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Doping with anabolic androgenic steroids (AAS): Adverse effects on non-reproductive organs and functions

Eberhard Nieschlag[1,2] · **Elena Vorona**[3]

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Abstract Since the 1970s anabolic androgenic steroids (AAS) have been abused at ever increasing rates in competitive athletics, in recreational sports and in bodybuilding. Exceedingly high doses are often consumed over long periods, in particular by bodybuilders, causing acute or chronic adverse side effects frequently complicated by additional polypharmacy. This review summarizes side effects on non-reproductive organs and functions; effects on male and female reproduction have been recently reviewed in a parallel paper. Among the most striking AAS side effects are increases in haematocrit and coagulation causing thromboembolism, intracardiac thrombosis and stroke as well as other cardiac disturbances including arrhythmias, cardiomyopathies and possibly sudden death. 17α-alkylated AAS are liver toxic leading to cholestasis, peliosis, adenomas and carcinomas. Hyperbilirubinaemia can cause cholemic nephrosis and kidney failure. AAS abuse may induce exaggerated self-confidence, reckless behavior, aggressiveness and psychotic symptoms. AAS withdrawal may be accompanied by depression and suicidal intentions. Since AAS abuse is not or only reluctantly admitted physicians should be aware of the multitude of serious side effects when confronted with unclear symptoms,

✉ Eberhard Nieschlag
eberhard.nieschlag@ukmuenster.de

[1] Centre of Reproductive Medicine and Andrology, University of Münster, Münster, Germany

[2] Center of Excellence in Genomic Medicine Research, King Abdulaziz University, Jeddah, Saudi Arabia

[3] Centre of Endocrinology, Diabetology and Rheumatology, Dortmund, Germany

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1 Introduction

Anabolic androgenic steroids (AAS) are the most widely used performance and appearance enhancing drugs (PAED) in competitive athletics, recreational sports and bodybuilding, as documented by epidemiologic studies [1] as well as by positive samples detected in the WADA worldwide anti-doping network (www.wada.org) [2]. Worldwide AAS are used—or rather abused—for doping with a lifetime prevalence rate of 6.4 % in males and 1.6 % in females, the highest rate being encountered in Middle Eastern countries, as discovered within the programme of the World Anti Doping Agency [3]. The increasing rates of AAS abuse among adults and in particular in adolescents are alarming, as the growing organism may be even more susceptible to unwanted side effects than the adult. AAS are obtained predominantly from the black market and through the internet and postal services [4], but healthcare providers are also involved in the procurement of AAS to a surprisingly high extent [5] and some states have even, or have had in the past, secret programmes for providing AAS to their elite athletes. As AAS abuse is reaching worldwide epidemic dimensions, untoward side effects—acute and long-term—become more and more evident and a cause for growing concern by the medical profession.

Recently a leading German newspaper published a list of 73 former GDR athletes—now in their 40s and 50s—suffering from ailments attributed to doping with AAS during their active sports career [6]. The most prevalent disorders on the list were

musculo-skeletal problems (44 %) and depressions (35 %), but cases of breast cancer and cardiac dysfunction were also recorded. This compilation highlights the problem of assessing the sequelae of doping, because the 73 athletes contributing to the list are members of the "Doping Victims' Association" ("Doping-Opfer-Hilfe e.V.") representing 700 of the about 10,000 former GDR high-performance athletes involved in the systematic governmental doping programme based on the AAS oral turinabol (dehydrochlormethyltestosterone) in the 1970s and 1980s. Thus the 73 of the 700 cases represent a biased selection of former athletes. Furthermore, there is no control group consisting of athletes who were free of any doping so that health effects of high-performance athletes as such can not be disentangled from possible additional sequelae of doping. Hence, it remains extremely difficult to assess whether current diseases are or are not consequences of doping.

This example illustrates the general dilemma when dealing with sequelae of doping on athletes' health. This has various reasons. None of the AAS (nor any other PAED) has ever been approved by regulatory agencies for the purpose of doping and has therefore never been subjected to any of the usual regulatory scrutinization requiring proper toxicology and randomized controlled trials (RCT). AAS doses used for doping exceed clinically applied doses five to 20 or even more times, doses which would only be used during drug development in toxicological animal studies but not in clinical trials. As the use of AAS is illicit, it is unimaginable to enrol current users in RCTs as they would not admit AAS use and would reject revealing their identity. In addition, most AAS users also administer other drugs simultaneously, often of unknown purity and at undefined doses. This makes it very difficult to establish any causal relationship between a specific substance and side effects, as illustrated by a 27-year old Olympic athlete who died in 1987 from toxic multiple organ failure; upon autopsy102 drugs were identified in her body, among others, stanozolol, aspirin, diclofenac, metamizol, codeine and heparin [7]. Retrospective systematic analyses are also lacking, as again, former consumers do not come forward, especially if they were champions and medal winners, except in a few rare cases. Often such successful users forget what they were taking and at what doses, or they never knew.

Another critical question is whether the influences of AAS are the same in male and female athletes. Except for the typical sex-dependent effects and side effects [8] it is generally assumed that AAS act similarly in men and women, but this remains unclear. In addition, the biological and clinical effects of AAS are dependent on the chemical structure of steroids, their capability to undergo aromatization to estrogens or 5α-reduction to 5α-dihydrotestosterone (DHT). A further important structural feature is 17α-alkylation of the steroid molecule which is responsible for hepatotoxicity (see Table 1). For further details of the mechanism of action the reader is referred to pertinent reviews (e.g., [9, 10]).

We have recently reviewed the effects of doping with AAS on female and male reproductive functions [8] and now summarize the adverse effects of AAS on non-reproductive organs and functions (Table 2). Our summary of AAS side effects is

Table 1 Androgenic anabolic steroids (AAS), their major metabolisation 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			
Metandione	x	x	x
Clostebol	–	–	–
Drostanelone	–	–	–

Table 2 Summary of sequelae of doping with AAS

Haematopoiesis and coagulation
Erythrocytes
Haemoglobin
Haematocrit
Polycythaemia
Hypercoagulability
Venous thromboembolism
Arterial thromboembolism
Stroke / Apoplexy
Musculo-skeletal system
Premature epiphyseal closure (in adolescents)
Rhabdomyolysis
Tendon ruptures (?)
Ligamentous injuries
Disc herniation
Cardiovascular system
HDL ↓ LDL ↑, ApoA1 ↓
Coronary heart disease
Myocardial infarction
Hypertension (?)
Abnormal ECG (QRS>114 ms)
Arrhythmia
Left ventricular hypertrophy
Hypertrophic cardiomyopathy
Dilative cardiomyopathy
Heart failure
Sudden cardiac death
Liver
Cholestasis /Hyperbilirubinaemia
Steatosis
Peliosis
Adenomas
Hepatocellular carcinoma
Liver coma
Kidney
Creatinine ↑, cystatin c ↑
Glomerulosclerosis
Cholemic nephrosis
Renal failure
Psyche and behavior
Irritability
Nervousness, unrest
Aggressiveness
Reckless behavior
Self-aggressiveness
AAS dependence
AAS withdrawal syndrome
Depression
Suicide thoughts
Skin[a]
Acne
Striae distensae
Profuse sweating
Alopecia
Hirsutism
Male reproductive functions[a]
Decreased testis volume
Suppressed spermatogenesis
Infertility
Loss of libido
Erectile dysfunction
Gynaecomastia
Anabolic steroid induced Hypogonadism (ASIH)
Female reproductive functions[a]
Anovulation
Amenorrhoea
Dysmenorrhoea
Infertility
Breast atrophy
Dysphonia
Deepening of voice

[a] These effects have been described by Nieschlag & Vorona [8]

based on extrapolation from effects observed in patients treated with AAS and on descriptions of individual cases or groups of cases, mainly retrospective and hardly ever controlled.

2 Haematopoiesis

Stimulation of haematopoiesis (stem cells, reticulocytes, erythrocytes, haemoglobin and haematocrit) is one of the important effects of testosterone and AAS exploited by athletes for higher performance. The increase of haemoglobin and haematocrit during puberty in boys results from rising testosterone [11] and the higher testosterone levels remain responsible for the differences between eugonadal men and women life-long. In healthy and hypogonadal men testosterone has a linear dose-dependent effect on haematopoiesis. Older men and those with higher BMI react more sensitively to testosterone stimulation than younger and leaner men [12, 13]. This has to be taken into account when treating patients with late-onset hypogonadism [14]. The haematopoietic effect of testosterone does not require aromatization, as shown in aromatase-deficient men [15]. DHT has a similar effect on haematopoiesis as testosterone itself, indicating that 5α-reduction does not impair the haematopoietic effect of testosterone and other androgens [16]. It remains controversial whether, in addition to direct stimulation, the haematopoietic effect of testosterone and AAS is also mediated by erythropoietin so that androgens may have two pathways to stimulate haematopoiesis [17, 18]. Before erythropoietin and its analogues became available for clinical use, testosterone was

widely used for the treatment of aplastic and nephrotic anaemia.

Androgens not only stimulate haematopoiesis, but also increase 2,3-diphosphoglycerat in erythrocytes which decreases the haemoglobin-oxygen affinity, thereby facilitating release of oxygen from haemoglobin and enhanced oxygen delivery to the tissues [9]. Androgens also appear to stimulate granulopoiesis and thrombopoiesis *in vitro* and *in vivo* [19, 20].

Testosterone can increase the activity of thromboxanA2-receptors and thrombocyte aggregation and thereby also the risk of thrombosis. Simultaneously the activity of the fibrinolytic system rises, in particular of antithrombin III and of protein S [21, 22]. Levels of plasmin-α2-antiplasmin-complex (PAP, terminal marker of fibrinolysis), of factor XIIc and of antithrombin sank significantly in hypogonadal men who received testosterone undecanoate as depot injections for substitution [23]. Short-term, low-dose administration of the AAS oxandrolone to healthy volunteers led to an increase in blood coagulation factors and plasminogen, producing a state of hypercoagulability [24].

High doses of ASS as used in doping cause a significant increase of erythrocytes und haemoglobin concentration [25, 26] which constitutes part of the intended effects as it increases oxygen transport. However, increases in the haematocrit above 52 % may lead to thromboembolism (VTE), intracardiac thrombosis and stroke [27–29]. Stroke may be associated with left ventricular thrombus and cardiomyopathy [30] or with fatal massive myocardial infarction [31] (see also Table 3). To what extent the AR polymorphism that modifies the erythropoiesis-stimulating effect of testosterone in substituted patients is of influence in athletes is not known [13].

3 Musculo-skeletal system

The main reason for AAS abuse for enhancing performance and appearance in sports and bodybuilding rests in their haematopoietic and musculotrophic effects. Whereas AAS abuse has been booming since the 1970s, the medical profession remained convinced that the muscle-building effect was rather a placebo than a real effect of AAS, as reflected in a review of all relevant publications between 1966 and 1990 [43]. However, research studies so far had only investigated clinical doses, incomparable with the AAS doses used in sports and bodybuilding. Only since the late 1990s were trials with supraphysiological doses—mainly of testosterone—performed, and the significant increases in skeletal muscle mass and voluntary strength produced by AAS were scientifically documented [44, 45].

Today there is general agreement that the anabolic effect on skeletal muscle is mediated through the androgen receptor (AR) by inducing hypertrophy of muscle fibres of type I as well as type II, and by an increase in the number of myonuclei and capillaries per fibre [46]. These effects are mediated by stimulation of muscle protein synthesis, of the GH/IGF-1 axis and mesenchymal muscle progenitor cells [45]. As with other androgen effects, muscle mass is determined by the polymorphism of the AR (shorter CAG repeats in exon 1 are associated with higher muscle mass) under physiologic conditions [47] and most likely this also plays a role in the response to supraphysiological doses of AAS. There are also ethnic differences in the AR polymorphism as Sub-Saharan Africans have shorter CAG repeats than Caucasians and East Asians [48, 49]. How this may contribute to differences in performance and in response to AAS is not known. Experiments in mice suggest that once muscle fibres are exposed to high AAS doses, they respond faster to further treatment even after a drug-free interval. This cellular memory appears to be located in the myonuclei which do not diminish in number after cessation of AAS intake [50].

Testosterone supports periost formation, radial bone growth and areal bone density. This explains the larger cross-section size of male compared to female bones. The action of testosterone on bones is mediated by the AR and by estrogens converted from testosterone through the RANKL-OPG-System by stimulation of osteoblasts and suppression of osteoclasts [51, 52]. AAS that cannot be aromatized may therefore have little effect on bones. AAS given to athletes in childhood or adolescence cause an acceleration of bone maturation. At the end of puberty, activation of endochondral bone formation leads to closure of the epiphyseal growth zones with growth retardation [28, 53, 54] so that early administration of testosterone or AAS may lead to growth arrest below the expected height.

Athletes often strain their musculo-skeletal system acutely and to an extreme extent over long periods, resulting in a high incidence of complaints, injuries and disorders in joints, tendons, bones and muscles. Individual sport categories have their specific pattern of injuries. These may become chronic so that the former athlete suffers long after discontinuing high-performance sports—and AAS abuse. There are, however, no appropriate investigations documenting a negative impact of AAS on the musculo-skeletal system and it is even suspected that AAS could possibly prevent more severe damage. It is also unclear whether the increased bone mass may prevent fractures as long as AAS are consumed as well as in later life. At least, no reports can be found that AAS abusing athletes/bodybuilders have higher or lower rates of osteoporosis (in advanced age) or bone fracture rates than “clean” athletes.

However, under acute intake of AAS rhabdomyolysis has been observed [55], with acute renal failure as a possible complication (see below under “Kidney”). The growth in muscle mass and power under AAS appears not to be paralleled by an equal increase in tendon strength as AAS abusers are supposed

Table 3 Fatal and non-fatal cardiopathies in 25 athletes using high dose AAS with or without other performance and appearance enhancing drugs (PAED)

Reference	Type of sport	Sex	Age (years)	AAS	Other substances	Duration of intake	Pathol. findings
Schollert and Bendixen [32]	Bodybuilder	m	33	Testosterone Retabolil Anasteron Primobolan Sustanon			Fatal DCM + myocarditis
Ferrera et al. [33]	Weightlifter	m	29	Sublingual TP 2x/dy since 3 mths	Tobacco chewing since 5 ys.		Non-fatal DCM
Vogt et al. [34]	Bodybuilder	m	21	19-Nortestosterone plus 8 further AAS	Thyroxin Diazepam Polypharmacy		Non-fatal DCM
Clark and Schofield [35]	Bodybuilder	m	40	200-400 mg/week Nandrolone Dianabol 20–40 mg/dy	Ephedra 80-120 mg/dy γ-OH butyrate 1–2 g/dy		Non-fatal DCM + hepatits, family history for congestive heart failure and early cardiac death
Kistler [36]	Bodybuilder	m	31	Testosterone Nandrolone Stanozolol Boldenone	Clenbuterol (Insulin?)		Fatal hypoglycemia cardiac hypertrophy
	Bodybuilder	m	32	Stanozolol			Fatal multiorgan failure, cardiac hypertrophy and fibrosis
	Bodybuilder	m	32	Testosterone Norandrosterone Stanozolol Epimethediol	Ephedrin		Fatal MI
	Bodybuilder	m	35	Metenolone Testosterone			Fatal MI, DCM
	Bodybuilder	m	45	Nandrolone Metadienone Mesterolone	Coffein		Fatal MI, cardiac hyper-trophy
Stergiopoulos et al. [37]	Recreational weightlifter	m	44	Stacked high-dose T im	Sildenafil occasionally	2x weeks for 6 weeks, intermittandly since 3 years	Non-fatal MI, family history of CVD, Hk 63%!
Ahlgrim and Guglin [38]	Competitive bodybuilder	m	41	High doses T 250 mg every 5 dys	Furosemid Spironolactone Hydrochloro-thiazid, IgF 1	Several yrs	Non-fatal DCM father several MIs
Bispo et al. [39]	Bodybuilder Bodybuilder	m	40	AAS po AAS im			Non-fatal DCM acute liver failure
Fanton et al. [40]	Weight-lifter	m	19	AAS			Fatal LV apoplexy
	Physical exercise teacher	m	22	AAS			Fatal LV apoplexy
	Bodybuilder	m	25	AAS			Fatal disseminated myocarditis
	Soccer	m	28	AAS			Fatal disseminated myocarditis

Table 3 (continued)

Reference	Type of sport	Sex	Age (years)	AAS	Other substances	Duration of intake	Pathol. findings
	Marathon	m	54	AAS			Fatal coronary thrombosis and DCM
	Marathon	m	48	AAS			Fatal LV hypertrophy
Youssef et al. [30]	Bodybuilder	m	39	Nandrolone im, 2x/week		Since 3 years	Non-fatal CM, LV thrombus, stroke
Montisci et al. [41]	Bodybuilder	m	32	AAS ++		7 years	Fatal DCM
	Bodybuilder	m	31	Stanozolol Boldenone Dromostanolone Metelonone Trenbolone		Several yrs	Fatal DCM, endocardial thrombosis
	Cyclist	m	32	AAS ++		Several yrs	Fatal DCM, pulmonary infarction
	Bodybuilder	m	25	Testosterone 19-Nortesto-sterone	Polypharmacy		Fatal eosinophilic myocarditis
Shamloul et al. [31]	Fitness athlete	m	37	Methandienone Methanolone (Doses not specified)		For since 2 years	Fatal massive MI and ischaemic stroke
Thiblin et al. [42]	Fitness athlete Prostitute Drug dealer	f	20	9 different AAS for last 12 mths (metandienone, mestanolon, stanozolol)	Ephedrin Tadalafil		Fatal sudden cardiac arrythmia

Abbreviations: m male, *f* female, *DCM* dilative cardiomyopathy, *CVD* cardiovascular disease, *MI* myocardial infarction, *LV* left ventricular, *T* testosterone, *TP* T proprionate, *Hk* hematocrit

to experience a higher rate of tendon ruptures [56]. This impression is based on single observations and a controlled investigation is not available. In fact, a self-reported survey of 2552 former US football players revealed that there was no association between AAS abuse and tendon as well as muscle injuries, while a higher rate of disc herniations, knee ligamentous and meniscal, elbow, spine and foot/ankle injuries was reported in AAS abusers. However, the authors caution against causal conclusions since the players often took AAS *after* an injury for faster recovery and the survey does not provide clues when the AAS were taken [57]. Frequent intramuscular injections of AAS may lead to local reactions such as myositis ossificans, a form of heterotopic ossification [58].

4 Cardiovascular system

During the last two decades testosterone has undergone a metamorphosis from a risk factor for cardiovascular diseases to a cardio-protective agent [59–61]. However, this applies to testosterone in the physiological range and to substitution in hypogonadal men. This is certainly different when excessive AAS doses are applied.

High doses of AAS, especially in cases of simultaneous consumption of several different preparations, can cause reduction of the HDL (high-density lipoprotein) fraction of cholesterol and increase of LDL (low-density-lipoprotein) cholesterol [62–65], as well as a decrease of apolipoprotein A1 [66]. These effects on lipoprotein levels can be noted approximately 2 months after the beginning of ASS abuse. Only several months after discontinuation of AAS administration does the lipid status return to normal [67]. After long-standing, high-dose AAS abuse atherosclerosis and consequential coronary heart disease, cerebral vessel disease or peripheral arterial obstructive disease can develop.

Whether AAS abuse causes arterial hypertension has not been definitely clarified. In some cases AAS abuse led to an elevation of blood pressure [68], which can persist up to 1 year after discontinuation of drug intake [69]. Some AAS in high doses cause water retention which may be associated with high blood pressure.

Long-term AAS abusers have an altered electrophysiological capacity of the myocardium with a significantly higher incidence of abnormal post-exercise electrocardiograms (e.g., extension of QRS-complex >114 ms, arrhythmias, including atrial fibrillation, ventricular fibrillation, ventricular tachycardia, supraventricular and ventricular ectopic beats) compared with controls [68, 70]. Compared to non-AAS abusers, chronic consumption of supraphysiological AAS doses by bodybuilders increased inter-atrial and intra-atrial electromechanical delay, as well as prolonged repolarization dispersion with significantly increased Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio- [71, 72].

AAS can often cause concentric left ventricular myocardial hypertrophy whose extent seems to be dose-related [73, 74] and may also depend on the AR polymorphism as in normal men: shorter CAG repeats are associated with higher maximal left ventricular wall thickness [75]. It has been shown that AAS exert a long-standing hypertrophic effect on the myocardium. There are no significant differences between current and previous AAS abusers [34, 76, 77]. An affected diastolic function of the left ventricle serves as a criterion for differentiation between physiologic, training-induced hypertrophy and a pathologic myocardium [63, 71, 78].

The athlete's heart is characterized by moderate proportional myocardial hypertrophy without functional limitations. Pathologic left ventricular myocardial hypertrophy, developing under AAS intake is often associated with a reduction of the ejection fraction of the left ventricle, as well as a restricted diastolic function of the affected heart chamber, probably caused by increasing myocardial fibrosis [79]. The second diagnostic criterion is the thickness of the left ventricular myocardium seen on echocardiography. A heart chamber wall thickness of more than 13 mm is suspicious of pathologic myocardial hypertrophy or AAS misuse [63, 73]. A left ventricular hypertrophy can persist on echocardiography several years after AAS withdrawal [68]. In a cardiac Magnetic Resonance Imaging (MRI) assisted study not only an increase of the LV wall mass, but also major volumes of both heart ventricles were described [79]. Myocardial scarring with severe left ventricular hypertrophy can occur in patients with normal coronary arteries after AAS abuse [80], potentially due to an apoptotic testosterone effect on cardiomyocytes, as shown in cell culture studies [81].

Even if the myocardial hypertrophy should regress, impaired diastolic function of the left ventricle and the decreased inotropic capacity of the myocardium may persist [10]. In case of acute advanced heart failure due to AAS abuse a maximal improvement in left ventricular ejection fraction was reached within 6 months after discontinuation of ASS intake and the beginning of treatment with angiotensin converting enzyme (ACE) inhibitors and beta-blockers. In severe cases a left ventricular assist device and a heart transplantation were required [82].

Uncontrolled AAS abuse by apparently healthy young athletes can cause a significantly increased incidence of cardiac death. This concerns mainly powerlifters and bodybuilders taking very high AAS doses, often in combination with other drugs. In his dissertation Kistler [36] describes effects of AAS-abuse on the human organism, based on autopsy data of ten young bodybuilders (mean age 33.7 years) who took combinations of AAS and other drugs to enhance appearance and performance (Table 3). In four cases the cause of death was acute cardiac dysfunction. In all ten cases the mean heart weight of 517 g was significantly higher than the mean physiological heart weight. Furthermore, in all cases chronic ischemic changes of the myocardium were found histologically. It is also notable that in almost all cases arteriosclerosis of the

coronary vessels and atheromatosis of the arteria carotis and aorta were found, despite the relatively young age of the athletes.

Some cases of dilative cardiomyopathy (DCM) have been described in young bodybuilders during intake of AAS (Table 3). In all cases there was uncontrolled high-dose AAS abuse, particularly in combination with other drugs [32, 34, 35] (Table 3). In cases with a genetic disposition for dilative cardiomyopathy using AAS it becomes specifically difficult to disentangle causal relationships (e.g., [83]). It has been suggested that up to 50 % of DCM cases show a familial accumulation and diverse genetic background [84]. In most cases the inheritance is autosomal-dominant, rarely X-chromosomal or autosomal-recessive. Because the probability of manifestation and gene expression have a high variability, some other predictive and environmental factors (e.g., viral infections or stress) can also be responsible for the development of cardiomyopathy [85].

5 Liver

Changes of liver structure and function have been described, mainly in cases of chronic abuse of the 17α-alkylated AAS, e.g., methyltestosterone, methandrostenolone, oxandrolone, oxymetholone, stanozolol [10, 86]. (Table 2) Because of their liver toxicity 17α-alkylated androgenic steroids have been considered obsolete for clinical use for decades (at least in Europe) [86], but continue to be available illegally for doping purposes. They may even be hidden undeclared in dietary food supplements, as revealed by two cases of severe hepatotoxicity following consumption of the supplement "Celtic Dragon" containing 2α-17α-dimethyl-etiocholan-3-one,17β-ol [87].

AAS play a key role in the development of steatosis hepatis, inhibiting the normal process of steroid metabolism and leading to cholesterol storage [10]. An increase of transaminases (aspartate aminotransferase AST and alanine aminotransferase ALT) is mostly reversible and several weeks after discontinuation of AAS normal ranges are achieved [65, 88].

As a direct toxic effect on hepatocytes with ultrastructural cell damage, oxidative stress leading to increased ROS (reactive oxygen species) production could play a role in the hepatotoxicity of 17α-alkylated AAS. Hepatotoxicity caused by AAS is characterized by high bilirubin levels and causes pronounced jaundice, but only moderately increased AST and ALT [89]. Changes often observed are intrahepatic cholestasis, peliosis hepatis (lacunar blood-filled cavities, which come from central veins or from focal necrosis of hepatocytes) and proliferative changes of the liver structure such as focal-nodular hyperplasia and liver adenomas [53, 86, 90–92]. The appearance of adenomas may be noted as early as 6 months or as long as 15 and more years of AAS abuse, as described in two cases by Socas et al. [92]. Both bodybuilders had taken five different AAS in high doses, among these stanozolol and oxymetholone. After stopping AAS intake the sonographically detected adenomas disappeared slowly and without surgical intervention despite considerable initial size.

Other cases take a more severe course, when the adenomas turn into liver carcinomas [93] and the AAS abusers die in liver coma, unless they have a chance for curative surgery or liver transplantation. This is illustrated by two recently published cases: a 39- year old professional bodybuilder had taken 11 (!) AAS in high doses for the last 5 years, among them four 17α-alkylated steroids. A sizable hepatocellular carcinoma could be removed by laparoscopic surgery and the patient had survived for at least 2 years when the publication appeared [94]. The second case is a 29- year old bodybuilder who had taken cycles of five AAS including stanozolol and methandienone at high doses over 2 years. In addition, he self-administered diuretics (aldosterone antagonists and thiazide for better muscle profiling) as well as human growth hormone, insulin and tamoxifen. He developed a hepatocellular carcinoma and was saved by liver transplantation; the explanted liver showed a mass of 8 kg (<2 kg normal), the tissue was AR positive. At the time of publication he had survived for 27 months [95]. The latter case also demonstrates the difficulty in establishing a possible causal relationship between the liver carcinoma and *a specific* hormone/agent consumed by the bodybuilder. This polypharmacy raises the same problem as with other disease entities diagnosed in AAS abusers.

6 Kidney

Testosterone and other AAS have been used in the past for over 25 years for anaemia treatment in patients with chronic kidney insufficiency before erythropoietin became available for clinical use. The doses used were in the normal clinical range and far below those in AAS abuse. The general condition and the serum parameters of the malnourished patients with chronic renal failure improved due to reduction of catabolism [96].

Renal disorders have been described mostly after long-term AAS use and range from a slight increase of serum creatinine to acute renal failure as a complication of rhabdomyolysis or liver damage. In addition to creatinine, cystatin c and cystatin c clearance should be used to assess renal function in athletes as elevated creatinine may be due to higher muscle mass and not necessarily a sign of renal function impairment. AAS-induced kidney damage may occur as a consequence of liver damage and toxic bilirubin concentrations, known as bile acid nephropathy or cholemic nephrosis [97]. Kidneys can also be affected as part of a multiple organ dysfunction syndrome [98, 99].

Histologically focal segmental glomerulosclerosis with tubular atrophy and interstitial fibrosis can be found with long-term abuse [10]. Mild forms of renal dysfunction with elevation of serum creatinine and cystatin c clearance, blood urine

nitrogen and uric acid without sclerotic/fibrotic morphological changes often return to normal ranges after discontinuation of AAS [10]. It has been hypothesized that the inter-individual differences concerning the grade of side effects depend on the genetically programmed function of the uridine diphosphate-glucuronosyltransferase (UGT) enzymes, which provide glucuronidation of steroids, the first phase of the deactivation and elimination pathway of AAS [100]. In-vivo measure of the UGT 1B17-activity revealed that low UGT2B17 activity, as a result of a UGT 2B17-deletion, was strongly associated with lower body-mass-index (BMI) in males, probably as a consequence of higher serum testosterone concentrations [101].

7 Psyche and behaviour

A number of studies have shown that AAS abusers may develop maniac or hypomaniac behaviour characterized by irritability, aggressiveness, exaggerated self-confidence, hyperactivity and psychotic symptoms (for review 1). This is primarily the case when very high AAS doses in the range of or equivalent to 500 to 1000 mg testosterone enanthate per week are consumed. As an anonymous self-administered questionnaire revealed, 60 % of the 500 bodybuilders and athletes surveyed indeed administered such doses—often in combination with further drugs [102].

Although the ignorance about deleterious side effects of AAS and other PAEDs is often surprising, it is common knowledge that any effective drugs also have negative effects, especially when taken at high doses over prolonged periods. Thus the athlete is torn between the desire for record achievements and the fear of unwanted side effects of AAS. Hence it is likely that persons subjecting themselves to such dangerous regimens are already predisposed to irrational actions before AAS abuse [103]. Dissatisfaction with the body (e.g., muscle dysmorphia and dysphoria) seems to be common in males using AAS [104], similar to males with eating disorders. Both groups have serious psychiatric symptoms such as anxiety, depression, obsessive-compulsive behaviour and interpersonal sensitivity and may be suicidal, but differ regarding self-image: the eating disorder group had lower scores for self-emancipation and active self-love and higher scores for self-blame and self-hate than former AAS abusers. There are no differences between these two groups concerning psychiatric symptoms [105]. Among 17,200 US adolescent boys lifetime prevalence for AAS abuse was 5 times higher (21 vs. 4 %) in the 635 homosexual than in the heterosexual boys. The homosexual adolescents showed a higher incidence of depressive symptoms/suicidality, substance use and victimization, but it could not be clarified whether these symptoms were precursors or outcomes of AAS abuse [106].

As with other drug addictions (amphetamines, hallucinogens, narcotics) AAS abuse may lead to neurotoxicity and cause encephalopathy, as evidenced by an altered mental state with memory loss and cognitive problems [107, 108].

AAS withdrawal may also be accompanied by depression or depressive symptoms such as depressed mood, loss of interest, loss of libido, sleep disturbances and suicidal intentions [1, 10]. In some former AAS abusers depression, anxiety and melancholy may persist for many years at a rate above non-abusers, as a 30-year follow-up among 683 Swedish power sport athletes revealed [109]. As many as 30 % of AAS abusers may develop AAS dependence, often combined with alcohol and other drug addictions [88, 110–112]. At least three etiologic mechanisms may lead to AAS dependence: body image disorders such as “muscle dysmorphia”, an experience of dysphory or depression after attempting to discontinue misuse, and possible hedonic effects of AAS [110]. A survey among 10,365 Swedish men showed a 5 times higher rate of conviction for violent crime in AAS abusers than in non-abusers, however, this rate was not higher than in other polysubstance abusers, indicating that the predisposed personality may be more important than AAS abuse as such [112]. Among forensic investigations in the cause of death among 34 AAS abusers there were 9 victims of homicide and 11 had committed suicide, highlighting the high incidence of aggressive behaviour or depression [113].

8 Conclusion

The foregoing description of the multiple adverse medical consequences of doping with AAS—some reversible, some irreversible—causing chronic illness and even death—demonstrates the dangers arising from abuse of very effective substances. The physician needs to be aware of these defects when confronted with the afflicted patient who will not or only reluctantly confess to his doping practice. In order to be aware of the multiple hormones and drugs used for doping the annually updated WADA “Prohibited List” (www.wada-ama.org) should be consulted as a reference.

Knowing the deleterious side effects the medical profession, together with sports organizations, should not only treat, but also warn and teach especially young athletes about the possible medical consequences [1, 114]. Hence, WADA and its worldwide network of doping controls has not only the task to prevent cheating and guarantee fair play and equal chances in competitive sports, but also to protect athletes from self-inflicted health problems arising from AAS abuse. In order to fulfil this task constant renewal of the methodology for detecting low doses of AAS and new substances is required [115]. While the health risks may be reduced by new forms of micro-doping, new forms of detecting fraud by the athlete need to be implemented [116] and existing technology

needs to be refined constantly [115]. Further health risks, mostly still unknown, arise from gene doping [117]. And the medical profession will continue to struggle with the adverse effects of doping as long as athletes want to win competitions and as long as the Olympic motto continues to read "Citius, altius, fortius".

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References

1. Pope Jr HG, Wood RI, Rogol A, Nyberg F, Bowers L, Bhasin S. Adverse health consequences of performance-enhancing drugs: an Endocrine Society scientific statement. Endocr Rev. 2014;35:341–75.
2. Geyer H, Schänzer W, Thevis M. Anabolic agents: recent strategies for their detection and protection from inadvertent doping. Br J Sports Med. 2014;48:820–6.
3. Sagoe D, Molde H, Andreassen CS, Torsheim T, Pallesen S. The global epidemiology of anabolic-androgenic steroid use: a meta-analysis and meta-regression analysis. Ann Epidemiol. 2014;24:383–98.
4. Brennan BP, Kanayama G, Pope Jr HG. Performance-enhancing drugs on the web: a growing public-health issue. Am J Addict. 2013;22:158–61.
5. Striegel H, Simon P, Frisch S, Roecker K, Dietz K, Dickhuth HH, et al. Anabolic ergogenic substance users in fitness-sports: a distinct group supported by the health care system. Drug Alcohol Depend. 2006;81:11–9.
6. Hecker A. Der Schmerz blüht. Frankfurter Allgemeine Zeitung 18.10.2014 Nr. 242, p. 40.
7. Fischer-Solms H. Spitzensport: Doping in Ost und West. In: Wir gegen uns: Sport im geteilten Deutschland. Darmstadt: Primus-Verlag; 2009. pp. 111–21.
8. Nieschlag E, Vorona E. Medical consequences of doping with anabolic androgenic steroids (AAS): effects on reproductive functions. Eur J Endocrinol. 2015.03.24.
9. Shahidi NT. A review of the chemistry, biological action, and clinical applications of anabolic-androgenic steroids. Clin Ther. 2001;23:1355–90.
10. Turillazzi E, Perilli G, Di Paolo M, Neri M, Riezzo I, Fineschi V. Side effects of AAS abuse: an overview. Mini Rev Med Chem. 2011;11:374–89.
11. Hero M, Wickman S, Hanhijärvi R, Siimes MA, Dunkel L. Pubertal upregulation of erythropoiesis in boys is determined primarily by androgen. J Pediatr. 2005;146:245–52.
12. Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. J Clin Endocrinol Metab. 2008;93:914–9.
13. Zitzmann M, Nieschlag E. Androgen receptor gene CAG repeat length and body mass index modulate the safety of long-term intramuscular testosterone undecanoate therapy in hypogonadal men. J Clin Endocrinol Metab. 2007;92:3844–53.
14. Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur J Endocrinol. 2008;15:507–14.
15. Rochira V, Zirilli L, Madeo B, Maffei L, Carani C. Testosterone action on erythropoiesis does not require its aromatization to estrogen: insights from the testosterone and estrogen treatment of two aromatase-deficient men. J Steroid Biochem Mol Biol. 2009;113:189–94.
16. Sakhri S, Gooren LJ. Safety aspects of androgen treatment with 5α-dihydrotestosterone. Andrologia. 2007;39:216–22.
17. Maggio M, Snyder PJ, Ceda GP, Milaneschi Y, Luci M, Cattabiani C, et al. Is the haematopoietic effect of testosterone mediated by erythropoietin? The results of a clinical trial in older men. Andrology. 2013;1:24–8.
18. Bachman E, Travison TG, Basaria S, Davda MN, Guo W, Li M, et al. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. J Gerontol A Biol Sci Med Sci. 2014;69:725–35.
19. Palacios A, Campfield LA, McClure RD, Steiner B, Swerdloff RS. Effect of testosterone enanthate on hematopoiesis in normal men. Fertil Steril. 1983;40:100–4.
20. De Caro L, Ghizzi A. Effect of testosterone on the *in vitro* proliferation of bone marrow granulocyte-macrophage cells (CFU-GM). II. Observations in hypogonadal subjects. Boll Soc Ital Biol Sper. 1989;65:203–10.
21. Ferenchick GS, Hirokawa S, Mammen EF, Schwartz KA. Anabolic-androgenic steroid abuse in weight lifters: evidence for activation of the hemostatic system. Am J Hematol. 1995;49:282–8.
22. Shapiro J, Christiana J, Frishman W. Testosterone and other anabolic steroids as cardiovascular drugs. Am J Ther. 1999;6:167–74.
23. Zitzmann M, Junker R, Kamischke A, Nieschlag E. Contraceptive steroids influence the hemostatic activation state in healthy men. J Androl. 2002;23:503–11.
24. Kahn NN, Sinha AK, Spungen AM, Bauman WA. Effects of oxandrolone, an anabolic steroid, on hemostasis. Am J Hemato. 2006;81:95–100.
25. Alén M. Androgenic steroid effects on liver and red cells. Br J Sports Med. 1985;19:15–20.
26. Nieschlag E, Behre HM, Nieschlag S, editors. Andrology: male reproductive health and dysfunction. 3rd ed. Heidelberg: Springer; 2010. p. 437–55.
27. Clasing D, Müller RK. Dopingkontrolle. Sportverlag Strauß. 2008;5. Auflage.
28. Sjöqvist F, Garle M, Rane A. Use of doping agents, particularly anabolic steroids, in sports and society. Lancet. 2008;371:1872–82.
29. Lippi G, Banfi G. Doping and thrombosis in sports. Semin Thromb Hemost. 2011;37:918–28.
30. Youssef MY, Alqallaf A, Abdella N. Anabolic androgenic steroid-induced cardiomyopathy, stroke and peripheral vascular disease. BMJ Case Rep. 2011;2011. doi:10.1136/bcr.12.2010.3650.
31. Shamloul RM, Aborayah AF, Hashad A, Abd-Allah F. Anabolic steroids abuse-induced cardiomyopathy and ischaemic stroke in a young male patient. BMJ Case Rep. 2014;2014. doi:10.1136/bcr-2013-203033.
32. Schollert PV, Bendixen PM. Dilated cardiomyopathy in a user of anabolic steroids. Ugeskr Laeger. 1993;155:1217–8.
33. Ferrera PC, Putnam DL, Verdile VP. Anabolic steroid use as the possible precipitant of dilated cardiomyopathy. Cardiology. 1997;88:218–20.
34. Vogt AM, Geyer H, Jahn L, Schänzer W, Kübler W. Cardiomyopathy associated with uncontrolled self medication of anabolic steroids. Z Kardiol. 2002;91:357–62.
35. Clark BM, Schofield RS. Dilated cardiomyopathy and acute liver injury associated with combined use of ephedra, gamma-hydroxybutyrate and anabolic steroids. Pharmacotherapy. 2005;25:756–61.

36. Kistler L. Todesfälle bei Anabolikamissbrauch. Todesursache, Befunde und rechtsmedizinische Aspekte. Dissertation zum Erwerb des Doktorgrades der Medizin an der medizinischen Fakultät der Ludwig-Maximilians-Universität zu München. 2006.
37. Stergiopoulos K, Brennan JJ, Mathews R, Setaro JF, Kort S. Anabolic steroids, acute myocardial infarction and polycythemia: a case report and review of the literature. Vasc Health Risk Manag. 2008;4:1475–80.
38. Ahlgrim C, Guglin M. Anabolics and cardiomyopathy in a bodybuilder: case report and literature review. J Card Fail. 2009;15:496–500.
39. Bispo M, Valente A, Maldonado R, Palma R, Glória H, Nóbrega J, et al. Anabolic steroid-induced cardiomyopathy underlying acute liver failure in a young bodybuilder. World J Gastroenterol. 2009;15:2920–2.
40. Fanton L, Belhani D, Vaillant F, Tabib A, Gomez L, Descotes J, et al. Heart lesions associated with anabolic steroid abuse: comparison of post-mortem findings in athletes and norethandrolone-induced lesions in rabbits. Exp Toxicol Pathol. 2009;61:317–23.
41. Montisci M, El Mazloum R, Cecchetto G, Terranova C, Ferrara SD, Thiene G, et al. Anabolic androgenic steroids abuse and cardiac death in athletes: morphological and toxicological findings in four fatal cases. Forensic Sci Int. 2012;217:e13–8.
42. Thiblin I, Mobini-Far H, Frisk M. Sudden unexpected death in a female fitness athlete, with a possible connection to the use of anabolic androgenic steroids (AAS) and ephedrine. Forensic Sci Int. 2009;184:e7–11.
43. Elashoff JD, Jacknow AD, Shain SG, Braunstein GD. Effects of anabolic-androgenic steroids on muscular strength. Ann Intern Med. 1991;115:387–93.
44. Bhasin S, Storer TW, Berman N, Callegari C, Clevenger B, Phillips J, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med. 1996;335:1–7.
45. Bhasin S, Ravi J, Serra C, Singh R, Storer TW, Guo W, Travison TG, Basaria S. Androgen effects on the skeletal muscle. In: Nieschlag E, Behre HM, editors. Testosterone: action, deficiency, substitution. Cambridge University Press; 2012. Pp. 191–206.
46. Yu JG, Bonnerud P, Eriksson A, Stål PS, Tegner Y, Malm C. Effects of long term supplementation of anabolic androgen steroids on human skeletal muscle. PLoS ONE. 2014;9:1–11.
47. Nielsen TL, Hagen C, Wraae K, Bathum L, Larsen R, Brixen K, et al. The impact of the CAG repeat polymorphism of the androgen receptor gene on muscle and adipose tissues in 20-29-year-old Danish men: Odense Androgen Study. Eur J Endocrinol. 2010;162:795–804.
48. Esteban E, Rodon N, Via M, Gonzalez-Perez E, Santamaria J, Dugoujon JM, et al. Androgen receptor CAG and GGC polymorphisms in Mediterraneans: repeat dynamics and population relationships. J Hum Genet. 2006;51:129–36.
49. Ackerman CM, Lowe LP, Lee H, Hayes MG, Dyer AR, Metzger BE, et al. Ethnic variation in allele distribution of the androgen receptor (AR) (CAG)n repeat. J Androl. 2012;33:210–5.
50. Egner IM, Bruusgaard JC, Eftestøl E, Gundersen K. A cellular memory mechanism aids overload hypertrophy in muscle long after an episodic exposure to anabolic steroids. J Physiol. 2013;591:6221–30.
51. Vanderschueren D, Vandenput L, Boonen S, Lindenberg M, Bouillon R, Ohlsson C. Androgens and bone. Endocr Rev. 2004;25:389–425.
52. Vanderschueren D, Sinnesael M, Gielen E, Claessens F, Boonen S. Testosterone and bone. In: Nieschlag E, Behre HM, editors. Testosterone: action, deficiency, substitution. Cambridge University Press; 2012. Pp. 177–99
53. Rolf C, Nieschlag E. Potential adverse effects of long-term testosterone therapy. Bailliere Clin Endocrinol Metab. 1998;12:521–34.
54. Przkora R, Jeschke MG, Barrow RE, Suman OE, Meyer WJ, Finnerty CC, et al. Metabolic and hormonal changes of severely burned children receiving long-term oxandrolone treatment. Ann Surg. 2005;242:384–9.
55. Farkash U, Shabshin N, Pritsch Perry M. Rhabdomyolysis of the deltoid muscle in a bodybuilder using anabolic-androgenic steroids: a case report. J Athl Train. 2009;44:98–100.
56. Hall RC, Hall RC. Abuse of supraphysiologic doses of anabolic steroids. South Med J. 2005;98:550–5.
57. Horn S, Gregory P, Guskiewicz KM. Self-reported anabolic-androgenic steroids use and musculoskeletal injuries: findings from the center for the study of retired athletes health survey of retired NFL players. Am J Phys Med Rehabil. 2009;88:192–200.
58. Schutzel MM, Johnson MH, Rosenthal HG. Bilateral deltoid myositis ossificans in a weightlifter using anabolic steroids. Orthopedics. 2014;37:844–7.
59. Channer KS, Jones TH. Testosterone and cardiovascular disease. In: Nieschlag E, Behre HM, editors. Testosterone: action, deficiency, substitution. Cambridge University Press; 2012. pp 207–34.
60. Corona G, Maseroli E, Rastrelli G, Isidori AM, Sforza A, Mannucci E, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. Expert Opin Drug Saf. 2014;13:1327–51.
61. Morgentaler A, Miner MM, Caliber M, Guay AT, Khera M, Traish AM. Testosterone therapy and cardiovascular risk: advances and controversies. Mayo Clin Proc. 2015;90:224–51.
62. Hartgens F, Rietjens G, Keizer HA, Kuipers H, Wolffenbuttel BH. Effects of androgenic-anabolic steroids on apolipoproteins and lipoprotein (a). Br J Sports Med. 2004;38:253–9.
63. Kindermann W. Kardiovaskuläre Nebenwirkungen von anabolandrogenen Steroiden. Herz. 2006;31:566–73.
64. Bonetti A, Tirelli F, Catapano A, Dazzi D, Dei Cas A, Solito F, et al. Side effects of anabolic androgenic steroids abuse. Int J Sports Med. 2008;29:679–87.
65. Carson P, Hong CJ, Otero-Vinas M, Arsenault EF, Falanga V. Liver enzymes and lipid levels in patients with lipodermatosclerosis and venous ulcers treated with a prototypic anabolic steroid (stanozolol): a prospective, randomized, double-blinded, placebo-controlled trial. Int J Low Extrem Wounds. 2015;14:11–8.
66. Singh AB, Hsia S, Alaupovic P, Sinha-Hikim I, Woodhouse L, Buchanan TA, Shen R, Bross R, Berman N, Bhasin S. The effects of varying doses of T on insulin sensitivity, plasma lipids, apolipoproteins, and C-reactive protein in healthy young men. J Clin Endocrinol Metab. 2002;136–43.
67. Gåverik N, Strahm E, Garlw M, Lundmark J, Ståhle L, Ekström L, et al. Long term perturbation of endocrine parameters and cholesterol metabolism after discontinued abuse of anabolic androgenic steroids. J Steroid Mol Biol. 2011;127:295–300.
68. Achar S, Rostamian A, Narayan SM. Cardiac and metabolic effects of anabolic-androgenic steroid abuse on lipids, blood pressure, left ventricular dimensions, and rhythm. Am J Cardiol. 2010;106:893–901.
69. Urhausen A, Albers T, Kindermann W. Are the cardiac effects of anabolic steroid abuse in strength athletes reversible? Heart. 2004;90:496–501.
70. Sculthorpe N, Grace F, Jones P, Davies B. Evidence of altered cardiac electrophysiology following prolonged androgenic anabolic steroid use. Cardiovasc Toxicol. 2010;10:239–43.
71. Akçakoyun M, Alizade E, Gündoğdu R, Bulut M, Tabakci MM, Açar G, et al. Long-term anabolic androgenic use is associated with increased atrial electromechanical delay in male bodybuilders. Biomed Res Int. 2014;2014:1–8.
72. Alizade E, Avcı A, Fidan S, Tabakçı M, Bulut M, Zehir R, Simsek Z, Evlice M, Arslantaş U, Çakır H, Emiroglu MY, Akçakoyun M. The effect of chronic a nabolic-androgenic steroid use on Tp-E

interval, Tp-E/Qt ratio, and Tp-E/Qtc ratio in male bodybuilders. Ann Noninvasive Electrocardiol. 2015. doi:10.1111/anec.12256.
73. Dickerman RD, Shaller F, McConathy WJ. Left ventricular wall thickening does occur in elite power athletes with or without anabolic steroid use. Cardiology. 1998;90:145–8.
74. Karila TA, Karjalainen JE, Mäntysaari MJ, Viitasalo MT, Seppälä TA. Anabolic androgenic steroids produce dose-dependant increase in left ventricular mass in power athletes, and this effect is potentiated by concomitant use of growth hormone. Int J Sports Med. 2003;24:337–43.
75. Lind JM, Chiu C, Ingles J, Yeates L, Humphries SE, Heather AK, et al. Sex hormone receptor gene variation associated with phenotype in male hypertrophic cardiomyopathy patients. J Mol Cell Cardiol. 2008;45:217–22.
76. De Piccoli B, Giada F, Benettin A, Sartori F, Piccolo E. Anabolic steroid use in body builders: an echocardiographic study of the left ventricle morphology and function. Int J Sports Med. 1991;12:408–12.
77. Di Bello V, Giorgi D, Bianchi M, Bertini A, Caputo MT, Valenti G, Furioso O, Alessandri L, Paterni M, Giusti C. Effects of anabolic-androgenic steroids on weight-lifters' myocardium: an ultrasonic videodensitometric study. Med Sci Sports Exerc. 1999;514–21.
78. Caso P, D'Andrea A, Caso I, Severino S, Calabrò P, Allocca F, et al. The athlete's heart and hypertrophic cardiomyopathy: two conditions which may be misdiagnosed and coexistent. Which parameters should be analysed to distinguish one disease from the other? J Cardiovasc Med (Hagerstown). 2006;7:257–66.
79. Luijkx T, Velthuis BK, Backx FJG, Buckens CFM, Prakken NHJ, Rienks R, et al. Anabolic androgenic steroid use is associated with ventricular dysfunction on cardiac MRI in strength trained athletes. Int J Cardiol. 2013;167:664–8.
80. Baumann S, Jabbour C, Huseynov A, Borggrefe M, Haghi D, Papavassiliu T. Myocardial scar detected by cardiovascular magnetic resonance in a competitive bodybuilder with longstanding abuse of anabolic steroids. Asian J Sports Med. 2014;5, e24058.
81. Nascimento AD, de Lima E, Boëchat G, Meyrelles S, Bissoli N, Lenz D, Endringer D, de Andrade T. Testosterone induces apoptosis in cardiomyocytes by increasing proapoptotic signaling involving tumor necrosis factor-α and renin angiotensin system. Hum Exp Toxicol. 2015. doi:10.1177/0960327115571766.
82. Sondergaard EB, Thune JJ, Gustafsson F. Characteristics and outcome of patients referred for management of advanced heart failure due to anabolic-androgenic steroid abuse. Scand Cardiovasc J. 2014;21:1–11.
83. Franke WW. Dualism in cardiac pathogenesis: illicit use of anabolic-androgenic steroids in a shot-put athlete homozygous for a missense desmoglein-2 (Dsg2) mutation. Cell Tissue Res. 2012;348:335–70.
84. Friedrich FW, Carrier L. Genetics of hypertrophic and dilated cardiomyopathy. Curr Pharm Biotechnol. 2012;13:2467–76.
85. Maisch B, Richter A, Sandmöller A, Porting I, Pankuweit S. Inflammatory dilated cardiomyopathy (DCMI). Herz. 2005;30:535–44.
86. Nieschlag E. Is the use of methyltestosterone obsolete? Dtsch Med Wochenschr. 1981;106:1123–5.
87. El Sherrif Y, Potts JR, Howard MR, Barnardo A, Cairns S, Knisely AS, et al. Hepatotoxicity from anabolic androgenic steroids marketed as dietary supplements: contribution from ATP8B1/ABCB11 mutations? Liver Int. 2013;33:1266–70.
88. Basaria S. Androgen abuse in athletes: detection and consequences. J Clin Endocrinol Metab. 2010;95:1533–43.
89. Robles-Diaz M, Gonzalez-Jimenez A, Medina-Caliz I, Stephens C, García-Cortes M, García-Muñoz B, et al. Distinct phenotype of hepatotoxicity associated with illicit use of anabolic androgenic steroids. Aliment Pharmacol Ther. 2015;41:116–25.
90. Nakao A, Sakagami K, Nakata Y, Komazawa K, Amimoto T, Nakashima K, et al. Multiple hepatic adenomas caused by long-term administration of androgenic steroids for aplastic anemia in association with familial adenomatous polyposis. J Gastoenterol. 2000;35:557–62.
91. Shah NL, Zacharias I, Khettry U, Afdhal N, Gordon FD. Methasteron-associated cholestatic liver injury: clinicopathologic findings in 5 cases. Clin Gastroenterol Hepatol. 2008;6:255–8.
92. Socas L, Zumbado M, Pérez-Luzardo O, Ramos A, Pérez C, Hernández JR, et al. Hepatocellular adenomas associated with anabolic androgenic steroid abuse in bodybuilders: a report of two cases and a review of the literature. Br J Sports Med. 2005;39, e27.
93. Giannitrapani L, Soresi M, La Spada E, Cervello M, D'Alessandro N, Montalto G. Sex hormones and risk of liver tumor. Ann N Y Acad Sci. 2006;1089:228–36.
94. Hardt A, Stippel D, Odenthal M, Hölscher AH, Dienes HP, Drebber U. Development of hepatocellular carcinoma associated with anabolic androgenic steroid abuse in a young bodybuilder: a case report. Case Rep Pathol. 2012;195607. doi:10.1155/2012/195607.
95. Solbach P, Potthoff A, Raatschen HJ, Soudah B, Lehmann U, Schneider A, et al. Testosterone-receptor positive hepatocellular carcinoma in a 29-year old bodybuilder with a history of anabolic androgenic steroid abuse: a case report. BMC Gastroenterol. 2015;15:60. doi:10.1186/s12876-015-0288-0.
96. Johnson CA. Use of androgens in patients with renal failure. Semin Dial. 2000;13:36–9.
97. Luciano RL, Castano E, Moeckel G, Perazella MA. Bile acid nephropathy in a bodybuilder abusing an anabolic androgenic steroid. Am J Kidney Dis. 2014;64:473–6.
98. Rosenfeld GA, Chang A, Poulin M, Kwan P, Yoshida E. Cholestatic jaundice, acute kidney injury and acute pancreatitis secondary to the recreational use of methandrostenolone: a case report. J Med Case Rep. 2011;5:138.
99. Unai S, Miessau J, Karbowski P, Baram M, Cavarocchi NC, Hirose H. Caution for anabolic androgenic steroid use: a case report of multiple organ dysfunction syndrome. Respir Care. 2013;58:e159–63.
100. Deshmukh N, Petroczi A, Barker J, Szekely AD, Hussain I, Naughton DP. Potentially harmful advantage to athletes: a putative connection between UGT2B17 gene deletion polymorphism and renal disorders with prolonged use of anabolic androgenic steroids. Subst Abuse Treat Prev Policy. 2010;5:1–7.
101. Zhu AZ, Cox LS, Ahluwalia JS, Renner CC, Hatsukami DK, Benowitz NL, et al. Genetic and phenotypic variation in UGT2B17, a testosterone-metabolizing enzyme, is associated with BMI in males. Pharmacogenet Genomics. 2015;25:263–9.
102. Parkinson AB, Evans NA. Anabolic androgenic steroids: a survey of 500 users. Med Sci Sports Exerc. 2006;38:644–51.
103. Piacentino D, Kotzalidis GD, Del Casale A, Aromatario MR, Pomara C, Girardi P, et al. Anabolic-androgenic steroid use and psychopathology in athletes. A systematic review. Curr Neuropharmacol. 2015;13:101–21.
104. Pope CG, Pope HG, Menard W, Fay C, Olivardia R, Phillips KA. Clinical features of muscle dysmorphia among males with body dysmorphic disorder. Body Image. 2005;2:395–400.
105. Björk T, Skåberg K, Engström I. Eating disorders and anabolic androgenic steroids in males – similarities and differences in self-image and psychiatric symptoms. Subst Abuse Treat Prev Policy. 2013;8:1–7.
106. Blashill AJ, Safren SA. Sexual orientation and anabolic-androgenic steroids in U.S. adolescent boys. Pediatrics. 2014;133:469–75.

107. Virmani A, Ali SF, Binienda ZK. Neuroprotective strategies in drug abuse-evoked encephalopathy. Ann N Y Acad Sci. 2010;1199:52–68.
108. Pomara C, Neri M, Bello S, Fiore C, Riezzo I, Turillazzi E. Neurotoxicity by synthetic androgen steroids: oxidative stress, apoptosis, and neuropathology: a review. Curr Neuropharmacol. 2015;13:132–45.
109. Lindqvist AS, Moberg T, Eriksson BO, Ehrnborg C, Rosén T, Fahlke C. A retrospective 30-year follow-up study of former Swedish-elite male athletes in power sports with a past anabolic androgenic steroids use: a focus on mental health. Br J Sports Med. 2013;47:965–9.
110. Kanayama G, Brower KJ, Wood RI, Hudson JI, Pope Jr HG. Treatment of anabolic-androgenic steroid dependence: emerging evidence and its implications. Drug Alcohol Depend. 2010;109:6–13.
111. Skarberg K, Nyberg F, Engstrom I. Multisubstance use as a feature of addiction to anabolic-androgenic steroids. Eur Addict Res. 2009;15:99–106.
112. Lundholm L, Frisell T, Lichtenstein P, Långström N. Anabolic androgenic steroids and violent offending: confounding by polysubstance abuse among 10,365 general population men. Addiction. 2015;110:100–8.
113. Thiblin I, Lindquist O, Rajs J. Cause and manner of death among users of anabolic androgenic steroids. J Forensic Sci. 2000;45:16–23.
114. Kersey RD, Elliot DL, Goldberg L, Kanayama G, Leone JE, Pavlovich M, et al. National Athletic Trainers' Association position statement: anabolic-androgenic steroids. J Athl Train. 2012;47:567–88.
115. Thevis M, Kuuranne T, Geyer H, Schänzer W. Annual banned-substance review: analytical approaches in human sports drug testing. Drug Test Anal. 2015;7:1–20.
116. Sottas PE, Vernec A. Current implementation and future of the athlete biological passport. Bioanalysis. 2012;4:1645–52.
117. Pokrywka A, Kaliszewski P, Majorczyk E, Zembroń-Łacny A. Genes in sport and doping. Biol Sport. 2013;30:155–61.