Ankara Ecz. Fak. Derg.
39 (3) 211-236, 2010

J. Fac. Pharm, Ankara
39 (3) 211-236, 2010

Review article

CARDIOTOXIC EFFECTS OF ANABOLIC-ANDROGENIC STEROIDS

GENERAL SPECIFICATIONS OF ALGAE AND THEIR IMPORTANCE ON PHARMACY

Eda EMER[1], Oguzhan YILDIZ[2], Zeliha KAYAALTI[1], Ahmet SAYAL[3]

[1] Ankara University, Institute of Forensic Sciences, 06590,Dikimevi-Ankara, TURKEY

[2] Gülhane Military Medical Academy, Department of Pharmacology, 06018Ankara, TURKEY

[3] Gülhane Military Medical Academy, Center of Pharmaceutical Sciences, 06018 Ankara, TURKEY

ABSTRACT

Anabolic Androjenic streoids (AAS) are synthetic derivatives of testosterone which promote growth of skeletal muscle (anabolic effect) and the development of the male sexual characteristics (androgenic effects). Illegally, these drugs are regulary self-administered by power lifters and bodybuilders to enhance their sportive performance. Abuse of AAS has been linked to a variety of different cardiovascular side effects. In case reports, acute myocardial infarction is the most common event presented, but other adverse side effects include left ventricular hypertrophy, reduced left ventricular contractile function, hypertension, arterial thrombosis, pulmonary embolism, endothelial dysfunction, alterations of lipid metabolism, life-threatening arrytmia and several cases of sudden cardiac death. However, to date, there are no prospective, randomized, interventional studies on the long term cardiovascular effects of abuse of AAS. In this review, we have tried to summarize recent literature and our recent observations in experimental animals related to AAS- induced cardiotoxicity. Additionally we will discuss possible mechanisms of this adverse effect.

Key words: *Anabolic androgenic steroids, Cardiotoxicity, Abuse*

ÖZET

Anabolik androjenik streoidler (AAS) testosteronun sentetik türevleri olup, iskelet kasının büyümesini ve (anabolik etki) erkek seks karakterlerinin gelişmesini (androjenik etki) sağlarlar. İllegal olarak, bu ilaçlar halterciler ve vücut geliştiriciler tarafından sportif performansı artırma amacıyla kullanılmaktadırlar. AAS suistimali birtakım kardiyovasküler yan etkilerle ilişkilidir. Vaka raporlarında, akut miyokard infarktüsü en sık görülen yan etki olarak bildirilse de, sol ventrikül hipertrofisi, azalmış sol ventrikül kontraktil fonksiyonu, hipertansiyon, arteriyel tromboz, pulmoner embolizm, endotel disfonksiyonu, lipid metabolizmasında değişiklikler hayatı tehdit eden aritmiler ve ani kardiyak ölüm gibi yan etkiler de görülebilir. Ancak bugüne kadar AAS suiistimalinin uzun süreli kardiyovasküler etkilerini gösteren prospektif, randomize çalışma yapılmamıştır. Bu derlemede, AAS ile indüklenen kardiyotoksisiteye ilişkin güncel literatürü ve kendi deneysel çalışmalarımızı da özetlemeye çalıştık. Buna ek olarak bu yan etkinin olası mekanizmalarını da tartışacağız.

Anahtar kelimeler: *Anabolik androjenik steroidler, Kardiyotoksisite, Suistimal*

INTRODUCTION

Anabolic androgenic steroids (AAS) were originally developed in the late 1930s and used since 1950s to improve atletic performance, male physical attractiveness and improves body image for both sexes (1). Athletes use AAS to increase strength, lean body mass, and, in some cases, improve physical appearance (2). Accordingly, AAS increase body weight, fat-free mass, muscle size and strength training in healthy men receiving 600 mg of testosterone weekly for 10 weeks (3-5). In the absence of strength training the muscle size is increased by higher doses of AAS (3,4). The life-time prevelance of AAS use among male adolescents typically ranges 1 to 5 % (6)**.** Although the topic is controversial, a consensus is beginning to emerge that chronic AAS abuse may be associated with an increased risk of sudden cardiac deaths, myocardial infarction, altered serum lipoproteins and cardiac hypertrophy (7). However there are no prospective, randomized, interventional studies on the long term cardiovascular effects of abuse of AAS. In this review, we have summarized the relevant literature regarding cardiotoxic effects of AAS together with possible mechnanisms of these adverse effects. Abuse of AAS has been associated with a range of different cardiovascular side effects, starting with a case report of left ventricular hypertrophy in 1986 (8) and one of a myocardial infarction in 1988 (9), affecting a bodybuilder and a weightlifter, respectively, both of them were very young. There was also a report of a young bodybuilder with an ischemic cerebrovascular event and signs of cardiomyopathy in 1988 (10)**.** By 2013, there were around 70 case reports altogether. Acute myocardial infarction in the most common event

presented (11-15). There are also several reports of left ventricular hypertrophy (16-18), reduced ventricle function (19-21), cerebrovascular incidents (10,22,23), atrial fibrillation (24,25), arterial thrombosis (23,26,27), pulmonary embolism (28,29), valve disease (30,31), and several cardiac sudden deaths (18,32-34).

An interesting repeated finding is that there are several cases of myocardial infarction without significant atherosclerotic coronary artery disease (9,13,35). Additionaly, severe premature coronary artery diseases have been observed (14,15,36). A number of animal studies have been conducted over the years to make mechanisms of AAS -induced cardiotoxicity clear. Almost all the studies that looked at cardiovascular consequences of testosterone or its synthetic derivatives show unfavourable effects. Among these findings, myocardial hypertrophy (37-40), reduced ejection fraction (41), increased myocardial stiffness (42), left ventricular remodeling (43), depressed cardiac contractile function (44), impaired exercise-induced microvascular adaptation (45), reduced endothelial function (46), destruction of mitochondria and myofibrils (47,48), myocardial necrosis, interstitial and endocardial fibrosis (49), disruption of morphological integrity of myocardial cells (7) and apoptotic cell death in ventricular myocytes (50) have been reported.

AAS –INDUCED CARDIOTOXICITY

Clinical use, abuse and prevelance of AAS

Hypogonadism (the late puberty and premature termination of adolescent growth, some types of impotance) is the most common indication for AAS therapy in men. At present, The United States Food and Drug Administration (FDA) approved clinical use of AAS for treatment of hypogonadism, anemia accompanying renal and bone marrow failure, endometriosis, cancer and wasting syndrome in human immunodeficiency virus infection (51,52). The other clinical uses of AAS include treatment of catabolic states and cachexia (i.e chronic obstructive pulmonary disease), corticosteroid therapy, osteoporosis, growth stimulation in male puberty, prophylaxis for hereditary angioedema, hepatic disease, female to male transsexualism, hypoplastic anemia, multiple sclerosis, sexual dysfunction and depression.

Unfortunately, approximately 4-6 % of boys and 2 % girls in high school admit to using AAS (53,54). Other estimates suggest that approximately 1 million Americans have used androgen during their lives (55). Testosterone, nandrolone, stanozolol and methandienone are the most frequently abused AAS (56). Abuse of AAS is common among athletes and bodybuilders, which results in side effects. Especially when AAS are used in high doses and in long term. The oral

administration of ASS at doses of 3-5 g per week may cause their blood levels to be more than one hundred times of physiologic ranges (57). In general, AAS are used in combination such as "stacking" (taking two or more AAS together in progressively increasing doses over a short period of time orally or intramuscularly), "pyramiding" (beginning with the low doses of the stacked substances, increasing dose gradually, then decreasing the dose to zero) and cycling (intermittent use of AAS where use of steroids is followed by a drug holiday in order to prevent desensitization to large doses of androgen (58). Abusers believe that pyramiding lets the body clock to adjust to the high doses and the drug- free cycle gives time for the body's hormonal system to recupate. However, there is no evidence on synergism or other benefits of pyramiding or stacking.

AAS were first used by atletes in the mid 1950s, and their use was widespread among bodybuilders by 1960s. The overall incidence of AAS abuse ranges between 1% and 6%. Additionally, others (adolescents) also used sysntetic substances for recreational purposes to increase their sportive performance and to improve their physical appearance (59). The typical AAS abuser is a male who has a poor self-esteem, poor academic performance with high rates of violence and aggression, childhood conduct disorder according to American sources (60).

In general, males abuse AAS 2-3 times more than females (60,61) and approximately 70% of these abusers participate in sportive activities (60). According to American surveys, prevelance of AAS abuse ranges between 4-11% and 2.5% in male and female high school students, respectively (60,61). The prevelance of AAS abuse among British college students ranges between 1-4%. In Sweden, abuse of AAS is reported to be 3.2% in male adolescents (62). In 2002, it was assessed that one year prevelance of AAS abuse was between 0% and 3% among 700 sportsmen and women in popular sports branches such as football, athletics and strenght sports (63). The prevalence is two fold higher among strength trainers. About 4 - 6% of clients of sport and fitness clubs in Netherlands use doping, most prevelant are AAS, growth hormone and insülin. The overall prevelence of doping reported at European countries is approximately 6% , most prevelant are AAS, growth hormone and drugs containing ephedra (64). In Brasil, the prevelance of AAS use is about 11.1 %, most used AAS are nandrolone and stanozolol (65). In brief, interviews of recreational sporters in the USA and several European countries show that 1- 6% have ever used AAS.

Adverse effects of AAS

AAS abuse causes both reversible and irreversible changes due to their distrupting effect on hormone production. However, side effects of AAS develop only during long term use (6). The

most common reversible side effect of AAS are cosmetic in nature. The orally used AAS may cause hepatotoxicity. However there is no report describing hepatotoxicity due to use of parenteral AAS preparations, which appear to damage heart muscles in long term use (66). There are several side effects of AAS use such as; headaches, gastrointestinal irritation, fluid retention in the extremities, diarrhea, stomach pains, oily skin. Additionaly jaundice, menstrual abnormalities, hypertension and infections at injection site may be observed. Acne develops in both sexes at puberty during treatment with AAS due to secretion of the natural oil sebum and growth of sebaceous glands (67). Males using high doses of AAS may have elevated circulating estrogen levels similar to women during a normal menstral cycle. This effect is result of aromatization of testosterone in part to estrogens. Therefore, gynecomastia and breast pain may be observed in men taking high doses of AAS (68).

Chronic adverse effects associated with AAS abuse include acne, urogenital problems, endocrine abnormalities, neuropsychiatric disorders, hepatic and cardiovascular diseases (7). Acne is common adverse effect of AAS use seen in almost 50% of the androgen uses. Acne fulminans and acne conglobata are the most common forms of acne associated with AAS (69). Subjects using AAS should be warned that acne associated with AAS can get worse with vitamin B supplement (69). Gynecomastia and supression of spermatogenesis are frequent consequences of AAS use. High dose of AAS supresses the hypothalamic-pituitary-gonadal axis due to negative feedback and, it may take weeks or months for the axis to recover. Consequently atrophy of the seminiferous tubules during this time may result in subfertility or infertility (70). Furthermore, subjects may continue to encounter symptoms of hypogonadism (erectile dysfunction, low libido and low vitality) even after discontinuation of AAS until the axis recovers. Recent reports suggest that use of clomiphene citrate may hasten the recovery of gonadal axis (71). Reversible urogenital problems include impotence, difficulty or pain in urinating, testicular atrophy and reduced sperm production. Nearly half of male bodybuilders experiences testicular atrophy and gynecomastia (72). Gynecomastia is specifically seen in atletes using aromatizable androgens. In women, AAS use results in menstrual irregularities and decrease in body fat and breast size, hoarse voice, excessive growth of body hair, baldness, clitoral enlargement. Some of these effects may become irreversible due to long term use of AAS. One of the most important association of AAS abuse is prostate cancer (73). Another important concern is premature physeal closure in child which may cause decrease in adult height (74). Use of AAS has been associated with a wide range of psychiatric effects such as; aggression, dysthymia, psychosis, violence and criminal behaviour. Approximately one fourth of AAS users report mood disturbances more frequent than non users (75). Results of a

recent study has shown that men displayed more aggressiveness while receiving supraphysicological doses of testosterone (76,77)**.** Additionally AAS use is also associated with delusions of grandeur, euphoria, criminal behaviour, and acute confusional states (78-80).

Recent studies have also shown that subjects using AAS exhibit dependency on other substances such as alcohol, opioids, benzodiazepines and caffeine (81,82). Various abnormal liver function tests (elevated aminotransferases, alkaline phosphatase, conjugated bilirubin and plasma proteins) are also reported (83,84). Jaundice occasionally occurs as an outcome of hypersensitivity type reaction and is usually seen after 2-5 months of therapy. Additionaly, cholestasis has been reported especially with the use of 17-α-alkylated agents (85). AAS abuse may increase risk of fatal liver cysts and hepatic adenoma (86). Peliosis hepatis has also been seen with the use of 17-α-alkylated agents (87).

In contrast with the anabolic effects of the androgens on bone and muscles, they have a paradoxical effect on tendons and ligaments. Recent reports have shown that atletes using AAS may experience rupture of biceps and quadriceps tendons (88). In a recent study, ultrastructural analysis of tendons in rodents treated with AAS has shown dysplasia of collagen fibrils (89). Further studies need to be done to explore the mechanism by which AAS effect tensile strenght of the tendence.

Cardiotoxic Effects of AAS

Evidence has accumulated over the last several years which associates AAS use with direct effects such as cardiac muscle hypertrophy and myocardial fibrosis, and indirect effects, including myocardial infarction, altered serum lipoproteins, cardiac hypertrophy and even sudden cardiac death in humans who habitually using these drugs (90). Even though some experimental data obtained from animals correlate well with the human findings, the adverse cardiovascular effects of AAS use are poorly understood. In general, human case reports, case series and comparative observational studies often lack control groups and do not account for individual variables (such as genetic predisposition, age, gender and nutritional status), environmental variables (such as streoid type, protein supplementation), exercise variables (such as; mode, intensity, duration, frequency and distribution of training sessions). In addition, animal studies do not account for species-or strain-specific responses to AAS and have difficulty simulating high dose combinations self-administered by athletes. Mortality appears to be significantly higher in AAS abusers than in non abusing atletes. Several post mortem studies suggested cardiac causes in 2/3 of that, while others

being attributed to suicide, hepatic coma and malignancy. As stated above, several types of cardiovascular events are associated with AAS abuse.

Androjen receptors are ubiquitously expressed in not only skeletal muscle cells but also in cardiac myocyctes. AAS are potent ligands of the human androjen receptors in muscles but also directly modulates trancription, translation and enzymatic function of numerous other tissues. Accordingly, long term use of AAS has been reported to be associated with hypertension, dislipidemia, and impaired fasting glucose, as well as alterations in heart structure, including left ventricular hypertrophy and dilation, and impaired contraction and relaxation (91).

AAS, particularly oral preparations, increase the level of low density lipoprotein cholesterol (LDL-cholesterol) and decrease the high density lipoprotein cholesterol (HDL-cholesterol). This effect is reversible and serum levels of lipoproteins return to baseline level within several weeks to months after drug cessation (78). High LDL-and low HDL-cholesterol may increase the risk of atherosclerosis. It has been reported that powerlifters who use AAS have a great risk of atherosclerosis secondary to increased concentrations of LDL cholesterol and decreases concantration of HDL cholesterol (92). In general, steroid hormones alter serum lipoproteins levels via lipolytic degradation of lipoproteins and their removal by receptors through modification of apolipoprotein A-1 and B synthesis. It has been suggested that serum LDL levels may increase through the induction of enzyme hepatic triglyceride lipase and catabolism of very low dansity lipoprotein. Induction of hepatic triglyceride lipase may also catabolize HDL and reduce its serum levels (93). Fortunately, the effect on lipid profile seem to be reversible and may normalize 5 months after discontinuation, since the duration of effect is longer than would be expected from the terminal half-lives of these agents (typically 7 to 12 days) (94). Further studies are needed to explain this effect.

AAS may elevate blood pressure. However, the relation between blood pressure and AAS abuse is controversial. Some studies have reported a link between AAS abuse and elevated blood pressure, whereas other studies have shown no association (95). There is dose-response relationship between blood pressure and AAS abuse and the effects of AAS abuse on blood pressure may persist for long periods. On the other hand, the link betwen AAS abuse and elevated blood pressure is not seen all studies (95). Therefore, additional studies are necessary to definitively reveal a link between AAS and blood pressure.

The abuse of AAS is associated with left ventricular hypertrophy (LVH). However, the interpretation of LVH in athletes who admit to AAS abuse is complex, because the hypertrophy

may be related with increased afterload from isometric exercise. LVH may develop secondary to hypertension or as a direct effect of AAS on the myocardium. Several studies have shown that AAS bind to androgen receptors in isolated human myocyctes and may directly cause hypertrophy, possibly through tissue up-regulation of the renin-angiotensin system (39,96-98). An ultasonic videodensitometric study has shown that textural changes in the myocardium appear before the onset of overt LVH (99). In a retrospective case-control study, AAS users have significantly enlarged interventricular septal wall thickness on echocardiography compared to nonusers and controls, although posterior wall thickness is only slightly larger (100). In contrast, other studies have reported increased LV posterior wall and interventricular septal thickness in AAS abusers compared to nonabusers (101,102). In a recent study, 87 dead males who tested positive for AAS at autopsy have been investigated and significantly higher heart mass has been found among AAS abusers compared to controls (103). However, it is difficult to interpret these results, because a variety of agents and doses are noted in the abusers and most studies do not account for differences in exercise protocols and, most are not blinded (100,104-107). There are a few randomized clinical trials investigating the association between AAS use and LVH with several limitations such as limited number of subjects and lack of control groups. Therefore, there is a need for closely monitored observational echocardiographic study over a long period to compare cardiac morphology between strength atletes and AAS abusers. Although some studies have suggested that LVH may persist for years after cessation of AAS, other studies have reported that LVH may be reversible (108,109). In a very recent study, cardiac magnetic resonance has been performed in 156 male subjects aged 18-40 years consist of three groups: 52 non athletes, 52 strength endurance athletes, and 52 strenght trained athletes. AAS- using strength trained athletes have significantly larger left ventricle and right ventricle wall mass than non-AAS using strength training athletes. Additionally AAS- using strength trained athletes show lower ejection fraction of both ventricules. Linear regression models demonstrated significant effect of AAS use on left ventricular end diastolic volume, left ventricular end diastolic mass and systolic function (110).

In our recent experimental study, we have evaluated effects of high dose subacute (14 days) and subchronic (90 days) testosterone (TES) and dehydroepiandrosterone (DHEA) in rats using echocardiography (111). In our study, 50 male Spraque Dawley albino rats have been randomly assigned to 5 groups of 10 animals each. TES (Sustanon®, containing testosterone propionate, testosterone phenylpropionate, testosterone isocaproate and testosterone decanoate) has been given by intramuscular injection once a week for two weeks at doses of 100mg/ 100 gr (body weight), 30 mg/100 gr and 10 mg/ 100 gr to group I, II and III of animals, respectively. Group IV has received

DHEA at dose of 10 mg/ 100 gr (body weight) by oral gavage daily for two weeks. Group V has served as control and has been given saline once a day by oral gavage or once a week by intramuscular injection, using the same volume as in treated animals. 14 days later, echocardiographic studies have been performed. Left parasternal and left apical echocardiographic images of anaesthetised rats lying in the dorsal recumbency position have been obtained. Our results have indicated that TES increases left ventricule posterior wall thickness at 30 mg/ 100 gr and 100 mg/100 gr doses compared to control group ($p<0.05$). TES has induced slight but not significant increase in ejection fraction and fractional shortening. DHEA has slightly but not significantly increased in left ventricule posterior wall thickness ejection fraction and fractional shortening. Conclusively, sub-acute high dose TES is associated with consistent increase in left ventricular wall, but not chamber, dimensions, indicating hyperthrophy without ventricular dilatation.

There are also some morphological findings indicating cardiotoxicity due to AAS abuse. Post mortem histopathological finding of young AAS abusers include cardiac hypertrophy that seems to be dose- dependent and reversible (112). In addition, several other complications have been described, such as cardiac steatosis, myocardial and endocardial fibrosis, myocardial coagulation necrosis, and coronary atheroma (113). In other studies, endomyocardial biopsy specimens have revealed increased fibrous tissue and fat droplets in the myocardium of AAS abusers (114). Direct cell injury occurs by disruption of myocardial mitochondria and induction of intrafibrillar collagen dysplasia. Cell injury ensures, and scar tissue replaces dead cells, leading to fibrosis and potential for ventricular arrhythmias. Left ventricular hypertrophy and structural changes to the ventricular wall precedes development of hypertension. Incidence of diastolic dysfunction, greater left ventricular posterior wall thickness and greater left ventricular end-diastolic dimensions have also been observed. AAS-induced changes such as cardiomyopathy, cardiomegaly, and diventricular dilatation are reversible after discontinuation of AAS administration. However, it is still not clear whether such detrimental effects are a consequence of hypertension and dysbalance in blood lipids or they are directly associated with action of AAS. Therefore, the interpretation of cardiac hypertrophy in elite athletes who are AAS abusers is complex, because the hypertrophy may relate to increase afterload from isometric exercise. Androgens are capable of mediating a hypertrophic response of cultured adult myocytes (47, 115). Accordingly, a clinical study has suggested that there are some alterations of myocardial textural parameters in weight lifters when analyzed by videodensitometry (99). In experimental animals, morphological and ultrastructural evidence for direct effects of AAS on the heart have been shown

(47,115). For example, methandrostenolone treated rats have more intermediate and disintegrated myofibrils and swollen and elonged mitochondria in ventricular myocardium in transmission electron microscopic study (TEM) (115). Similar changes have been demonsrated in species other than rats. For example, methandrostenolone –treated quinea pig hearts display mitochondrial destruction (47). In spontaneously contracting primary neonatal rat myocardial cell structures, a similar disintegration of mitochondria with TEM after treatment with 100 μM testosterone cypionate has also been reported (116). Several AAS (testosterone cypionate, fluoxymesterone, and stanozolol) on primary myocardial cell cultures derived from neonatal rats has also been observed (117). Additionally, increased release of the cytoplasmic enzyme lactate dehydrogenase (LDH) has been demonstared 4h after treatment with 100 μM testosterone cypionate indicating cytotoxic effect (117). Other studies have shown that specific enzyme systems, ion fluxes, and structurel matrices in the myocardium may also be involved. For example, AAS may stimulate calcium fluxes and membrane transport processes in rat ventricular myocytes via stimulation of ornithine decarboxylase (59). Furthermore, another direct effect of AAS on collagen synthesis and concentration in myocardium has been shown (118). Takala et al., have reported that methandienone has further enhanced exercise -stimulated increase in collagen concantrations in the dog heart.

The first experimental evidence on association between AAS, in particular testosterone, cardiotoxicity and sub-chronic exposure in rabbits has revealed that cardiotoxic effect resulting in heart lesions are similar to those seen in toxic myocarditis (49). In our recent study, we have shown that high dose (100mg/ 100g bodyweight) testosterone for 14 and 90 days induces several mild myocardial lesions such as misshapen nuclei, disorganized myocardial fibers and leukocytic infiltrates in rat hearts (119).

Possible mechanisms of AAS -induced cardiotoxicity

The potential pathophysiological mechanisms responsible for adverse cardiac effects are not clearly understood. Four mechanisms of AAS -induced cardiovascular toxicity have been proposed: atherogenic, thrombotic, vasospastic, and direct myocardial injury (7).

Several investigations have provided insight into the mechanism of atherogenesis and AAS -induced alterations in plasma LDL and HDL concentrations. An association between AAS use and increases in hepatic triglyceride lipase (HTGL), an enzyme that facilitates HDL catabolism, has been reported (120,121). The decrease in plasma HDL concentrations may contribute to a decrease in regression of existing atherosclerotic plaques (122). However, less information is available on

the mechanisms of AAS -induced elevations of plasma LDL concantrations. It has been suggested that the effects of AAS on increasing HTGL activity may also account for the elevation of LDL. Changes in lipoprotein concentrations are associated with atherosclerosis since AAS could cause fatty streaks to occur coronary endothelium which subsequently induces endothelial cell injury which could then enhance platelet aggregation that could also be augmented directly by AAS (123).

Less evidence is available about a positive link AAS use and thrombosis (2,7). AAS are thought to facilitate thrombosis by altering vascular reactivity, enhancing platelet aggregation, and increasing the concentration and activity of particular procoagulant factor proteins (2). Danazol (17-α alkylated AAS) can increase factor IX in hemophilic patients and it also produces an increase in factor VII through the extrinsic blood clotting pathway (124). However, similar changes in factor VII are not seen in body builders who self administrate AAS. AAS may enhance platelet aggregation though increasing production of thromboxane A_2 and /or decreasing platelet production of prostaglandin I_2 (2,7).

An interesting hypotheses for AAS -induced myocardial infarction involves vasospasm in coronary arteries (2,7). Chronic administration of nandrolone to rabbits results in decreased in thoracic aorta vasodilation possibly by inhibiting guanylyl cyclase which stimulates guanosine monophosphate, second messenger of endothelium factor nitric oxide (125). Self- administration of nandrolone in men results in similar effects such as inhibition of vasodilatory response to methacholine and sodium nitroprusside in the brachial artery (126). Additionally, AAS may cause myocardial growth to occur so rapidly that the blood supply is unable to keep up with myocardial oxygen demand (32). It is possible that an increase in myocardial muscle mass with relative decrease in capillary density could promote a hypertrophic myocardial compression of coronary arteries during systole, that could then trigger acute myocardial infarction.

Several studies have also shown that AAS may have direct effects on individual myocardial cells. The heart would be directly influenced by AAS because it expresses androjen receptors. AAS may also have nonandrojen receptor mediated effects that could result in injury. Mitochondria is the most likely target of AAS within individual myocardial cells. Accordingly, disruption of normal mitochondrial morphology secondary to AAS has been reported *in vitro* and *in vivo* (48,115,116). This kind of severe disruption would cause a decrease in aerobic energy production and myocardial cell injury. The resulting replacement of death cells with scar tissue may potentially induce fatal ventricular arrhythmias (127).

Other hypotheses have also been suggested to help explain AAS -induced cardiotoxicity. For example AAS induced red blood cell synthesis by enhancing renal production of erythropoietin. Additionally, AAS may elevate hematocrit and may cause sodium and water retention because of the structural similarity to aldosterone, and the associated increase in blood volume can cause hypertension which contributes to AAS -induced cardiovascular events (128,129).

Oxidative stress and AAS -induced cardiotoxicity

Oxidative stress is the result of imbalance between the production of reactive oxygen species (ROS) and antioxidant defence mechanisms. Cells have a variety of defense mechanisms including low –molecular-weight-antioxidants (ascorbic acid, vitamin E, and glutathione) and antioxidants enzymes such as thioredoxins, superoxide dismutase (SOD), catalase, and glutathione peroxidase (130). ROS are unstable and very reactive by-products of normal metabolism, causing damaging effects on the principal biomolecules (130). As a consequence of these activities, physiological levels of ROS are low. However, with increased levels of ROS, defense systems can be overwhelmed resulting in cellular damage, since AAS usually enhance the metabolic rate (131-133). One could expect that high testosterone levels which is necessary to the production of sexual ornaments, might alter the balance between ROS production and antioxidants defense mechanisms, resulting in an enhanced risk of oxidative stress. Additionally, some testosterone -dependent ornaments are produced by pigments with antioxidant properties (134-136). Testosterone has been shown to generate an oxidative stress in mammalian tissues (137,138). Several other studies have also suggested that testosterone has pro-oxidant properties (139-141).

Accordingly, high testosterone levels produce oxidation in rats and rabbit testicular tissues (137,142,143), rat muscles (137,144), and human placenta (138). On the other hand, antioxidant properties of testosterone has been shown in human prostate (145) and rat nervous system (14). According to our unpublished observations, the levels of antioxidants enzymes (SOD and glutathione peroxidase) were lower and malondealdehide level were higher in rats treated with testosterone for 3 months. These findings together show that pro-oxidant or antioxidant effects of testosterone is tissue- and sex- dependent.

ROS is one of the apoptotic pathways leading to cardiotoxic effect. Cardiac dysfunction due to oxidative stress may be related to mitochondrial dysfunction, uncoupling of oxidative phosphorylation and increased mitochondrial permeability. Accordingly, the ROS on one hand causes disruption of mitochondrial bioenergetics and calcium homeostasis, on the other hand results in membrane lipid peroxidation, mitochondrial DNA damage, activation of mitogen or

stress activated protein kinase (MAPK, SAPK) and uncoupling of the oxidative phosphorylation (147). In brief, one of the primary cellular targets of ROS is DNA. Oxidation of DNA leads to the formation of lesions including oxidized bases, neutral sites, and DNA single- and/ or double-strand breaks. High levels of DNA damage may exceed the cellular repair capacity, generating mutations triggering apoptosis. Oxidative stress can induce radical- mediated damage to cellular biomembranes resulting in lipid peroxidation, which converts unsaturated lipids into polar lipidhydroperoxides. Lipid peroxidation can also lead to the generation of a variety of oxidized products including reactive electrophiles such as, epoxides and aldehydes, which are capable of modifying DNA, protein, and other macromolecules. Examples include malondialdehyde (MDA), acrolein, and isoprostanes, which can be measured as an indirect index of oxidative stress. Additionally, oxidative stress may induce protein damage. Oxidation-sensitive proteins include phosphatases, kinases, transcription factors and metabolic enzymes, so consequently protein oxidation can have a major impact on cellular homeostasis by directly affecting cell signaling, cell structure, and enzymatic processes such as metabolism (148).

CONCLUSION

AAS may increase blood pressure, vascular reactivity by leading endothelial dysfunction. In addition, AAS confer an enhanced prothrombotic state most prominently through activation of thrombocyte activation. AAS may also lead changes in plasma lipids. The most prominent changes are concomitant elevation of LDL and decrease of HDL. Additionally, AAS may also induce arrhythmias and sudden death (149). However, there are no prospective, randomized, interventional studies on the long term cardiovascular effects of abuse of AAS. In addition, the potential pathophysiological mechanisms responsible for adverse cardiac effects are not clearly understood. Taken together, various lines of evidence involving a variety of proposed pathophysiological mechanisms suggest an increased risk for cardiovascular diseases in AAS users.

REFERENCES

1. Hoberman J, Yesalis C.E, The history of synthetic testosterone, Sci Am., 272(2), 76–81, 1995.
2. Sullivan ML, Martinez CM, Gennis P, Gallagher EJ, The cardiac toxicity of anabolic steroids, Prog Cardiovasc Dis, 41, 1–15, 1998.

3. Bhasin S, Storer TW, Berman N, Callegari C, Clevenger B, Phillips J, Bunnell TJ, Tricker, R, Shirazi A, Casaburi R, The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men, N Engl J Med, 335, 1–7, 1996.

4. Forbes GB, The effect of anabolic steroids on lean body mass: the dose response curve, Metabolism, 34, 571–573, 1985.

5. Young NR, Baker HW, Liu G, Seeman E, Body composition and muscle strength in healty men receiving testosterone enanthate for contraception, J Clin Endocrinol Metab, 77, 1028–1032, 1993.

6. Thiblin I, Petersson A, Pharmacoepidemiology of anabolic androgenic steroids: a review, Fundam Clin Pharmacol, 19, 27–44, 2005.

7. Russell B, Melchert RB, Welder AA, Cardiovascular effects of androgenic-anabolic steroids, Med Sci Sports Exerc, 27, 1252–126, 1995.

8. McKillop G, Todd IC, Ballantyne D, Increased left ventricular mass in a bodybuilder using anabolic steroids. Brit J Sports Med, 20, 151–152, 1986.

9. McNutt RA, Ferenchick GS, Kirlin PC, Hamlin NJ, Acute myocardial infarction in a 22-year-old World class weight lifter using anabolic steroids, Am J Cardiol, 62, 164, 1988.

10. Mochizuki RM, Richter KJ, Cardiomyopathy and cerebrovascular accident associated with anabolic-androgenic steroid use, Physician Sports Med, 16, 109–114, 1988.

11. Appleby M, Fisher M, Martin M, Myocardial infarction, hyperkalaemia and ventricular tachycardia in a young male body-builder, Int J Cardiol, 44, 171–174, 1994.

12. Capezzuto A, Achilli A, Serra N, Myocardial infarction in a 21-year-old body builder, Am J Cardiol, 63,1539, 1989.

13. Ferenchick GS, Adelman S, Myocardial infarction associated with anabolic steroid use in a previously healthy 37-year-old weight lifter, Am Heart J, 124, 507–508, 1992.

14. Fisher M, Appleby M, Rittoo D, Cottler L, Myocardial infarction with extensive intracoronary thrombus induced by anabolic steroids, Br J Clin Pract, 50(4), 222–223, 1996.

15. Günes Y, Erbas C, Okuyan E, Babalik E, Gürmen T, Myocardial infarction with intracoronary thrombus induced by anabolic steroids, Anatolian J Cardiol, 4, 357–358, 2004.

16. Dickerman RD, Schaller F, Prather I, McConathy WJ, Sudden cardiac death in a 20-year-old bodybuilder using anabolic steroids, Cardiology, 86, 172–173, 1995.

17. Hausmann R, Hammer S, Betz P, Performance enhancing drugs (doping agents) and sudden death–a case report and review of the literatüre, Int J Legal Med, 111, 261–264, 1998.

18. Kennedy MC, Lawrence C, Anabolic steroid abuse and cardiac death, Med J Aust, 158, 346–348, 1993.

19. Clark BM, Schofield RS, Dilated cardiomyopathy and acute liver injury associated with combined use of ephedra, gamma-hydroxybutyrate, and anabolic steroids, Pharmacotherapy, 25, 756–761, 2005.

20. Ferrera PC, Putnam DL, Verdile VP, Anabolic steroid use as the possible precipitant of dilated cardiomyopathy, Cardiology, 88, 218–220, 1997.

21. Mark PB, Watkins S, Dargie HJ, Cardiomyopathy induced by performance enhancing drugs in a competitive bodybuilder, Heart, 91, 888, 2005.

22. Frankle MA, Eichberg R, Zachariah SB, Anabolic androgenic steroids and a stroke in an athlete: case report, Arch Phys Med Rehabil, 69, 632–633, 1988.

23. Laroche GP, Steroid anabolic drugs and arterial complications in an athlete–a case history, Angiology, 41, 964–969, 1990.

24. Lau DH, Stiles MK, John B, Atrial fibrillation and anabolic steroid abuse, Int J Cardiol,117, e86–e87, 2007.

25. Sullivan ML, Martinez CM, Gallagher EJ, Atrial fibrillation and anabolic steroids, J Emerg Med., 17, 851–857, 1999.

26. Alvarado RG, Liu JY, Zwolak RM, Danazol and limb-threatening arterial thrombosis: Two case reports, J Vasc Surg, 34, 1123–26, 2001.

27. Falkenberg M, Karlsson J, Ortenwall P, Peripheral arterial thrombosis in two young men using anabolic steroids, Eur J Vasc Endovasc Surg, 13,223–226, 1997.

28. Gaede JT, Montine TJ, Massive pulmonary embolus and anabolic steroid abuse, JAMA, 267, 2328–2329, 1992.

29. Liljeqvist S, Hellde´n A, Bergman U, Pulmonary embolism associated with the use of anabolic steroids, Eur J Int Med, 19, 214–215, 2008.

30. Medras M, Tworowska U, Jozkow P, Dumanski A, Dubinski A, Postoperative course and anabolic-androgenic steroid abuse–a case report, Anaesthesia, 60, 81–84, 2005.

31. Stevens QEJ, Dickerman RD, McConathy WJ, Schaller F, Aortic and mitral valve thickening with concentric left ventricular hypertrophy in an elite bodybuilder: a biochemical and/or physiological adaptation?, Cardiology, 98, 159–161, 2002.

32. Luke JL, Farb A, Virmani R, Sample RHB, Sudden cardiac death during exercise in a weight lifter using anabolic androgenic steroids: pathological and toxicological findings, J Forensic Sci, 35, 1441–1447, 1990.

33. Di Paolo M, Agozzino M, Toni C, Luciani AB, Molendini L, Scaglione M, Inzani F, Pasotti M, Buzzi F, Arbustini E, Int J Cardiol, 114 (1), 114–117, 2007.

34. Dickerman RD, Schaller F, Prather I, McConathy WJ, Sudden cardiac death in a 20-year-old bodybuilder using anabolic steroids, Cardiology, 86, 172–173, 1995.

35. Fineschi V, Baroldi G, Monciotti F, Paglicci Reattelli L, Turillazzi E, Anabolic steroid abuse and cardiac sudden death, A pathologic study, Arch Pathol Lab Med, 125, 253–255, 2001.

36. Huie MJ, An acute myocardial infarction occurring in an anabolic steroid user, Med Sci Sports Exerc, 26, 408–413, 1994.

37. Kinson GA, Layberry RA, He´bert B, Influences of anabolic androgens on cardiac growth and metabolism in the rat, Can J Physiol Pharmcol, 69, 1698–1704, 1991.

38. Koenig H, Goldstone A, Lu CY, Testosterone-mediated sexual dimorphism of the rodent heart, Ventricular lysosomes, mitochondria, and cell growth are modulated by androgens, Circ Res, 50(6), 782–787, 1982.

39. Marsh JD, Lehmann MH, Ritchie RH, Gwathmey JK, Green GE, Schiebinger RJ, Androgen receptors mediate hypertrophy in cardiac myocytes, Circulation, 98, 256–261, 1998.

40. Moore LG, McMurtry IF, Reeves JT, Effects of sex hormones on cardiovascular and hematologic responses to chronic hypoxia in rats, Proc Soc Exp Biol Med, 158, 658–662, 1978.

41. Ramo P, Kettunen R, Timisjarvi J, Takala T, Hirvonen L, Anabolic steroids alter the haemodynamic effects of endurance training on the canine left ventricle, Pflu¨gers Arch., 410, 272–278, 1987.

42. Trifunovic B, Norton GR, Duffield MJ, Avraam P, Woodiwiss AJ, An androgenic steroid decreases left ventricular compliance in rats, Am J Physiol, 268, H1096–H1105, 1995.

43. Woodiwiss AJ, Trifunovic B, Philippides M, Norton GR, Effects of an androgenic steroid on exerciseinduced cardiac remodeling in rats, J Appl Physiol, 88, 409–415, 2000.

44. Liang MTC, Paulson DJ, Kopp SJ, Glonek T, Meneses P, Gierke LW, Schwartz FN, Effects of anabolic steroids and endurance exercise on cardiac performance, Int J Sports Med, 14, 324–329, 1993.

45. Tagarakis CV, Bloch W, Hartmann G, Hollmann W, Addicks K, Anabolic steroids impair the exercise-induced growth of the cardiac capillary bed, Int J Sports Med, 21, 412–418, 2000.

46. Cunha TS, Moura MJ, Bernardes CF, Tanno AP, Marcondes FK, Vascular sensitivity to phenylephrine in rats submitted to anaerobic training and nandrolone treatment, Hypertension, 46, 1010–1015**,** 2005.

47. Appell HJ, Heller-Umpfenbach B, Feraudi M, Weicker H, Ultrastructural and morphometric investigations on the effects of training and administration of anabolic steroids on the myocardium of guinea pigs, Int J Sports Med, 4, 268–274, 1983.

48. Behrendt H, Boffin H, Myocardial cell lesions caused by an anabolic hormone, Cell Tiss Res7, 181, 423-426, 1977.

49. Belhani D, Fanton L, Vaillant F, Cardiac Lesions Induced by Testosterone: Protective Effects of Dexrazoxane and Trimetazidine, Cardiovasc Toxicol*.,* 9, 64-69, 2009.

50. Zaugg M, Jamali NZ, Lucchinetti E, Xu W, Alam M, Shafiq SA, Siddiqui MA, Anabolic-androgenic steroids induce apoptotic cell death in adult rat ventricular myocytes, J Cell Physiol, 187, 90–95, 2001.

51. Saseen J, MacLaughlin EJ, Appetite stimulants and anabolic steroid therapy for AIDS wasting, AIDS Read, 9, 398, 401–402, 407, 1999.

52. Basaria S, Wahlstrom JT, Dobs AS, Clinical review 138: Anabolic androgenic steroid therapy in the treatment of chronic diseases, J Clin Endocr Metab, 86, 5108 –5117, 2001.

53. Yesalis CE, Barsukiewicz CK, Kopstein AN, Bahrke MS, Trends in anabolic-androgenic steroid use among adolescents, Arch Pediatr Adolesc Med, 151, 1197–1206, 1997.

54. Buckley WE, Yesalis CE, Friedl KE, Anderson WA, Streit AL, Wright JE, Estimated prevalence of anabolic steroid use among male high school seniors, JAMA, 260, 3441–3445, 1988.

55. Yesalis CE, Kennedy NJ, Kopstein AN, Bahrke MS, Anabolic androgenic steroid use in the United States, JAMA, 270, 1217–1221, 1993.

56. Evans NA, Gym and tonic: a profile of 100 male steroid users, Br J Sports Med, 31, 54–58, 1997.

57. Brower KJ, Eliopulos GA, Blow FC, Catlin DH, Beresford TP, Evidence for physical and psychological dependence on anabolic–androgenic steroids in eight weight lifters, Am J Psychiatry, 147, 510–512, 1990.

58. Basaria S, Androgen Abuse in Athletes: Detection and Consequences. J Clin Endocrinol Metab, 95(4), 1533-1543, 2010.

59. Rashid H, Osmerod S, Day E, Anabolic–androgenic steroids: what the psychiatrist needs to know, Adv Psychiatry Treat, 13, 203–211, 2007.

60. Bahrke MS, Yesalis CE, Kopstein AN, Stephens JA, Risk factors associated with anabolic–androgenic steroid use among adolescents, Sports Med, 29, 397–405, 2000.

61. DuRant RH, Escobedo LG, Heath GW, Anabolic–steroid use, strength training, and multiple drug use among adolescents in the United States, Pediatrics, 96, 23–28, 1995.

62. Nilsson S, Androgenic–anabolic steroid use among male adolescents in Falkenberg, Eur J Clin Pharmacol, 48, 9–11, 1995.

63. Van den Heuvel M, Van Kalmthout J, Van den Houdt F, 2002. Doping in de Breedtesport Een onderzoek naar de aard en omvang van het gebruik van dopinggeduide middelen in de georganiseerde breedtesport, NeCeDo/W.J.H. Mulier Instituut, Amsterdam, 2002.

64. Surmann A, Baberowski HP, Müller-Platz C, Dopingbekämpfung in kommerziell geführten Fitnessstudios. Niedersächsisches Innenministerium, Hannover, 2002.

65. Silva PR, Machado LCJ, Figueiredo VC, Cioffi AP, Prestes MC, Czepielewski MA, Prevalencia do uso de agentes anabolicos em praticantes de musculacao de Porto Alegre. [Prevalence of the use of anabolic agents among strength training apprentices in Porto Alegre, RS], Arq Bras Endocrinol Metabol, 51, 104–110, 2007.

66. Ishak KG, Zimmerman HJ, Hepatotoxic effects of the anabolic/androgenic steroids, Semin Liver Dis, 7, 230–236, 1987.

67. Király CL, Collan Y, Alén M, 1987, Effect of testosterone and anabolic steroids on the size of sebaceous glands in power athletes, Am J Dermatopathol, 9, 515– 519, 1987.

68. Wilson J, Androgen abuse by athletes, Endocr Rev, 9, 181–199, 1988.

69. Melnik B, Jansen T, Grabbe S, Abuse of anabolic-androgenic steroids and bodybuilding acne: an underestimated health problem, J Dtsch Dermatol Ges, 5, 110–117, 2007.

70. Lloyd FH, Powell P, Murdoch AP, Anabolic steroid abuse by body builders and male subfertility, BMJ, 313, 100–101, 1996.

71. Tan RS, Vasudevan D, Use of clomiphene citrate to reverse premature andropause secondary to steroid abuse, Fertil Steril, 79, 203–205, 2003.

72. Wilson JD, Androgens, Goodman and Gilman's The Pharmacological Basis of Therapeutics, Vol. 8. McGraw-Hill Inc, pp1413–1462, 1992.

73. Creagh TM, Rubin A, Evans DJ, Hepatic tumours induced by anabolic steroids in an athlete, J Clin Pathol, 41, 441–443, 1988.

74. Soe KL, Soe M, Gluud C, Liver pathology associated with the use of anabolic–androgenic steroids, Liver, 12, 73–79, 1992.

75. Pope Jr HG, Katz DL, Psychiatric and medical effects of anabolic- androgenic steroid use. A controlled study of 160 athletes, Arch Gen Psychiatry, 51, 375–382, 1994.

76. Kouri EM, Lukas SE, Pope Jr HG, Oliva PS, Increased aggressive responding in male volunteers following the administration of gradually increasing doses of testosterone cypionate, Drug Alcohol Depend, 40, 73–79, 1995.

77. Pope Jr HG, Kouri EM, Hudson JI, Effects of supraphysiologic doses of testosterone on mood and aggression in normal men: a randomized controlled trial, Arch Gen Psychiatry, 57, 133–140, 2000.

78. Hartgens F, Kuipers H, Effects of androgenic-anabolic steroids in athletes, Sports Med, 34, 513- 554, 2004.

79. Klötz F, Garle M, Granath F, Thiblin I, Criminality among individuals testing positive for the presence of anabolic androgenic steroids, Arch Gen Psychiatry, 63, 1274–1279, 2006.

80. Clark AS, Henderson LP, Behavioral and physiological responses to anabolic-androgenic steroids, Neurosci Biobehav Rev, 27,413–436, 2003.

81. McCabe SE, Brower KJ, West BT, Nelson TF, Wechsler H, Trends in non-medical use of anabolic steroids by U.S. college students: results from four national surveys, Drug Alcohol Depend, 90, 243- 251, 2007.

82. Arvary D, Pope Jr HG, Anabolic-androgenic steroids as a gateway to opioid dependence, N Engl J Med, 342, 1532, 2000.

83. Foss GL, Simpson SL, Oral methyltestosterone and jaundice, Br Med J, 1,259–263, 1959.

84. Delorimier AA, Gordan GS, Lowe RC, Carbone JV, Methyltestosterone, related steroids, and liver function, Arch Intern Med, 116, 289–294, 1965.

85. Ishak KG, Hepatic lesions caused by anabolic and contraceptive steroids, Semin Liver Dis, 1, 116–128, 1981.

86. Pais-Costa S, Lima O Soares A, Giant hepatic adenoma associated with anabolic-androjenic steroid abuse: case report, ABCD Arq Bras Cir Dig, 25(3), 180-182, 2012.

87. Søe KL, Søe M, Gluud C, Liver pathology associated with the use of anabolic-androgenic steroids, Liver, 12, 73–79, 1992.

88. Visuri T, Lindholm H, Bilateral distal biceps tendon avulsions with use of anabolic steroids, Med Sci Sports Exerc, 26, 941–944, 1994.

89. Michna H, Tendon injuries induced by exercise and anabolic steroids in experimental mice, Int Orthop, 11,157–162, 1987.

90. Higgins JP, Heshmat A, Higgins CL, Androjen abuse and increased risk, South Med J, 105(12), 670-674, 2012.

91. Klimas J, "Drug- Induced Cardiomypaties" in Cardiomyopathies- From Basic Research to clinical management, Veselka J. (Ed), Intech, Rijeka, Croatia, 2012.

92. Hurley BF, Seals DR, Hagberg JM, Goldberg AC, Ostrove SM, Holloszy JO, Wiest WG, Goldberg AP, High-density-lipoprotein cholesterol in bodybuilders v powerlifters Negative effects of androgen use, JAMA, 252, 507-513, 1984.

93. Glazer G, Atherogenic effects of anabolic steroids on serum lipid levels. A literature review, Arch Intern Med, 151, 1925–1933, 1991.

94. Lenders JW, Demacker PN, Vos JA, Jansen PL, Hoitsma AJ, Van't Laar A, Thien T, Deleterious effects of anabolic steroids on serum lipoproteins, blood pressure, and liver function in amateur bodybuilders, Int J Sports Med, 9, 19 –23, 1988.

95. Achar S, Rostamian A, Cardiac and metabolic effects of anabolic-androjenic steroid abuse on lipids, blood pressure, left ventricular dimensions, and rhythm, Am J Cardiol, 106, 893-901, 2010.

96. Kuhn C, Anabolic steroids, Recent Prog Horm Res, 57, 411– 434, 2002.

97. Liu P, Death AK, Handelsman DJ, Androgens and cardiovascular disease, Endocr Rev, 24, 313–340, 2003.

98. Payne J, Kotwinski PJ, Montgomery HE, Cardiac effects of anabolic steroids, Heart, 90, 473– 475, 2004.

99. 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 Sport Exer, 31, 514–521, 1999.

100. Krieg A, Scharhag J, Albers T, Kindermann W, Urhausen A, Cardiac tissue Doppler in steroid users, Int J Sports Med, 28, 638–643, 2007.

101. Dickerman R, Schaller F, Zachariah NY, McConathy WJ, Left ventricular size and function in elite bodybuilders using anabolic steroids, Clin J Sport Med,7, 90 –93, 1997.

102. Dickerman R, Schaller F, McConathy WJ, Left ventricular wall thickening does occur in elite power athletes with or without anabolic steroid use, Cardiology, 90, 145–148, 1998.

103. Far H, Agren G, Thiblin I, Cardiac hypertrophyin deceased users ofanabolic androgenic steroids: an investigation of autopsy findings, Cardiovascular Pathology, 21, 312-316, 2012.

104. Sader MA, Griffiths KA, McCredie RJ, Handelsman DJ, Celermajer DS, Androgenic anabolic steroids and arterial structure and function in male bodybuilders, J Am Coll Cardiol., 37, 224 –230, 2001.

105. Zuliani U, Bernardini B, Catapano A, Campana M, Cerioli G, Spattini M, Effects of anabolic steroids, testosterone, and HGH on blood lipids and echocardiographic parameteres in body builders, Int J Sports Med,10, 62– 66, 1989.

106. D'Andrea A, Caso P, Salerno G, Scarafile R, De Corato G, Mita C, DiSalvo G, Severino S, Cuomo S, Liccardo B, Esposito N, Calabro R, Left ventricular early myocardial dysfunction after chronic abuse of anabolic androgenic steroids: a Doppler myocardial and strain imaging analysis, Br J Sport Med, 41, 149 –155, 2006.

107. Sachtleben T, Berg KE, Elias BA, Cheatham JP, Felix GL, Hofschire PJ, The effects of anabolic steroids on myocardial structure and cardiovascular fitness, Med Sci Sport Exer, 25, 1240 –1245, 1993.

108. De Piccoli B, Giada F, Benettin A, Sartori F, Piccolo E, Anabolic steroid use in body builders: an echocardiographic study of left ventricle morphology and function, Int J Sports Med, 12, 408–412, 1991.

109. Urhausen A, Albers T, Kindermann W, Are the cardiac effects of anabolic steroid abuse in strength athletes reversible? Heart, 90, 496–501, 2004.

110. Luijkx T, Velthuis B, Backx F, Buckens C, Anabolic androjenic steroid use is associated with ventricular dysfunction on cardiac MRI in strength trained athletes, Int J Cardiol, 167, 664-668, 2013.

111. Emer E, Demirkol S, Yildiz O, Seyrek M, Macit E, Sayal A, Cardiotoxic effect of subacute high dose testosterone and dehydroepiandrosterone administration: An echocardiographic study in rats, Toxicol Lett,221S, 90, 2013.

112. Ahlgrim C, Guglin M, Anabolics and cardiomyopathy in a bodybuilder: case report and literature review, J Card Fail, 15, 496-500, 2009.

113. Figueredo VM, Chemical cardiomyopathies: the negative effects of medications and nonprescribed drugs on the heart, Am J Med, 124, 480-488, 2011.

114. Nieminen MS, Rämö MP, Viitasalo M, Heikkilä P, Karjalainen J, Mäntysaari M, Heikkilä J, Serious cardiovascular side effects of large doses of anabolic steroids in weight lifters, Eur Heart J, 17, 1576-1583, 1996.

115. Behrendt H, Effect of anabolic steroids on rat heart muscle cells. I. Intermediate filaments. Cell Tissue Res, 180, 303-315, 1977.

116. Melchert RB, Herron TJ, Welder AA, Testosterone- induced ultrastructural changes in primary neonatal rat myocardial cell cultures, In Vitro Cell. Dev. Biol, 28, 136A, 1992.

117. Melchert RB, Herron TJ , and Welder AA, The effects of anabolic-androgenic streoids on primary myocardial cell cultures, Med Sci Sports Exerc, 24,206-212, 1992.

118. Takala TES, Ramo P, Kıvıluoma K, Vihko V, Kainulainen H, Kettunen R. Effects of training and anabolic steroids on collagen synthesis in dog heart. Eur J Appl Physiol, 62,1-6, 1991.

119. Melik S, Emer E, Kurt B, Yildiz O, Macit E, Sayal A, Cardiac lesions induced by testosterone in rats, Toxicol Lett, 221S, 89-90, 2013.

120. Friedi KE, Hannan CJ, Jones RE, Plymate SR, High-density lipoprotein cholesterol is not decreased if an aromatizable androgen is administered, Metabolism, 3, 69-74, 1990.

121. Thompson PD, Cullinane EM, Sady SP, Contrasting effects of testosterone and stanozolol on serum lipoprotein levels, JAMA, 261, 1165-1165, 1989.

122. Badimon JJ, Badimon L, Fuster V, Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol- fed rabbit, J Clin Invest, 85, 1234-1241, 1990.

123. Steinberg D, Witztum JL, Lipoproteins and atherogenesis: current concepts, JAMA, 264,3047-3052, 1990.

124. Ferenchick GS, Adelman S, Myocardial infarction associated with anabolic steroid use in a previously healthy 37-year-old weight lifter, Am Heart J, 124 ,507–508, 1992.

125. Ferrer M, Encabo AJ, Marin J, Balfagon G, Chronic treatment with anabolic steroid, nandrolone, inhibits vasodilatory responses in rabbit aorta, Eur J Pharmacol, 252, 223-241, 1994.

126. Green DJ, Cable NT, Rankin JM, Fox C, Taylor RR, Anabolic steroids and vascular responses, Lancet, 342, 863, 1993.

127. Zaim S, Walter PF, Diagnosis and treatment of ventricular tachycardia, Heart Dis Stroke, 1, 141-147, 1992.

128. Al-Habet SMH, Redda KK, Lee HJ, Users and abuses of anabolic steroids by athletes. In: Cocaine, Marijuana, and Designer Drugs: Chemistry, Pharmacology, and Behavior, K.K. Redda, C.A. Walker, and G. Barnett (Eds.). Boca Raton, FL: CRC Press, pp.212-231, 1989

129. Kopera H, The history of anabolic steroids and review of clinical experience with anabolic steroids, Acta Endocrinol Suppl. (Copenh.) 110, 11-18, 1985.

130. Finkel T, Holbrook NJ, Oxidants, oxidative stress and the biology of ageing, Nature, 408, 239–247, 2000

131. Feuerbacher I, Prinzinger R, The effects of the male sex-hormone testosterone on body temperature and energy metabolism in male Japanese quail (Coturnix coturnix japonica), Comp Biochem Physiol, 70A, 247–250, 1981

132. Fryburg DA, Weltman A, Jahn LA, Weltman JY, Samojlik E, Hintz RL, Veldhuis JD, Shortterm modulation of the androgen milieu alters pulsatile, but not exercise- or growth hormone (GH)-releasing hormone stimulated GH secretion in healthy men: impact of gonadal steroid and GH secretory changes on metabolic outcomes, J Clin Endocrinol Metab, 82, 3710–3719, 1997.

133. Buchanan KL, Evans M, Goldsmith AR, Bryant DM, Rowe LV, Testosterone influences basal metabolic rate in male house sparrows: a new cost of dominance signalling? Proc R Soc, B 268, 1337–1344, 2001.

134. Stoehr AM, Hill GE, The effects of elevated testosterone on plumage hue in male house finches, J Avian Bio, 32, 153–158, 2001.

135. Jayasooriya AP, Weisinger RS, Weisinger HS, Mathai ML, Sinclair AJ, Attraction to orange: sexiness, not gluttony, Science, 296, 847-48, 2002.

136. Alvarez F, Sanchez C, Angulo S,The frontal shield of the moorhen: sex differences and relationship with body condition, Ethol Ecol Evol. 17, 135–148, 2005,

137. Chainy GBY, Samantaray S, Samanta L, Testosterone-induced changes in testicular antioxidant system, Andrologia, 29, 343–349, 1997.

138. Zhu XD, Bonet B, Knopp RH, 17 b-estradiol, progesterone, and testosterone inversely modulate lowdensity lipoprotein oxidation and cytotoxicity in cultured placental trophoblast and macrophages, Am J Obstet Gynec, 177, 196–209, 1997.

139. Royle NJ, Surai PF, Hartley IR, Maternally derived androgens and antioxidants in bird eggs: complementary but opposing effects?, Behav Ecol, 12, 381–385, 2001.

140. Gil D, Heim C, Bulmer E, Rocha M, Puerta M, Naguib M, Negative effects of early developmental stress on yolk testosterone levels in a passerine bird, J Exp Biol, 207, 2215–2220, 2004.

141. Rutkowska J, Cichon M, Puerta M, Gil D, Negative effects of elevated testosterone on female fecundity in zebra finches, Horm Behav, 47, 585–591, 2005.

142. Aydilek N, Aksakal M, Karakilcik AZ, Effects of testosterone and vitamin E on the antioxidant system in rabbit testis, Andrologia, 36, 277–281, 2004.

143. Peltola V, Huhtaniemi I, Ketala TM, Ahotupa M, Induction of lipid peroxidation during steroidogenesis in the rat testis, Endocrinology, 137, 105–112, 1996.

144. Pansarasa O, D'Antona G, Gualea MR, Marzani B, Pellegrino MA, Marzatico F, "Oxidative stress": effects of mild endurance training and testosterone treatment on rat gastrocnemius muscle, Eur J Appl Physiol, 87, 550–555, 2002.

145. Tam NNC, Gao Y, Leung YK, Ho SM, Androgenic regulation of oxidative stress in the rat prostate—involvement of NAD(P)H oxidases and antioxidant defense machinery during prostatic involution and regrowth, Am J Pathol, 163, 2513–2522, 2003.

146. Ahlbom E, Prins GS, Ceccatelli S, Testosterone protects cerebellar granule cells from oxidative stressinduced cell death through a receptor mediated mechanism, Brain Res, 892, 255–262, 2001.

147. Simunek T, Sterba M, Popelova O, Adancova M, Hrdina R, Gersl V, Anthracycline-induced cardiotoxicity: overview of studies examining the roles of oxidative stress and free cellular iron, Pharmacol Rep, 61 (1), 154-171, 2009

148. Deavall DG, Martin EA, Horner JM, Roberts R**,** Drug- induced oxidative stress and toxicity, J. Toxicol, 1-13, 2012,

149. Rocha FL, Carmo EC, Roque FR, Hashimoto NY, Rossoni LV, Frimm C, Aneas I, Negrao CE, Krieger JE, Oliveira EM, Anabolic steroids induce cardiac renin-angiotensin system and impair the beneficial effects of aerobic training in rats, Am J Physiol Heart Circ Physiol, 293, H3575–H3583, 2007.

Received = 30.10.2013

Accepted = 10.01.2014