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Steroid Use and Long-Term Health Risks in Former Athletes

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Abstract

This article focuses on anabolic steroid adverse effects on the cardiovascular system and mental health issues as well as the possible increase in the incidence of neoplasms in anabolic steroid users. On the basis of findings in the literature, the authors consider these three issues as the most significant concerning morbidity and mortality among anabolic steroid users. A study by Pärssinen et al. (2000) has shown an increased incidence of premature mortality among power lifters. Anabolic steroids and other concomitantly used drugs are the probable cause of this increased mortality, as power training itself does not increase health risks and all types of physical activity promote health.

Anabolic steroids and testosterone derivatives are effective and well tolerated pharmaceutical agents when administered for proper medical indications such as androgen replacement therapy, osteoporosis, aplastic anaemia and cachexia caused by cancers. Unfortunately, the abuse of anabolic steroids has spread to competitive sports as well as leisure sports. It has been estimated that 2.7 to 2.9% of young American adults have taken anabolic steroids at least once in their lives. One study suggests that the abuse of anabolic androgenic steroids (AAS) has increased 50% since 1991.[1] According to the International Olympic Committee statistics for the year 2000, AAS are the most common group of doping agents.

The anabolic steroids have androgenic, anabolic and anticatabolic effects, and they induce size and strength gain.[2] AAS, especially when used in large doses, interact with multiple receptors including progesterone-, estrogen-, as well as mineralo- and glucocorticosteroid receptors.[3,4] This may explain why they may exert multiple and sometimes unpredictable adverse effects in athletes abusing them (table I).

Generally, the theoretical basis of AAS-induced adverse effects is based on animal studies. In particular, when studying long-term effects, animal studies may be advantageous. Some animal studies have implicated AAS in causing cardiomyopathy. AAS-induced decreases in myocardial compliance[5] and AAS-induced direct toxic effects have been identified in animals.[6] These changes are similar to those observed in the early phase of cardiac failure in humans.[6,7] Both male monkeys and rats treated with testosterone propionate increased dominant behaviour. Rats treated with methyltestosterone displayed increases in aggressive behaviour, whereas rats treated with equivalent doses of stanozolol showed no changes in aggressive behaviour. This may suggest that the psychological effects of AAS in humans might depend upon the different pharmacological agents used.[8] Adult male rats treated with stanozolol showed liver damage[9] and the lifespan of male mice was decreased dramatically by exposing them to AAS for 6 months. Furthermore, the mor-

Table I. Adverse effects associated with the use of anabolic androgenic steroids

Cardiovascular system
Myocardial hypertrophy
QT dispersion
Increased risk of thrombosis
Decreased HDL
Increased LDL
Increased triglycerides
Elevated blood pressure
Risk of myocardial infarction
Risk of sudden death
Behaviour
Increased aggressive behaviour
Depression
Mania, hypomania
Psychotic episodes
Suicides
Dependence
Mood swings
Increased irritability
Euphoria
Cancer
Increased risk of hepatic tumours
Increased risk of malignant tumours
Hormonal system
Testicular atrophy
Impaired spermatogenesis
Transient infertility
Decreased testosterone production
Gynaecomastia
Impotence
Musculoskeletal system
Premature epiphyseal closure
Increased risk of tendon tears
Skin
Acne
Male pattern baldness
Immunological system
Decrease in immunoglobulins
Metabolic system
Altered glucose tolerance
Hyperinsulinism
Effects in women
Altered menstruation
Clitoral enlargement
Hirsutism
Decreased breast size
Alopecia
Deepening of the voice

HDL = high-density lipoprotein; **LDL** = low-density lipoprotein.

tality was increased 4.3-fold compared with control mice.[10]

Several reviews[11-14] have focused on AAS-induced adverse effects. Many of these adverse effects are known to be reversible. The adverse effects on the male reproductive system include decreased testosterone production, testicular atrophy and impaired spermatogenesis, which are the result of induced hypogonadism. In addition, anabolic steroids cause male pattern baldness, altered libido, acne and the development of gynaecomastia, which is the result of the estrogen effect of aromatised anabolic steroids. The orally active anabolic steroids may cause an increase in serum liver enzymes, effects which are caused also by weight lifting alone. With more prolonged use, peliosis hepatis, a cystic haemorrhagic degeneration of the liver, and both benign and malignant tumours of the liver may occur. Transient decreases in the immunoglobulins have been demonstrated, but the exact clinical effects on the immune system are not known. Anabolic steroids induce changes in other hormone levels and endocrinological systems, probably mediated by multiple receptor interactions. These effects seem to be reversible.[11]

This review focuses on the adverse effects of AAS on the cardiovascular system and effects on mental health, as well as on the possible increase in the incidence of neoplasms in AAS abusers. We consider that these three issues are the most significant concerning morbidity and mortality among AAS users. These well known, potentially severe, adverse effects of anabolic steroids on the cardiovascular system and mental health of AAS users are discussed in detail in this article.

1. Pattern of Anabolic Androgenic Steroid (AAS) Use

AAS abusers get instructions on how to use steroids from the unauthorised 'underground' manuals. Steroid administration has special characteristics. Anabolic steroids are usually taken in cycles lasting 6 to 12 weeks. However, there are athletes who use these drugs on a relatively continuous basis. Athletes often take more than one steroid at a time,

which is referred to as stacking. Steroid users 'pyramid' their use of the steroids: they move from low daily doses at the beginning of the cycle to higher doses, and then taper the doses down again toward the end of the cycle. Plateauing (developing a tolerance to a particular steroid) is avoided by staggering the steroids: taking the steroids in an overlapping pattern or stopping taking one steroid and starting another. Athletes use stimulants, diuretics, antiestrogens, human chorionic gonadotropin (hCG), human growth hormone (hGH), antiacne medications and anti-inflammatories to further enhance physical capacity or to counteract the common adverse effects of the steroids.[15]

Dependence on steroids determine the pattern of steroid use as well as the lifestyle of the steroid users. Diet and the exercise schedule are strictly followed. Steroid cycles tend to become longer and to be repeated more frequently over time until some athletes take the steroids almost continuously.

2. Quality of the Studies investigating AAS

Qualitative comparisons of the studies on AAS-induced adverse effects are not straightforward because the study settings vary. With regard to AAS administered in high doses there are only a few placebo-controlled studies which are considered to be reliable and to produce evidence-based information. The limitation of these studies is that ethical regulations often prohibit administering AAS to voluntary participants at such high doses and for such long periods as is used by AAS abusers. The results from these studies may underestimate the true adverse effects of AAS, as dose-response relationships have been confirmed to exist in AAS-induced effects. Furthermore, AAS abusers rarely, if ever, use only one anabolic steroid or other anabolic agent at a time. The purity of the compounds used by AAS abusers is not guaranteed, as the steroids are obtained from the black market.

AAS-induced adverse effects are often studied within naturalistic settings, that is, recruiting AAS abusers without limiting the substances used independently from the study. However, this kind of study setting is exposed to selection bias. As ethical regulations find it dubious to pay compensation for attending the study, the AAS abusers have to be recruited on a voluntary basis. Naturally, because of doping and ethical regulations, the voluntary study participants have to be noncompetitive athletes only. This possibly leads to the selection of individuals with possible pre-existing symptoms or concerns regarding AAS-induced adverse effects. Consequently, results concerning the adverse effects may then be biased. A number of studies[6,8,12,13] have indicated that the mixed use of several anabolic steroids, as well as other drugs, is common among steroid users. This makes it more difficult to interpret the observational studies on AAS use.

Case reports often introduce the most severe and unexpected complications, which have aroused clinicians' or researchers' attention. Such case reports usually fail to avoid the bias that temporal association does not necessarily mean causative connection. Because of this they often exaggerate the problem.

3. The Health of Former Athletes

A population based study of 2613 Finnish male world class athletes (competing during the years 1920 to 1965, before anabolic steroids and other performance-enhancing drugs were widely, if at all, in use) and 1712 healthy male controls confirmed the positive health effects of sports training. Survival curves of the athletes differed significantly from the control group. The highest life-expectancy estimate, 77.9 years, was observed in endurance athletes and the lowest life-expectancy estimate was in the reference group, 69.9 years. Life-expectancy estimates for the weight lifters were practically the same as for the controls, 70.0 years. The total mortality for all athletes was lower than that of the controls, while mortality for the power sport athletes was the same as that of the controls. Decreased cardiovascular mortality in the athletic group largely explained the differences in mortality and life-expectancy estimates. Power sport athletes had an increased risk of death from external causes, decreased risk of cancer mortality and the same risk

of cardiovascular mortality as the controls.[16,17] All athletes had a lower risk for ischaemic heart disease compared with controls. Power sport athletes had a higher risk for high body mass index (BMI) compared with control group. Both athletes and controls with a high BMI and smokers had an increased risk of diabetes mellitus, hypertension and ischaemic heart disease.[18]

Altogether, former athletes were healthier and had lower mortality than the controls. Even though power sport athletes may have a genetic predisposition to cardiovascular morbidity, the genetically increased risk of cardiovascular mortality is compensated by physical activity. Thus, power training itself does not increase health risks and all kinds of physical activity promote health.

4. The Cardiovascular System

4.1 Cardiac Adaptations to Exercise

The cardiovascular adaptations to exercise and physiologic changes in the myocardium differ from pathologic conditions associated with sudden cardiac deaths in athletes.

Isotonic exercise increases the venous return to the heart by repetitive muscle contractions. Greater respiratory ventilation causes reduced intrathoracic pressure, which also enhances ventricular filling and ventricular stroke. Ventricular stroke volume increases. Early ventricular suction caused by catecholamine-mediated ventricular relaxation enhances ventricular filling further, and this is important for maintaining the higher cardiac output during elevated heart rates. Physiologic myocardial hypertrophy occurs as a result of regular isotonic exercise. Left ventricular (LV) cavity size and LV end-diastolic diameter become larger. To maintain the normal tension, the LV wall thickens and thus ventricular mass increases. However, the mass-to-volume ratio remains constant. Physiologic hypertrophy tends to be symmetric.[19]

Isometric conditioning momentarily increases systolic blood pressure up to 200 to 400mm Hg. In response to this pressure load, the ventricular wall thickens. Because the venous return does not change remarkably, there is no increase in LV end-diastolic diameter. Therefore, the mass-to-volume ratio increases. This kind of myocardial hypertrophy has no impact on ventricular compliance. Anabolic steroids do not increase ventricular mass beyond that caused already by isometric training. However, anabolic steroids cause abnormalities in diastolic filling and lead to myocardial stiffness.[19]

After cessation of physical activity, LV wall thickness decreases significantly in 7 to 14 days. There is ~20% decrease in LV mass after 3 weeks of physical inactivity. However, pathologic hypertrophy will remain.[19]

The ECGs of athletes who do not use AAS have demonstrated sinus bradycardia, possibly with pauses greater than 2 seconds, first or second degree atrioventricular blocks and incomplete right bundle branch block. Left ventricular hypertrophy (LVH) criteria (S1 + R5/6 > 35mm) are usually met. ST-segment elevation with narrow T-waves is a criterion for early repolarisation. T-wave inversion is sometimes seen and the QT interval is prolonged. The ST-segment, QT- and T-wave changes should normalise during exercise as vagal tone becomes inhibited.[19]

4.2 Risk of Coronary Heart Disease

The most significant predictor for the incidence of coronary heart disease in both athletes and nonathletes is physical activity. Both genetic selection and continuity of physical activity contribute to low occurrence of coronary heart disease. The prevalence of coronary heart disease in power athletes does not differ significantly from that of nonathletes and is significantly higher than that of endurance athletes, despite the greater physical activity of power athletes compared with nonathletes.[16,18] Here, an influence of genetic factors on the occurrence of coronary heart disease is very probable. Endurance capacity has been related to a predominance of slow twitch muscle fibres whereas fast twitch muscle fibres are related to power and speed capacity. Muscle fibre composition is also associated with many metabolic and cardiovascular variables and thus modifies the risk of coronary heart

disease. Other studies[20-22] have reported that men with a natural ability in power sports at a young age appear to have a higher risk of developing cardiovascular disorders. It is suggested that muscle fibre distribution may explain some of the low occurrence of coronary heart disease and continuity of physical activity.[23]

4.3 AAS-Induced Hypertrophy of the Myocardium

Some case reports and comparative observational studies suggest that AAS would cause LVH and impaired diastolic function. One recently finished study (unpublished observations) showed that AAS promoted the growth of the myocardium dose-dependently and demonstrated LVH during AAS administration. This was potentiated by concomitant use of growth hormone. In some studies[6,24] these effects appeared to be irreversible and to last even after cessation of AAS use. Resistance training increases the thickness of the myocardium independently of AAS use, but as noted before, physiologic hypertrophy does not impair the compliance of the myocardium. It has also been suggested that AAS may cause hypertrophy only as a compensatory result of sustained increases in heart rate and blood pressure, caused by more intensive training. Some studies were again unable to demonstrate any remarkable hypertrophy caused by AAS use.[6,7,24-26]

In a case of sudden cardiac death in a 21-year-old AAS user, LVH and fibrosis of the myocardium were revealed in the autopsy. In this case there was no evidence of atherosclerosis.[6] A report of young men with previous use of high doses of anabolic steroids for many years confirmed the possibility of serious pathological cardiac events.[27]. One weight lifter who used anabolic steroids had LVH and dilatation and fibrosis of the heart but had no complications during the follow-up. Another weight lifter using the steroids had ventricular tachycardia during exercise, which degenerated to ventricular fibrillation and unconsciousness. Dilatation and hypertrophy of the left ventricle, slow coronary flow, 40% ejection fraction and focal fibrosis of the heart were found. After cessation of the use of anabolic steroids, the hypertrophy had reduced slightly. One weight lifter using anabolic steroids had congestive heart failure, LVH and dilatation, myocardial scar formation, diffuse cardiomyopathy and periods of Wenckebach type atrioventricular block. After cessation of the use of anabolic steroids, hypertrophy was reduced.[27]

4.4 QT Dispersion

QT dispersion is defined as the difference between maximal and minimal QT-interval measurements in different leads in a standard 12-lead ECG. A prospective cohort study of 104 patients with severe chronic heart failure (CHF), New York Heart Association classes II to IV, with a LV ejection fraction <35%, examined whether the QT dispersion predicts increased risk of mortality or sudden cardiac death. All the patients experienced CHF secondary to ischaemic heart disease or idiopathic dilated cardiomyopathy. A measurement of QT dispersion >90 msec or QRS dispersion >46 msec identified patients at increased risk of cardiac death. The mortality risk was increased 2.8-fold among heart failure patients whose QT dispersion was >90 msec. In addition, there was a 3.8-fold increased mortality risk and a 4.8-fold increased sudden death risk among patients whose QRS dispersion was >46 msec.[28]

The QT dispersion was also studied in 30 male orienteering runners and male high-ranking long-distance runners, 15 male power athletes using anabolic steroids, and a control group of 15 sedentary men. Endurance athletes had the longest QT intervals and power athletes had the shortest QT intervals in every lead, the differences being highly significant even when the QT intervals were adjusted for heart rate. The duration of the QT interval did not correlate with LV mass in any of the study groups. Power athletes had the greatest amount of QT dispersion, 61 msec, and endurance athletes the least, 49 msec. The study concluded that physiologic adaptive LV hypertrophy does not increase QT dispersion in endurance athletes, although the QT interval is prolonged because of increased vagal tone. However, power training combined with the use of large doses of AAS is associated with increased QT

dispersion, despite short QT intervals. This possibly reflects altered myocardial structure in the pathologically hypertrophied heart and increased risk of malignant arrhythmias.[29] These arrhythmias may be responsible for cases of sudden death in which no direct cause was found.

4.5 Effect of AAS on Lipoprotein Profile

In clinical trials and human case studies, AAS have been shown to cause significant increases in low-density lipoprotein (LDL) and decreases in high-density lipoprotein (HDL) levels. Although these changes are reversible, they increase the AAS user's risk of cardiac disease by 3-fold. The effect on the lipoprotein profile is still somewhat controversial. Most studies have not controlled the diet, exercise or the type and dose of AAS used. The mechanism leading to an abnormal lipoprotein profile is unclear, hepatic triglyceride lipase (HTGL), being the strongest candidate to mediate the changes. *In conclusion*, AAS can reduce HDL levels, but the effect of individual anabolic steroid compounds may vary and there is no direct evidence to support the hypothesis of AAS causing atherosclerosis. Several case reports[6,7,24] have shown an association between acute myocardial infarction and AAS use in young athletes. In some of the cases reported, an abnormal serum lipoprotein profile was found. Some case reports also demonstrated evidence of AAS-associated acute myocardial infarction, without coronary thrombosis or atherosclerosis.

4.6 Effect of AAS on Thrombosis

Depending on the steroid compound, AAS appear to have both anticoagulative and procoagulative activity. AAS stimulate platelet aggregation and therefore predispose individuals to thrombosis. There is also some evidence of AAS altering vascular reactivity and the endothelial nitric oxide dilator system, resulting in coronary artery occlusion, which increases the risk of cardiac insult in AAS users. There are several case reports showing an association between thrombosis and AAS use.[6] A weight lifter receiving AAS had cardiac dilatation, an arterial thrombus in the left leg, large intraventricular thrombi in the right and left ventricles of the heart, hypertrophy and dilatation of the heart, and right bundle branch block. In addition, systemic embolism has been reported in bodybuilders using AAS. Two bodybuilders had large thrombi in the left ventricle of the heart and both also developed embolic occlusions in the arteries of the legs. Both bodybuilders had a history of several years of AAS use.[30]

4.7 Models of AAS-Induced Adverse Cardiovascular Effects

Melchert and Welder[6] have listed some hypothetical models of AAS-induced adverse cardiovascular effects. The first one is the atherogenesis model: AAS use increases HTGL concentrations, which causes a decrease in plasma HDL. This would lead to decreased regression of existing atherosclerotic plaques. The situation is worsened by AAS-induced elevations of plasma LDL concentrations. Little evidence is available on the association between AAS use and thrombosis, in which the most significant effects seem to be mediated by enhanced platelet aggregation. The second model, the coronary artery vasospasm model, would offer an explanation for myocardial infarcts without signs of atherosclerosis or thrombosis. AAS use has been shown to inhibit nitric oxide-mediated vasodilatory responses. It has also been suggested that discrepancy between increased myocardial muscle mass and relative decreases in capillary density would trigger myocardial ischaemia or infarction. The third model, the direct injury model, implies that AAS would cause disruption of normal mitochondrial morphology. This would lead to a decrease in aerobic energy production and ultimately myocardial cell injury. This would then lead to the formation of fibrous scar tissue within the myocardium. Fibrotic areas predispose to potentially fatal ventricular arrhythmias.[6]

4.8 Sudden Death

Several case reports have demonstrated the possible fatal adverse effects of AAS use.[19,28,31-35] The sudden cardiac death of a 23-year-old bodybuilder who used multiple AAS combined with other drugs,

including spironolactone and clenbuterol, shows an association between AAS use and sudden death. The autopsy revealed cardiac hypertrophy, right ventricle dilatation, changes in liver parenchyma, cerebral oedema and acute vascular congestion of the liver, spleen and kidneys. Histological examination showed enlargement of the heart muscle and focal necrosis and interstitial fibrosis of the myocardium. Several fibrinous clots were found in the lungs, liver and kidneys. Multiple small cystic blood-filled pools were scattered throughout the liver parenchyma (peliosis hepatis). Urine drug testing confirmed that the drugs mentioned above had been used, but nothing else.[31]

The incidence of sudden death among athletes is relatively small, ~1 in 200 000 athletes.[32,33] Among athletes <30 years of age, the most common cause of death seems to be hypertrophic cardiomyopathy (24%), followed by congenital coronary artery abnormalities (18%), coronary artery disease (14%) and myocarditis (12%). In hypertrophic cardiomyopathy the myocardium is grossly thickened and the LV cavity is small, whereas in the heart of an athlete who does not use AAS, increased septal and free wall LV wall thickness with cavity enlargement is found. Fatal arrhythmias may be caused by Wolff-Parkinson-White syndrome and long QT syndrome. These conditions may often be diagnosable from the resting ECG. Among athletes >30 years of age, ischaemic coronary heart disease is the predominant cause of sudden death, and is responsible for >75% of all sudden deaths. Among nonathletes, coronary heart disease has a high incidence (21 to 24%) in individuals <30 years, and among those >30 years of age coronary heart disease is the predominant (88%) cause of sudden death. In these cases, exercise-induced symptoms are often present.[32-35]

In athletes using AAS, other factors predisposing to sudden death can also be present. As concluded before, the risk of myocardial infarction is increased. Thrombosis in myocardial arteries, basilar veins or in pulmonary arteries may be the cause of sudden death in athletes using AAS. A grossly dilatated and/or hypertrophied heart is predisposed to fatal ventricular arrhythmias, which of course will lead to sudden death without rapid resuscitation. It is not known whether or not the incidence of sudden death is increased in athletes using AAS, however, several case reports[31,36,37] and clinicians' experience suggest numerous premature deaths in AAS abusers.

5. Mental Health

5.1 Effect of AAS on Aggression and Mood

Serum concentrations of testosterone appear to be positively associated with aggression in humans, especially in response to provocation. Difficulties in defining aggression may affect the interpretation of the data on testosterone levels and aggression.[38] Although changes in hormone concentrations alter the mood, mood may influence the degree and direction of the change in hormone concentration. In one study 95% of AAS users admitted increased hostility and aggression.[8] Indeed, in a number of studies, AAS users self-reported significantly more aggression and hostility than nonusers did.[39] However, psychological or behavioural changes caused by AAS use often fail to be objectively confirmed.[39] The effects may be too subtle or the inventories used may be too insensitive to detect them. One double-blind study[8] revealed significant placebo effects as both the testosterone group and control group scored higher on anger, irritation, impulsivity and frustration.

5.2 AAS-Induced Psychiatric Symptoms

In many of the studies[39] AAS users self-reported significantly more depressive and paranoid thoughts than nonusers. In one study,[8] 70% of the steroid users had paranoid thoughts and 65% had psychotic features during steroid use. In the studies[8] hypomania has been associated with steroid use, and major depression with steroid discontinuation. Mania, hypomania and major depression were the most frequent psychiatric symptoms associated with AAS use. A total of 23% of AAS users were found to express some of these major mood symptoms in association with steroid use in

one study[40] of 88 AAS users and 68 nonusers, diagnosing psychiatric syndromes using the SCID (Structured Clinical Inventory for DSM-III-R). A relationship has been found between the total dose of steroids used and the prevalence of mood disorders.[40] AAS may both relieve and cause depression. Depression may evolve during the use of AAS or as a serious adverse effect after discontinuation of the use of these drugs. Controversy regarding the effects of AAS on mood may be due to different pharmacological agents and different doses being studied.[8,38-40]

One randomised, placebo-controlled crossover trial[41] investigated the adverse psychiatric effects of AAS: 84% of the participants exhibited minimal psychiatric effects, 12% became mildly hypomanic and 4% became markedly hypomanic. In the study,[41] placebo and testosterone cipionate were administered for 6 weeks (in doses increasing to 600 mg/wk) to 56 men aged 20 to 50 years. Several participants described instances of uncharacteristic aggressiveness. Administration of 300 mg/wk of testosterone, or the equivalent, produced few psychiatric effects, and dosages of 500 mg/wk or more produced occasional prominent manic or hypomanic reactions in those individuals not known to be predisposed to psychiatric disorders.[41]

In one prospective double-blind study,[42] major mood disturbances were found after administering nandrolone decanoate 100 or 300 mg/wk and testosterone enanthate 100 or 300 mg/wk for 6 weeks. In another double-blind and placebo-controlled study,[43] significant increases in positive moods (euphoria and sexual arousal) and negative moods (irritability, mood swings, violent feelings and hostility) as well as mania and hypomania were found after administering methyltestosterone 240 mg/day. In one study,[2] in which testosterone enanthate 600 mg/wk was administered for 10 weeks, no mood nor behavioural changes were recorded. This supports the findings in animal studies,[8] that different steroid compounds may have different psychological effects.

Thiblin et al.[44,45] studied eight medicolegally examined suicides of individuals with a history of current or lately discontinued use of AAS. In five cases, depressive symptoms were present after AAS withdrawal, and in four cases, individuals developed depressive symptoms during current prolonged use of AAS. Only one had experienced suicidal ideation before starting to use AAS. Furthermore, 34 deaths of AAS users were medicolegally investigated. Nine out of the 34 were victims of homicide, 11 had committed suicide, 12 deaths were judged as accidental, and two as indeterminate.[44,45]

Several case reports[8,44,45] have described the association between AAS use and violent crimes, such as murders, child abuse, spouse battery, rapes and other forms of violence. One study[8] described a case which related AAS use to the development of psychiatric illness (hallucinations and delusion) and violent crime. Psychotic symptoms improved in this case after cessation of AAS use.

5.3 AAS Dependence

Anabolic steroid dependence was first noted in the medical literature in 1980. Several case reports[44,45] thereafter described power athletes who felt or manifested dependence on AAS. Survey studies[8,44,45] on dependence have found that 14.3 to 57% of anabolic steroid users met the DSM-III-R criteria for dependence. The mechanism of AAS dependence is far from confirmed. It is possible that AAS could produce dependence by primary reinforcement; acting directly in the brain and causing a 'high' or good feeling. Dependence may also develop by secondary, social reinforcement. Both positive and negative reinforcements are encountered. Steroid use is either continued or increased because of consequences the user perceives as positive (muscle growth, euphoria) or the user avoids the consequences perceived as negative (withdrawal symptoms, depression).[15]

A study[44] on dependence and withdrawal effects of anabolic steroids showed that 94% of AAS users reported at least one DSM-III-R symptom of dependence and three or more symptoms were reported by 57% of the users. It was concluded that steroids can be addictive and that very large dosages and dissatisfaction with body size were the

best predictors of dependent use. Both psychological dependence (DSM-III-R symptoms 1 to 6) and physical dependence (DSM-III-R symptoms 7 to 9) were reported with the use of AAS. Withdrawal was the most commonly reported symptom of dependence (84%). There was also a nonsignificant trend for more dependent users to report feeling high on AAS.[46]

One patient using AAS met the DSM-III-R criteria for psychoactive substance dependence. The patient complained of depression and outbursts of anger, and he felt controlled by the steroids. He had fleeting suicidal thoughts. With withdrawal symptoms he felt depressed, low in energy, fatigued and weak, and experienced headaches and missed the high he felt from the steroids. When receiving the steroids, he was disturbed by his temper outbursts over which he lacked control.[47]

6. Risk of Cancer

Anabolic steroids have been proved to be aetiologic factors for some cancers. These agents have been documented as risk factors for hepatocellular carcinoma (HCC)[48] and have also been associated with the development of soft tissue sarcomas.[49]

6.1 Hepatic Tumours

HCC has been known to occur more frequently in males than females. Expression of hepatic androgen receptors is not down-regulated by testosterone over a relatively short follow-up. This may partially explain the preferential development of HCC in males.[50] Elevated serum testosterone levels, together with decreased serum estrogens, may promote the development of HCC.[51]

Moreover, testosterone treatment for medical indications may also cause hepatic tumours. Hepatic adenomas (HA) appeared in a 20-year-old Japanese girl treated for 6 years with anabolic androgens (oxymetholone 30 mg/day) for aplastic anaemia. Several other similar cases can be found in the literature.[52] In a female patient with acromegaly, multiple HA appeared soon after danazol treatment for uterine fibromatosis.[53]

6.2 Prostate Cancer

A longitudinal population-based case-control study[54] studied the possible association between testosterone, sex hormone-binding globulin androstenedione and the incidence of prostate cancer. 16 481 men were followed-up for 24 years, during which time 166 prostate cancer cases were diagnosed. Two controls were selected for each prostate cancer case. Testosterone was not significantly associated with prostate cancer incidence rates. The study[54] found no support for the suggestion that high androgen levels predicted the incidence rate of prostate carcinoma.

Two studies[55,56] found an association between high androgenic hormone levels and increased incidence of prostate cancer. A blinded, case-control study[55] was undertaken to determine if hair patterning was associated with risk of prostate cancer, as well as specific hormonal profiles. There were 159 individuals with prostate cancer and 156 controls. Free testosterone was greater among individuals with prostate cancer than in controls. Conversely, androstanolone (dihydrotestosterone)-related ratios of testosterone were greater among controls. Data suggested that increased levels of free testosterone may be a risk factor for prostate carcinoma.[55] In another study,[56] blood samples were collected from 52 incident cases of histologically confirmed prostate cancer and 52 age- and town-of-residence-matched healthy controls in Athens, Greece. Androstanolone was associated inversely, significantly and strongly with the risk of prostate cancer, whereas testosterone was associated marginally positively with the disease.[56]

6.3 Renal Cell Cancer

Two male bodybuilders using AAS developed clear-cell renal adenocarcinomas. One of the bodybuilders had been using AAS for 6 years and the other for 20 months. Both had an episode of haematuria. An ultrasound revealed tumour masses in both patients. Histological examination confirmed adenocarcinoma for both individuals.[57] A third bodybuilder, a 39-year-old man with a history of ana-

bolic steroid use for 15 years, specifically testosterone propionate (2-week cycles), mixed testosterone esters (16-week cycles with 1-month interval), stanozolol (24-week cycles with 1-month interval) and metenolone (16-week cycles with 1-month interval), had a large symptomatic renal neoplasm with small multiple metastasis in both lungs. An ultrasound and abdominal computerised tomography (CT) showed a large $8 \times 6 \times 7$cm mass arising from the upper pole of the right kidney consistent with renal cell carcinoma. Histological examination confirmed a clear-cell renal adenocarcinoma with sarcomatoid aspects.[58,59]

6.4 Leiomyosarcoma

A 32-year-old man who reported a 5-year history of systematic use of high-dose 4-chloro-1-dehydro-17α-methyltestsˆterone that began at age 18 years and stopped ~9 years before presentation, underwent right radical orchiectomy for a tumour of the right testicle. The tumour was identified as an intratesticular leiomyosarcoma. The rarity of intratesticular leiomyosarcoma, the experimental induction of similar tumours in animals by androgens and estrogens, and the unusually young age at presentation of the patient in the current study support the hypothesis that high dose AAS could have played a cocarcinogenic role in the development of the tumour in this case.[60]

7. Mortality Rates

Adult male laboratory mice were exposed for 6 months to a combination of four AAS at the relative levels to which human athletes and bodybuilders expose themselves. A year after the termination of steroid exposure, 52% of the mice given the high dose of AAS had died compared with 35% of the mice given the low dose of AAS, and only 12% of the control mice. Autopsy revealed tumours in the liver and kidney, other forms of damage in these two organs, broadly invasive lymphosarcomas, heart damage, and usually more than one of these conditions. The lifespan of male mice was decreased dramatically by exposing them to AAS for 6 months and the mortality was increased 4.3-fold compared with control mice.[10]

Interestingly, strikingly similar increases in mortality were found in power lifters who most probably had used multiple anabolic steroids to enhance performance. The mortality of 62 male power lifters placed 1st to 5th in the weight series 82.5 to 125kg in Finnish championships during 1977 to 1982 was compared with the mortality of population controls. The use of anabolic steroids among top-level power lifters during these years was considered to have been widespread as power lifting did not come within doping controls until 1984. The mortality during the 12-year follow-up was 12.9% for the power lifters compared with 3.1% in the control population. By 1993, 8 of 62 power lifters and 34 of 1094 population controls had died, thus the risk of death among the power lifters was 4.6 times higher (95% confidence interval 2.04 to 10.45; $p = 0.0002$). The causes of premature death among the power lifters were suicide,[3] acute myocardial infarction,[3] hepatic coma[1] and non-Hodgin's lymphoma.[1,61] Furthermore, in 12 of the 34 deaths of AAS users that were investigated, medicolegally chronic, possibly lethal cardiac changes were observed.[44,45]

Studies with former athletes suggest that power training in itself does not increase mortality.[16] The similarity in the increased mortality and in the causes of death as well as the findings in autopsies in the previously mentioned studies[2,10,43,59] add to the evidence that anabolic steroids have detrimental long-term effects on health.

8. Conclusion

There is only few studies bringing up any evidence on long-term effects of anabolic steroids. Many of the detrimental effects on health seem to be reversible. The authors conclude that the effects on cardiovascular system, on mental health and the possible increase in incidence of neoplasms cause the most severe consequences of anabolic steroid use. More experimental studies on animals or survey studies on anabolic steroid users should be completed to add the evidence of increasing morbidity

and premature mortality caused by anabolic steroid use. However, on the basis of studies published until today, the authors think that young adults should be advised about the health risks of anabolic steroids.

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