether the use of AAS in boys during puberty may be permanently detrimental to spermatogenesis. Although systematic studies in pubertal AAS users are lacking, the treatment of tall boys with high doses of testosterone to reduce final body size provides an analogy. Initially, it was suspected that this treatment would harm the testes and cause permanent damage. However, when appropriate control groups were co-sampled, the incidence of subnormal semen parameters was the same in both groups (Lemcke et al. 1996), indicating that at this age the testes do not differ from adult males in their ability to recover from suppression.

With high-dose use of aromatizable AAS, **bilateral gynecomastia** may develop in males with a prevalence of 20–30% (O'Sullivan et al. 2000). Concomitant application of estrogen receptor or aromatase inhibitors has been used to counteract this development. In cases of persistent, refractory gynecomastia, liposuction with mastectomy may be required (Babigian and Silverman 2001). After abrupt discontinuation of AAS abuse, athletes may exhibit **transient signs of hypogonadotropic hypogonadism,** such as decreased libido, erectile dysfunction, and depression (Basaria 2010).

An isolated case of a former GDR weightlifter who used oral turinabol in high doses (up to 20 tablets per day) between the ages of 18 and 23 years has been reported. He developed gynecomastia while on treatment and underwent surgery for unilateral **intratesticular leiomyosarcoma** at age 32 (Froehner et al. 1999). Because these tumors are extremely rare and have been described in hamsters after treatment with testosterone propionate and diethylstilbestrol, the authors suspected a causal relationship between AAS abuse and sarcoma. Since this is the only reported case, the pathogenesis of the tumor remains unclear.

37.3.2 Specific Side Effects in Women

Because the effects of testosterone also have a clear performance-enhancing effect in women (Bermon and Garnier 2017; Lindén Hirschberg et al. 2020), more and more male-to-female transgender athletes and 46,XY-DSD patients are entering women's sports, raising ethical, social, and legal issues, specific side effects of AAS in women will be discussed here.

37.3.2.1 Hypothalamic-Pituitary-Gonadal Axis

In women, small differences in endogenous testosterone levels appear to affect athletic performance. For example, female 400 and 800-m runners have been shown to have higher free testosterone in the upper third among female competitors (Bermon and Garnier 2017). Therefore, female athletes expect strong effects of AAS abuse, but pay through consequences on reproductive functions. **Dysmenorrhea, secondary amenorrhea with anovulation, and conse-**

quently infertility are the changes most commonly caused by AAS abuse.

A large study aimed at evaluating the side effects of therapeutic doses of testosterone administration in women showed that there were no significant differences in the incidence of cerebrovascular disease, coronary heart disease, breast carcinoma, deep-vein thrombosis/pulmonary embolism, and diabetes mellitus, or acute hepatitis between women receiving testosterone therapy and the control group (van Staa and Sprafka 2009).

Changes in the reproductive system due to suppression of the hypothalamic-pituitary-gonadal axis such as dysmenorrhea, secondary amenorrhea with anovulation, and **reduction in breast size** are reversible. It may take weeks or months for the axis to fully recover. **Clitoral hypertrophy** is among the irreversible effects of AAS abuse, but the incidence is not well documented.

37.3.2.2 Hirsutism

Hirsutism is the most common and reversible side effect of AAS use in women. The degree of increased facial or body hair growth depends on dose and duration of AAS excess and can be described according to the Ferriman-Gallwey hirsutism score (Ferriman and Gallwey 1961), which is based on the intensity of hair growth in nine facial/body areas. In some cases, it has been reported that it may take up to 2 years for serum testosterone concentrations to decrease to normal levels and for hirsutism to disappear after AAS administration in women (Urman et al. 1991).

37.3.2.3 Changes in the Voice

Deepening of the voice is part of the virilization that AAS can cause in women. Unlike acne, hirsutism, alopecia, and breast atrophy, deepening of the voice is irreversible. These effects of androgens in women have been repeatedly described (Strauss et al. 1985; Baker 1999). Lowering of the voice is caused by growth of the larynx in girls and by thickening of the vocal cords in women after puberty. The voice change can be so pronounced that women may be mistaken for men on the telephone. It is accompanied by hoarseness, which may increase with prolonged use of the voice. This dysarthria can become a problem for teachers, actors, and singers who depend on their voices for work. Such voice changes are also observed with endogenous elevation of testosterone levels, such as in congenital adrenal hyperplasia (Nygren et al. 2009) or in women who are sensitive to the androgenic effects of some oral contraceptives. Because voice changes are usually irreversible, use of AAS or other steroids must be suspended at the earliest sign of symptoms. Although no studies of women abusing AAS are available, in **female-to-male transsexuals** receiving testosterone treatment for virilization, a decrease in baseline voice frequency occurred within a few weeks, and attainment of full male frequency was documented within 6 months (Deuster et al. 2016).

37.4 Effects on Nonreproductive Organs (Table 37.3)

Table 37.3 Summary of the consequences of doping with AAS on nonreproductive organs and functions

Hematopoiesis and coagulation	Liver
Erythrocyte count increase	Arrhythmia
Hemoglobin increase	Cholestasis/ hyperbilirubinemia
Hematocrit increase	Steatosis
Polycythemia	Peliosis
Hypercoagulation	Adenomas
Venous thromboembolism	Hepatocellular carcinoma
Arterial thromboembolism	Liver failure
Stroke/apoplexy	
	Kidney
Musculoskeletal system	Creatinine increase
Premature epiphyseal occlusion (in adolescents)	Glomerulosclerosis
Rhabdomyolysis	Cholemic nephrosis
Tendon rupture	Renal failure
Ligament injuries	
Herniated disc	**Psyche and behavior**
	Irritability
Cardiovascular system	Nervousness, restlessness
HDL ↓ LDL ↑, ApoA1 ↓	Aggressiveness
Coronary heart disease	Reckless behavior
Myocardial infarction	Self-aggressiveness
Hypertension (?)	AAS dependence
Abnormal ECG (QRS > 114 ms)	AAS withdrawal syndrome
Arrhythmia	Depression
Left ventricular hypertrophy	Suicidal thoughts
Hypertrophic cardiomyopathy	
Dilated cardiomyopathy	**Skin**
Heart failure	Acne
Sudden cardiac death	Striae distensae
	Heavy sweating
	Alopecia
	Hirsutism

37.4.1 Hematological Side Effects

Stimulation of hematopoiesis (stem cells, reticulocytes, erythrocytes, hemoglobin, and hematocrit) is one of the important effects of testosterone and AAS used by athletes for higher performance. The increase in hemoglobin and hematocrit during puberty in boys results from an increase in testosterone (Hero et al. 2005), and the higher testosterone levels remain responsible for the differences between eugonadal males and females throughout life. In healthy and hypogonadal men, testosterone has a linear dose-dependent effect on hematopoiesis. Older men and those with higher BMI are more sensitive to testosterone stimulation than younger and leaner men (Zitzmann and Nieschlag 2007). This must be considered when treating patients with late-onset hypogonadism (Wang et al. 2008).

The hematopoietic effect of testosterone does not require aromatization, as shown in men with aromatase deficiency (Rochira et al. 2009). DHT has a similar effect on hematopoiesis as testosterone itself, indicating that 5α-reduction does not affect the hematopoietic effect of testosterone and other androgens (Sakhri and Gooren 2007). It is possible that, in addition to direct stimulation of bone marrow erythroid progenitor cell proliferation, the hematopoietic effects of testosterone and AAS are also mediated by erythropoietin and by increases in iron utilization due to hepcidin suppression, so that androgens may have three stimulatory pathways for hematopoiesis (Cheung and Grossmann 2018). Before erythropoietin and its analogs were available for clinical use, testosterone was widely used to treat aplastic and nephrotic anemia.

Androgens not only stimulate hematopoiesis but also increase 2,3-diphosphoglycerate in erythrocytes, thereby decreasing **hemoglobin oxygen affinity**, facilitating the release of oxygen from hemoglobin and improving oxygen delivery to tissues (Shahidi 2001). Androgens also appear to stimulate **granulopoiesis and thrombopoiesis** in vitro and in vivo (Inamdar Doddamani and Jayamma 2012; Roşca et al. 2021). High doses of AAS, as used in doping, cause significant increases in erythrocyte and hemoglobin concentrations (Kanayama and Pope Jr 2018), which is part of the intended effects as they increase oxygen transport. However, an increase in hematocrit above 52% can lead to **thromboembolism, intracardiac thrombosis, and stroke** (Lippi and Banfi 2011). Stroke may be associated with **left ventricular thrombus** and **cardiomyopathy** (Youssef et al. 2011) or fatal **massive myocardial infarction** (Shamloul et al. 2014).

Administration of testosterone and AAS to healthy men causes transient **activation of the coagulation system and fibrinolysis**. Both changes were reversible after discontinuation (Kahn et al. 2006). For example, testosterone can increase thromboxanA2 receptor activity and platelet aggregation and thus increase the risk of thrombosis. At the same time, the activity of the fibrinolytic system, particularly antithrombin III and protein S, increases (Shapiro et al. 1999). Levels of plasmin-α2-antiplasmin complex (PAP, terminal marker of fibrinolysis), factor XIIc, and antithrombin decreased significantly in men receiving testosterone undecanoate as depot injections (Zitzmann et al. 2002). Short-term low-dose administration of AAS-oxandrolone to healthy subjects resulted in an increase in blood coagulation factors and plasminogen, leading to a state of hypercoagulability (Kahn et al. 2006). Androgen-containing hormone replacement therapy decreased plasminogen activator inhibitor-1 (PAI-1) in premenopausal women, resulting in enhanced fibrinolytic activity (Winkler 1996).

Changes in the hemostatic system during testosterone therapy were also studied in female transsexuals (female-to-male) who received 250 mg testosterone enanthate injections every 2 weeks for a prolonged period (Toorians et al. 2003). This therapy had a mild **antithrombotic effect**. To what extent the AR polymorphism, which alters the erythropoiesis-stimulating effect of testosterone in substituted patients, is of influence in athletes is not known (Zitzmann and Nieschlag 2007).

37.4.2 Side Effects on the Cardiovascular System

37.4.2.1 Arrhythmias

Long-term AAS users show altered electrophysiological capacity of the myocardium with a significantly higher incidence of abnormal electrocardiograms (e.g., **prolongation of the QRS complex, arrhythmias, including atrial fibrillation, ventricular fibrillation, ventricular tachycardia, supraventricular, and ventricular extrasystoles**) after exercise compared to controls (Achar et al. 2010). Also, chronic consumption of supraphysiological doses of AAS increased interatrial and intra-atrial electromechanical delay and prolonged repolarization dispersion with significantly increased Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio compared with bodybuilders without AAS abuse (Alizade et al. 2015).

37.4.2.2 Myocardial Hypertrophy

AAS can cause **concentric left ventricular myocardial hypertrophy**, the extent of which appears to be dose-dependent (Dickerman et al. 1998). In one study, AAS was shown to exert a long-standing hypertrophic effect on the myocardium. Here, there were no significant differences between current and former AAS users (Di Bello et al. 1999). AAS does not appear to affect systolic cardiac function. However, because anabolic steroids affect left ventricular diastolic function, this serves as a criterion for distinguishing physiological exercise-induced hypertrophy from pathological myocardium (Caso et al. 2006; Kindermann 2006). A recent study found no differences in previous users who discontinued androgens for at least 3 months compared with nonusers in terms of left and right ventricular dimensions and systolic and diastolic functions (Shankara-Narayana et al. 2020).

The athlete's heart is characterized by moderately proportional myocardial hypertrophy without functional limitations. Pathological **left ventricular myocardial hypertrophy** that develops with AAS use is often associated with impaired diastolic function of the affected ventricle, likely caused by increasing myocardial fibrosis. The second diagnostic criterion is the thickness of the left ventricular myocardium, which can be determined during echocardiography. A ventricular wall thickness greater than 13 mm is suspected of pathological myocardial hypertrophy or AAS abuse

(Dickerman et al. 1998; Kindermann 2006). Left ventricular hypertrophy can be detected echocardiographically several years after AAS withdrawal (Achar et al. 2010). Although myocardial hypertrophy appears to be reversible, impaired left ventricular diastolic function and decreased inotropic capacity of the myocardium are irreversible (Turillazzi et al. 2011; Baggish et al. 2017). A cardiac magnetic resonance imaging (MRI)-assisted study described not only an increase in LV wall mass but also in the main volume of both cardiac ventricles (Luijkx et al. 2013). **Myocardial scarring** with severe left ventricular hypertrophy may occur in patients with normal coronary arteries after AAS abuse (Baumann et al. 2014), possibly due to an apoptotic testosterone effect on cardiomyocytes, as shown in cell culture studies (Nascimento et al. 2015).

In cases of **acute advanced heart failure** due to AAS abuse, maximal improvement in left ventricular ejection fraction was achieved within 6 months after discontinuation of AAS uptake and initiation of treatment with angiotensin-converting enzyme (ACE) inhibitors and beta-blockers. In severe cases, left ventricular assist device (LVAD) implantation and heart transplantation were required (Sondergaard et al. 2014).

37.4.2.3 Sudden Cardiac Death

AAS abuse can cause a significantly higher incidence of **sudden cardiac death** in apparently healthy young athletes. This mainly affects weightlifters and bodybuilders who take very high doses of AAS, often as a mixture with other drugs. The effects of AAS abuse based on autopsy data from ten young bodybuilders who had suffered sudden cardiac death and had taken unsupervised drug mixtures for performance enhancement were described (Kistler 2006). In all cases, the mean heart weight was significantly higher than the mean physiologic heart weight and histologically **chronic ischemic changes** of the myocardium were found. In almost all cases, **atherosclerosis of the coronary arteries and atheromatosis of the carotid and aortic** arteries were found despite the relatively young age of the athletes.

The most common cause of sudden death in young competitive athletes was **hypertrophic cardiomyopathy**, which occurred in one-third of cases (Maron et al. 2016) and previously undiagnosed **congenital heart failure** (Sullivan et al. 1998). Other potential causes of cardiac death in AAS users discussed include the following: **coronary artery spasm** due to inhibition of NO release, premature coronary atherosclerosis due to increased atherogenesis, thrombotic coronary artery occlusion due to increased platelet aggregation and/or increase in hematocrit and blood viscosity, and direct **cardiotoxic effects** with impairment of mitochondria and myofibrils and associated destruction of cardiomyocytes and their replacement by fibrous tissue (Kistler 2006; Sullivan et al. 1998; Dickerman et al. 1995; Fineschi et al. 2001).

37.4.2.4 Dilated Cardiomyopathy (DCM)

Some cases of **dilated cardiomyopathy (DCM)** have been described in healthy young bodybuilders while taking AAS. All cases involved uncontrolled high-dose AAS abuse, especially in combination with other drugs (Clark and Schofield 2005). In patients with a genetic predisposition to dilated cardiomyopathy using AAS, it becomes particularly difficult to disentangle causal relationships. Approximately 30% of DCM is thought to have familial accumulation. In most cases, inheritance is autosomal dominant, rarely X-linked or autosomal recessive. Because there is high variability in the probability of manifestation and gene expression, some other risk and environmental factors (e.g., viral infections or stress) may be responsible for the development of cardiomyopathy (Maisch et al. 2005).

37.4.2.5 Arterial Hypertension

It is not clear whether AAS cause arterial hypertension. In some cases, AAS abuse resulted in long-term (up to 1 year) elevation of blood pressure (Achar et al. 2010). AAS abuse-induced arterial hypertension may persist for up to 1 year after drug discontinuation. Activation of the sympathetic autonomic nervous system, as well as depression of parasympathetic modulation and structural cardiac changes such as interventricular septal hypertrophy, left ventricular wall hypertrophy, and diastolic ventricular wall thickness, appear to be a possible cause of arterial hypertension in AAS users (Barbosa Neto et al. 2018). Some AAS in high doses cause water retention, which may be associated with high blood pressure.

37.4.2.6 Atherosclerosis

High doses of AAS, especially when taken concomitantly with multiple preparations, can lead to a **decrease in high-density lipoprotein (HDL) cholesterol fraction, and an increase in low-density lipoprotein (LDL)** cholesterol (Kindermann 2006; Hartgens et al. 2004). These effects on lipoprotein levels can be seen approximately 2 months after the onset of ASA abuse. Lipid status returns to normal only a few months after discontinuation of administration. After long-term, high-dose AAS abuse, atherosclerosis and resulting coronary artery disease, cerebral vascular disease, or peripheral arterial disease (CAD) may develop. While no association was found between current AAS abuse and atherosclerotic plaque volume, the degree of atherosclerosis appears to be dependent on the duration of AAS exposure (Baggish et al. 2017).

37.4.3 Liver Disease

Changes in liver structure have been described, mainly in cases of chronic abuse of **17α-alkylated AAS**, e.g., methyl-

testosterone, methandrostenolone, oxandrolone, stanozolol (Turillazzi et al. 2011). 17α-alkylated AAS are considered obsolete for clinical use (at least in Europe) because of their liver toxicity (Rolf and Nieschlag 1998), but they are still available illegally for doping purposes. They may even be hidden undeclared in dietary supplements, as shown by two cases of severe hepatotoxicity after ingestion of the dietary supplement "Celtic Dragon" containing 2α-17α-dimethyl-etiocholan-3-one, 17β-ol (El Sherrif et al. 2013).

AAS are thought to play a key role in the development of **steatosis hepatis**, inhibiting the normal process of steroid biosynthesis and leading to the storage of cholesterol (Turillazzi et al. 2011). A slight increase in transaminases is usually completely reversible a few weeks after discontinuation of AAS (Basaria 2010).

As a direct toxic effect on hepatocytes with ultrastructural cell damage, oxidative stress leading to increased reactive oxygen species (ROS) production could play a role in the hepatotoxicity of AAS. Commonly observed changes include **intrahepatic cholestasis, peliosis hepatis** (lacunar blood-filled cavities originating from central veins or from focal necrosis of hepatocytes), and **proliferative changes in liver structure** such as focal nodular hyperplasia and hepatic adenomas (Rolf and Nieschlag 1998; Nakao et al. 2000). The appearance of adenomas can be detected as early as 6 months or after 15 or more years of AAS abuse, as described in two cases (Socas et al. 2005). Both bodybuilders had taken five different AAS in high doses, including stanozolol and oxymetholone. After cessation of AAS intake, the sonographically detected adenomas slowly disappeared without surgical intervention despite considerable initial size.

A causal relationship between AAS abuse and **hepatocellular carcinoma (HCC)** has been described mainly in patients with other severe liver diseases (Giannitrapani et al. 2000). Liver damage appears to be AAS dose-dependent (Schwingel et al. 2015).

37.4.4 Nephropathies

Renal disorders have been described mainly after prolonged use of AAS and range from a slight increase in serum creatinine to **acute renal failure as a complication of rhabdomyolysis**. It has been hypothesized that interindividual differences in the magnitude of adverse effects depend on the genetically determined function of the **uridine diphosphate glucuronosyltransferase (UGT)** enzyme, which enables glucuronidation of steroids, the first phase of the deactivation and elimination pathway of AAS (Deshmukh et al. 2010). Due to the UGT 2B17 deletion polymorphism, large interindividual variations in urinary testosterone metabolite concentrations are explained (Strahm et al. 2015). In vivo measurements of UGT 2B17 activity showed that low activity as a result of UGT 2B17 deletion was strongly associated with lower body mass index (BMI) in men, likely as an effect of higher serum testosterone concentration (Zhu et al. 2015).

Histologically, **focal segmental glomerulosclerosis** with tubular atrophy and interstitial fibrosis may be found in long-term AAS abuse. Mild forms of renal dysfunction with elevation of serum creatinine, blood urea nitrogen, and uric acid without sclerotic/fibrotic morphologic changes often return to normal range after discontinuation of AAS (Turillazzi et al. 2011).

37.4.5 Influence on the Musculoskeletal System

AAS in childhood or adolescence cause an acceleration of bone maturation in young athletes. At the end of puberty, activation of endochondrial bone formation leads to premature closure of growth zones with growth retardation, so early administration of testosterone or AAS can lead to growth arrest below expected levels (Kanayama and Pope Jr 2018; Przkora et al. 2005). AAS including testosterone support radial bone growth and periosteum formation. This also explains the larger cross-sectional size of male compared to female bone (Vanderschueren et al. 2012). The effect of testosterone on bone is mediated via the androgen receptor (AR) and via estrogens converted from testosterone through stimulation of osteoblasts and suppression of osteoclasts via the RANKL-OPG system (Vanderschueren et al. 2012). AAS that cannot be aromatized may therefore have little effect on bone.

Athletes often place extreme stress on their musculoskeletal system over long periods of time, resulting in a high incidence of **joint, tendon, bone, and muscle discomfort, injury, and dysfunction**. These can become chronic, causing the former athlete to suffer long after they have stopped playing high-performance sports and abusing AAS. However, there are no conclusive studies documenting a negative effect of AAS on the musculoskeletal system, and it is even suggested that AAS may prevent more severe damage. Synergistic effects of testosterone treatment and resistance training on muscle have also been outlined (Cheung and Grossmann 2018).

The anabolic effects of AAS on skeletal muscle are mediated by the androgen receptor (AR) and growth hormone (GH) and insulin-like growth factor-1(IGF1) mechanisms. Activation of the androgen receptor induces hypertrophy of type I as well as type II muscle fibers and an increase in the number of myonuclei and capillaries per fiber (Yu et al. 2014). These effects are mediated by stimulation of muscle protein synthesis, the GH/IGF-1 axis, and muscle mesenchymal progenitor cells (Bhasin et al. 2012).

As with other androgen effects, muscle mass under physiological conditions is determined by **androgen receptor (AR) polymorphism**. Shorter CAG repeats in exon 1 of the receptor are associated with higher muscle mass (Nielsen et al. 2010). This most likely also plays a role in the response to supraphysiological doses of AAS. There are also ethnic differences in AR polymorphism, for example, sub-Saharan Africans have shorter CAG repeats than Caucasians and East Asians (Ackerman et al. 2012). How this may contribute to performance differences and response to AAS is not yet known. Experiments in mice suggest that once muscle fibers are exposed to high doses of AAS, they respond more rapidly to further AAS treatment, even after a drug-free interval. This cellular memory appears to reside in myonuclei, whose numbers do not decrease after cessation of AAS ingestion (Egner et al. 2013).

Rhabdomyolysis has been observed with acute ingestion of AAS, with acute renal failure a possible complication. Tendon rupture and disc herniation may occur due to massive increases in muscle mass and strength without parallel increases in tendon strength and cartilage resistance.

37.4.6 Dermatological Side Effects

AAS act via the androgen receptor present in epidermal and follicular keratinocytes, sebocytes, sweat gland cells, dermal papilla cells, dermal fibroblasts, endothelial cells, and genital melanocytes. The use of AAS can rapidly lead to skin alterations in previously unaffected athletes, such as disruption of sebaceous gland growth and differentiation, hair growth, epidermal barrier homeostasis, and wound healing. AR polymorphism appears to play a role in the severity of symptoms (Zouboulis et al. 2007). The most common skin manifestations are **acne vulgaris, oily skin, seborrhea, striae, hirsutism, and androgenetic alopecia** (Walker and Adams 2009). Over 50% of athletes who participated in a questionnaire to identify unsupervised AAS therapies and side effects of AAS reported acne (Evans 1997).

After cessation of AAS use, these changes are usually reversible. To accelerate recovery, antiandrogenic therapy with cyproterone acetate or spironolactone could be tried (Zouboulis et al. 2007). However, severe forms of AAS-induced **acne conglobata** leave severe scars on the affected skin areas (Gerber et al. 2008). After acne, **striae distensae** resulting from rapid muscle hypertrophy supported by AAS ingestion are the most common skin side effect in athletes, especially bodybuilders. Over 40% of athletes complained of **stretch marks** of the skin (Parkinson and Evans 2006) with typical localization in the pectoralis muscle or upper arm area. After discontinuation of drug abuse, striae may persist as white streaks (Wollina et al. 2007).

37.4.7 Neoplasms

There is no evidence that testosterone at substitution doses has any effect on tumor development or growth, except in the prostate, where it stimulates the growth of an existing carcinoma. However, there are no reports of an association between current or past AAS abuse and **prostate carcinoma**. This lack of accumulation of case reports despite massive AAS abuse supports the hypothesis that androgens may protect against rather than cause prostate carcinoma.

The most feared malignancy after long-term AAS use is **hepatocellular carcinoma (HCC)**. The possible cause of tumor development in abuse of 17α-alkylated AAS is direct hepatotoxicity. In the case of aromatization of AAS (e.g., endogenous testosterone), a toxic effect of estrogens on liver tissue is discussed. It has been observed that human HCC tissue has increased aromatase activity. However, attempts to treat HCC with aromatase inhibitor tamoxifen did not yield positive results (Giannitrapani et al. 2006).

37.4.8 Side Effects on the Psyche

Headache, insomnia, increased irritability, depressed mood status after AAS abuse have been described (Turillazzi et al. 2011). Individuals exposed to such dangerous regimens may already be predisposed to irrational actions prior to AAS abuse (Piacentino et al. 2015). Dissatisfaction with one's body (e.g., muscle dysmorphia and dysphoria) appears to be common among men who use AAS, similar to men with eating disorders (Björk et al. 2013). Both groups share severe psychiatric symptoms such as **anxiety, depression, obsessive-compulsive behavior, and interpersonal sensitivity** and may be at **risk for suicide**. However, they differ in terms of self-image. The eating-disorder group had lower scores for self-emancipation and active self-love and higher scores for self-blame and self-loathing than former AAS users. There were no differences between these two groups in terms of psychiatric symptoms.

In a study of 17,200 adolescent boys in the United States, the lifetime prevalence for AAS abuse was five times higher among 635 homosexuals (21% vs. 4%) than among heterosexual boys. The homosexual youth showed a higher incidence of **depressive symptoms/suicidality, substance use, and victimization.** But whether these symptoms were precursors or outcomes of AAS abuse could not be determined (Blashill and Safren 2014).

As with other drug addictions (amphetamines, hallucinogens, narcotics), AAS abuse can lead to neurotoxicity and cause encephalopathy, which can present as altered mental status with memory loss and cognitive problems (Pomara et al. 2015).

AAS withdrawal may also be accompanied by **depression or symptoms such as depressed mood, loss of interest, loss of libido, sleep disturbances, and suicidal thoughts** (Turillazzi et al. 2011; Pope Jr et al. 2014). In some former AAS users, depression, anxiety, and melancholy persisted for many years, as noted by a 30-year follow-up of 683 Swedish strength athletes (Lindqvist et al. 2013). Up to 30% of AAS abusers may develop substance-dependence, often combined with alcohol and other drug addictions (Basaria 2010; Lundholm et al. 2015). At least, three etiological mechanisms may lead to AAS dependence:

- Body image disturbances such as muscle dysmorphia
- Dysphoria or depression following attempts to discontinue abuse
- Possible hedonic effects of AAS

Another attempt to explain the psychological causes of doping detects two predictors of doping abuse: fear of competitive failure, which may be associated with low self-esteem, and ego-oriented perspective (Blank et al. 2016).

Key Points

- Due to negative feedback in the regulation of the hypothalamic-pituitary-gonadal axis, AAS cause anabolic steroid-induced hypogonadism (ASIH) in men, characterized by reversible suppression of spermatogenesis, testicular atrophy, infertility, and erectile dysfunction. If spermatogenesis does not recover after AAS abuse, there may be an underlying preexisting fertility disorder. Other common side effects include gynecomastia and acne.
- In women, hirsutism, irreversible deepening of the voice, dysmenorrhea, secondary amenorrhea with anovulation, and infertility are the most common changes caused by AAS abuse.
- High doses of AAS cause significant increases in erythrocyte and hemoglobin concentrations in both sexes, which can lead to thromboembolism, intracardiac thrombosis, and stroke. Long-term AAS abusers have a higher incidence of arrhythmias, atherosclerosis, concentric left ventricular myocardial hypertrophy with impaired diastolic function, and sudden cardiac death. Alterations in liver function and structure, up to and including hepatocellular carcinoma, are mainly caused by chronic abuse of 17α-alkylated AAS. Insomnia, increased irritability, and depressed mood status are commonly observed with AAS abuse and may persist for many years after AAS discontinuation.
- The adverse effects of AAS described above pose a serious risk to individuals who participate in competitive sports, bodybuilding, or recreational sports, as well as to individuals who abuse these substances to enhance performance and/or appearance.
- Adverse effects are caused by supraphysiological doses of AAS and steroids that are known for their toxicity and have never been approved for clinical use or taken out of clinical use. Adverse effects of high doses of AAS may be exacerbated by concomitant use of a variety of other drugs in inappropriate doses and combinations.
- Detection of AAS abuse through the World Antidoping Agency (WADA) control network aims not only to ensure fair conditions for athletes, but also to protect them from health consequences of AAS abuse.
- Regardless of abuse, under physiological conditions testosterone remains the most important hormone for turning boys into men and maintaining adult masculinity. Deficiency of testosterone leads to clear symptoms of hypogonadism, which deserves proper diagnosis and treatment, testosterone substitution being the most important component.

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