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# Medical consequences of long-term anabolic-androgenic Steroids (AASs) abuses in athletes.

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## Abstract

**Although anabolic-androgenic steroids (AASs) enhance the ability of athletes, but it can cause the destructive effects on athletes' health. In this paper, we reviewed and introduced medical consequences of long-term AASs abuses in athletes and the risks of AASs utilization have been investigated. Some side effects were reduced spermatogenesis, testicular shrinkage in men, menstrual disorders and the development of male characteristics in women, liver toxicity and liver cancer. Some changes such as blood cells counts, hemoglobin, hematocrit, changes in glucose concentration, sex hormones, liver enzymes, changes in the parameters concentration related to iron metabolism, BUN, urea, uric acid, creatinine, LDH have also been observed. The other changes were blood clots, fluid retention, high blood pressure, cardiovascular diseases, changes in lipid profiles, liver toxicity, jaundice, nausea, vomiting, oily hair, persistent bad breath, problem with sleeping, severe acne, feet swelling, trembling, shrinking of the testicles, reduced sperm count and sexual functioning, infertility. In addition, baldness, gynecomastia, risk of prostate cancer, changes in menstrual cycle, enlargement of the clitoris, growth of facial hair, increased sex drive, male pattern baldness in women, and shrinking of the breasts have been observed. Also, behavioural and psychological side effects were identified such as aggressive behaviours, mood swings, getting angry and very irritable over trivial daily incidences, forgetful, distracted, depressive behaviours, hallucinations and delusions. Because the potential benefits were not enough for consumers; therefore, identification and prevention of adverse effects on athletes taking these medications should be warned.**

**Keywords:** Medical consequences, Anabolic-androgenic steroids (AASs) abuses, Athletes.

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## Introduction

The anabolic–androgenic steroids (AASs) are a family of hormones that contain the innate male hormone, testosterone, and a group of synthetic testosterone derivatives. These medicines are widely misused by men and rarely women to increase muscle content and body fat lose. Previous to about 1980, abuse of AAS was limited to a great extent to elite competitive athletes, but AAS abuse has broken out of the athletic association and into the general people. Some AAS users have no particular athletic intakes at all, but simply like to be bigger and more muscular. Some people such as "muscle dysmorphia" become manifest more amenable to abuse AAS. Muscularity of male is more forcefully emphasized and compensated in industrialized Western cultures compare to in Asia, and this difference likely describes the distribution of geographic of AAS abuse [1]. Surprisingly, Middle East and South America are the regions with the highest rate of AAS use but perhaps can be made clear because most studies in these regions based on self-reports from athletes and recreational athletes among whom AAS use have been diagnosed to be extremely widespread [2,3]. In Europe, North America, and Oceania possess higher rates of AAS use compare to Africa and Asia. Perhaps due to the confirmation on "muscularity" as a "masculinity definition" in Western cultures [4-7].

Given that these supplements are sometimes associated both advantages and side effects, this study was conducted for the purpose of evaluating the possible effects and medical consequences of long-term AASs abuses in athletes [1]. Studies found that AAS use was most common between recreational sports people, athletes, prisoners and arrestees, high school students, drug users and non-athletic and was stable with accessible evidence [8-10]. This result was also consistent with evidence suggesting that the odds of AAS use increases by about 91% with participation in at least one sport [11-13]. Unfortunately, ASS effects on genes and consecutive

gene expression are imperfectly understood. Currently, human myostatin has been cloned and is identified to have a negative regulator effect of muscle growth. It was speculated that AAS might operate by influencing myostatin concentration. As well as, all tissues are susceptible to androgen function. No tissues are deprived of androgen receptors, and all androgen receptors distributed all over the body bear similar binding affinity for a special steroid. Studies have not indicated marked discrepancy among AAS in receptor-binding affinity. Juvenile are more delicate to androgen function of AAS for containing a great number of cytosol androgen receptors. Likewise together with the biologically active unbound fraction of testosterone in blood flow, androgen receptor sites are formerly saturated in striated muscles [14].

### *Mood disorders*

AAS bring some significant short-term medical effects, however during the long term may bring suppression of function hypothalamic–pituitary–gonadal pathway. Several psychiatric effects of AAS are mood disorders. These are idiosyncratic, affecting a minority of AAS users, but are often severe. Individuals displaying AAS abuse or dependence may also present other forms of substance dependence [1]. For instance, both humans and animals display a proven AAS withdrawal syndrome due to neuroendocrine and cortical neurotransmitter systems. AAS affiliation may exclusively bring in opioidergic mechanisms. Dependence to AAS is a reliable diagnostic essence, and presumably a great public health difficulty. Dependence to AAS may contribute brain mechanisms by other forms of material dependence, principally dependence to opioid. So, detrimental psychiatric and medical effects of long AAS dependence would presumably not upraise till age 30 or later. Various reports have proposed that dependence to AAS might contribute aspects by opioid dependence in humans. Relation between AAS and opioids would show stable by a few human studies .As a result, why do about 30% of AAS consumers improve from more benignant accidental AAS utilization compare to more chronic and malignant AAS dependence, while 70% do not? Unfortunately, common information of human AAS dependence remains confined actually, probably more restricted compare to any other main form of substance dependence [15].

Some hypotheses are suitable for consideration. Firstly, AAS dependence progression might be accelerate *via* body image disorders such as "muscle dysmorphia" or "reverse anorexia nervosa, "determined not to seem enough muscular. Muscle dysmorphia persons may expand a maladaptive schema of chronic AAS consumption because they often are increasingly discontented with their muscularity despite becoming bigger on AAS [16-27]. Secondary probable hypothesis is that persons with AAS dependence progress are more biologically sensitive to the dysmorphic effects of AAS withdrawal. Thirty is proposed by the obvious overlap of AAS dependence with other forms of material dependence and with manner disorder. Persons with plenty other forms of substance dependence show a cluster of cognitive properties that might be summarized at "risk-taking/decision-making deficits; enhanced impulsivity; and deductions in decision-making such as on gambling tasks performance and other grade of risk-taking. These deficiencies are also related to antisocial or "psychopathic" behaviours, such as conduct disorder [15,28-42]. Studies based on AAS effects in male rats proposed that androgens might cause the brain reward systems sensitivity. Treatment by means of amphetamine-type stimulants previous to and after the androgen administration displays that the AAS may raise brain sensitivity due to an amphetamine induced reward effect [43].

### *Cardiac side effects*

It was proven that having a suitable AAS utilization and diet can enhance in body weight, especially thin body mass and muscle strength gains attained by high severity practice. These effects can be further potentiated, the utilization of supraphysiological amount, but there are no scientific evidences to help their amelioration in the aspect of aerobic power. With respect to side effects of AAS utilization, disorders in cardiovascular system always determined by the non-therapeutic and misapplication of AAS [44,45]. In addition, it is found an enhancement in left ventricular muscle content, hypertrophy of concentric myocardial, disorder of left ventricular diastolic function, hypertension related to arterial, prothrombotic effects, changes in the cholesterol levels concentration, such as reduction in concentration of HDL cholesterol, myocardial infarctions in pertaining to endothelial dysfunction, vasospasms or thrombosis and maybe unexpected cardiac death [45].

Interestingly, healthy young athletes abusing AAS may display high levels of low-density lipoprotein and low levels of high-density lipoprotein. However, information are contradictory, AASs utilization have also been connected with high systolic and diastolic blood pressure and with left ventricular hypertrophy that may insist after AAS suspension. Totally, in small case studies, AAS abuse has been related to acute myocardial infarction and fatal ventricular arrhythmias. As a result, assessment of these detrimental effects may ameliorate the awareness of athletes and enhance attention when considering young athletes with cardiovascular abnormalities [46].

### *Periodontitis*

AAS users possess remarkably higher outbreak of drastic periodontitis. AS well as, AAS users possess greater gingival inflammation and clinical attachment loss of ≥ 3 mm compare to nonusers. AAS use may enhance the risk for severe periodontitis and can causes a subgingival selection of some *Candida* species. *Candida dubliniensis* and *Candida albicans* as periodontopathogens seem to be negatively affected by AAS users. Perhaps, the higher risk for disease promotion in AAS users due to being higher proportions of *Candida* species, *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Porphyromonas intermedia*. Unfortunately, information related to the effect of AAS consumption on subgingival periodontopathogens microbiota and disease

progression is rare. Higher ratios of specific periodontopathogens are acceptable in AAS users. AAS users possess a higher spread of gingival inflammation, drastic periodontitis, and clinical attachment loss. Men who receiving AAS are at main hazard of periodontitis infection related to particular periodontopathogen [47].

Totally AAS nonusers display a lower incidence of the three main periodontopathogens such as *A. actinomycetemcomitans*, *P. intermedia*, and P. *gingivalis* and *Candida* species. AAS consumption enhances severe periodontitis risk and gave rise to select specific subgingival *Candida* species. Some *Candida* species such as *C. albicans* and *C. dubliniensis* were remarkably more widespread in AAS nonusers and *C. guilliermondii* and *C. parapsilosis* were common in AAS users [48-51]. It shows to be widely well accepted that male and female sex hormones can possess an impact on oral tissues, and there is document proposing that sex hormones may stimulate periodontal inflammation by means of modifying the microvascular component of the periodontium. So, the effect of sex steroids on progression of periodontal disease, inflammation, and microbiota combination is arguable yet [47,52-55].

### *Gonadal side effects*

The misapplication of AAS is related to a sustained detention of LH and FSH for several months, even one year. The detention associate importantly, with the 19- norandrosterone (19-NA) metabolite of nandrolone in urine in individuals without co-misusage of narcotics. It was reported in healthy candidates, LH stayed overwhelm overhead of 6 weeks after a dose of 500 mg consumption and maybe tranquillize under lower range of reference limited area for individuals. It is found that AAS has a more significant endocrine effect on the hypothalamic-pituitary-adrenal pathway compare to formerly investigate [56]. Among long-term AAS misusers, AAS-withdrawal hypogonadism becomes to be prevalent, often prolonged, and related to substantial malady. AAS-induced hypogonadism mechanisms are incompletely recognized. It seems presumably that various several mechanisms may be operative in different subsets of persons. Some persons display incomplete gonadotrope function recovery and possess hypogonadotropic hypogonadism. Several information have qualified prosperous recovery of HPT function in AAS users subsequent using of gonadotropin releasing hormone agonists, for example triptorelin, selective estrogen receptor modulators such as clomiphene citrate or agents mimicking pituitary LH and FSH, for example human chorionic gonadotropin or human menopausal gonadotropin [57-61].

However, such strategies are not always successful. Specially, some patients may reacted to clomiphene, however in spite of increased LH and FSH levels, do not normalize testosterone amounts, indicating possibly irreversible detriment to Leydig cells [60,62-63]. Interestingly, still another subset emerges to display continued detriment of sexual tendency and erectile impairment even when levels of normal testosterone are repaired. These cases may possibly demonstrate end organ resistance-reflecting a very likely irreversible down-regulation of androgen receptors or androgen receptor signaling mechanisms [15,64]. Due to the negative feedback in the regulation of the hypothalamic-pituitary-gonadal path, in AASs user men motivate reversible suppression of testicular atrophy, spermatogenesis, infertility, and erectile disorders. Spermatogenesis could not meliorate after AASs misapplication; a pre-existing fertility disorder may have resurfaced. In women, AASs may interrupt ovarian function. Chronic intense physical activity leads to menstrual irregularities and, in severe cases, to the female athletes' triad (such as low energy intake, menstrual disturbance and low bone mass), making it difficult to abandon sports effects and AASs. Acne, hirsutism and deepening of the tone are major outcomes of AASs misapplication. There is no proof that AASs can cause carcinoma of breast [65].

The effect and time profile of different doses of testosterone enanthate on the blood lipid profile and gonadotropins indicate that testosterone has a more profound endocrine effect on the hypothalamic-pituitary-gonadal path compare to be formerly concept. There was no change in 25-hydroxyvitamin D3 levels after testosterone usage compared to baseline levels. The 250 and 500 mg doses enforce reduced concentrations of ApoA1 and HDL, whiles the lowermost dose (125 mg) did not possess any effect on the lipid index. The single doses of testosterone exhibit a dose-dependent enhancement in serum testosterone levels together with detention of s-LH and s-FSH. Changes in ApoA1 and HDL levels have been seen after consumption of the two highest single doses [66]. AAS is generally related to transient or persistent impairment on male reproductive action, *via* several pathways. A further review concerning fertility consequences between male AAS abusers is reported too, containing the classic reportages on transient anabolic steroid-induced hypogonadism (ASIH), and the more current experimental reports on constructional and genetic sperm detriment [67].

### *Liver toxicity*

Chronically, the utilization of AAS at high dose is related to liver toxicity, sexual disorders [68]. Recreational AAS users show a wide range of liver damages that contain fatty liver and liver neoplasm, hepatotoxicity, elevated liver enzyme levels, and hepatic steatosis. As well as, they exhibit risk factors for liver diseases such as alcohol usage and hepatitis B and C virus infection [69]. It was reported that use of AAS remarkably enhanced hepatic aminotransferases serum concentrations, albeit measurements stayed within normal range. As a result, high-dose AAS consumption gave mild impairment in liver function. However, AAS do not cause irreversible detriment to liver function. According to former reports indicate that AAS utilization motivate hepatic dysfunction are based on high serum aminotransferase concentrations. Cholestatic jaundice is due to utilization of 17α alkylated AAS, not to structurally distinct steroids. By contrast, peliosis hepatitis or dilated hepatic venous sinuses is not associated to C17-alkylating, however determining with administration of testosterone.

It was proven that AAS is as a risk factor for hepatocellular carcinoma altogether with viral hepatitis, alcohol consumption and several genetic factors. The utilization of 17α-alkylated AAS has also been attributed to cause diffuse hyperplasia, benign hepatic neoplasias, focal nodular hyperplasia and nodular regenerative hyperplasia. On the other words, a rare androgen-specific form of a hepatic tumors can be identified in man that emerges to operate more like a benign hepatocellular adenoma. These androgen-associated tumors possess an affiliation to return after androgen remedy has stopped. Hepatocellular carcinoma is related to long-term AAS treatment. On the other words, the malignant character of AAS-induced hepatocellular carcinoma is suspicious whereas reversion happens in the majority of cases after AAS utilization withdrawal. AAS have also been related to soft tissue sarcomas expansion. So long as obvious persuasive document of AAS mutagenicity is still lacking, they do at least have tumor growth-promoting activity [14].

### *Biochemical and hematological parameters*

Some studies were proven the relationship among dietary supplement and biochemical and hematological parameters was significant and some of these parameters including creatinine, blood aspartate aminotransferase (AST), alanine aminotransferase (ALT), and red blood cell distribution (RDW) have a significant role than others. Even in a multivariate regression model, it is found that WBC, platelets, blood urea nitrogen (BUN), creatinine, AST, and ALT were higher in athletes compare to in controls [70]. Also bile acid nephropathy is an entity that may be observed in severe cholestatic liver disease patients. It is occurred a kind of acute kidney injury (AKI) due to bile acid nephropathy in a bodybuilder who developed severe cholestatic liver disease during anabolic androgenic steroid use [71].

It is demonstrated AAS users present a decrease in HDL cholesterol concentration, enhanced inflammatory markers, and oxidative stress. Also, it has been reported that fortified document related to AAS use with blood pressure at hypertensive levels. Both epidemiological and autopsy studies testify the connection among AAS use and early mortality [72]. Another effect observed in AAS abusers was the retention of urea, creatinine and uric acid in blood, which are typical values found in individuals with renal dysfunctions. The clinical relevance of these elevated renal biomarkers remains unclear. Urea production is increased when a greater number of amino acids are metabolized in the liver [73,74]. The high levels of amino acids found in these individuals are associated with the high consumption of proteins and/or dietary supplements. The creatinine levels in combination with weight and age parameters are used to estimate the glomerular filtration rate (GRF). The determination of GFR must be assessed to detect and to evaluate a chronic kidney disease (CKD) [75-77].

However as high protein diet increases the creatinine levels, and consequently the GFR levels, these individuals should further investigate the possibility of having some renal malfunction [73]. Hematocrit and mean corpuscular hemoglobin concentration (MCHC) levels were statistically higher in abusers compare to in non-users, at 5% of significance ($p<0.0001$). The MCV values were higher for abusers group but without a statistically significance variation in relation to non-abusers group ($p>0.005$). Abusers presented higher testosterone levels in relation to non-users with distinct inter-individual variations in abusers. The average levels of total testosterone of the users showed an increase of 20-60% compared to reference values. The measure sodium and potassium in serum did not show any significant differences between both groups. Our results show that the consumption of AAS, DS and drugs of abuse induced hematological alterations, including erythrocytosis. The higher values of red blood counts (erythropoiesis) observed in the abusers group in comparison with the non-users group can be associated with steroids use. Similar findings were reported after the administration in rats with 200 mg of testosterone per week with correlated increments in hematocrit levels Another effect observed in AAS abusers was the retention of urea, creatinine and uric acid in blood, reaching values of up to 60.6; 1.9; and 7.5 mg/dL, respectively, which are typical values found in individuals with renal dysfunctions. The clinical relevance of these elevated renal biomarkers remains unclear. Urea production is increased when a greater number of amino acids are metabolized in the liver. The high levels of amino acids found in these individuals are associated with the high consumption of proteins and/or dietary supplements [44,73,74].

### *Cutaneous microbial*

AAS abuse might enhances the skin lipids and increases the cutaneous microbial propagation. It was attended the potential side effects of AAS on the bacterial normal flora colonization of the bodybuilders` skin. The skin lesions were more frequent in the body builders compare to the controls. The spread of bacteria such as *Staphylococcus aureus* and *Propionibacterium acnes* in the athletes were higher compare to non-AAS user athletes. In addition, there was a considerable difference in distribution of P. acnes between the bodybuilders who used AAS and non-user AAS. A higher number of bacterial flora was found in the bodybuilders exclusively those using AAS in comparison to the controls, which might be pertaining to the influence of these AAS on the skin normal flora and bacterial transmission *via* the direct contact of the naked skin with the exercise devices [78].

Utilizing performance enhancing drugs has dramatically increased among the young athletes to rebuild body mass and strength, increase delivery of oxygen to muscles and treat pain without any concern about their serious side effects. On the other hand, all adverse effects of these drugs are not clearly investigated [79-81]. The occurrence of the cutaneous striae, oily skin, alopecia and male patter hair loss is commonly reported as a result of AAS abuse in athletes. In addition, the frequency of acnes in AAS users was 40%-54%. The current study reported statistically significant higher skin lesions in AAS abusers compared to the others [79,80,82-84]. Previously, it was indicated that methyl testosterone and its metabolites

may enhance the bacterial proliferation and their enzymatic activities [85]. In another study, Kiraly showed that mild acne induced following eight weeks of self-administration of high dose testosterone and anabolic steroids. Kiraly also found that high doses of testosterone and AAS may increase the skin surface lipids which in turn may provide a suitable condition for the growth of *P. acnes* [83].

On the other hand, supra-physiologic doses of AAS may or can affect the immune system. Several common AAS alter the immune reaction by adversely influencing lymphocyte differentiation and proliferation, antibody production, natural killer cytotoxic activity and the production of certain cytokines, and thereby enhancing bacterial proliferation [86-88]. The higher colonization of *S. aureus* in the athletes in comparison with the controls may be caused by the bacterial transient skin flora passing through the exposure of bare skin to the exercise instruments. A significant association was previously reported by Singh et al. between high colonization of *S. aureus* and the possibility of the skin infection. Therefore, as shown previously, the high number of colonies (>50) isolated in about one third of the bodybuilders may predispose them to skin infections [88-90].

### *Atherothrombotic markers*

The utilization of AAS may be related to alter in atherothrombotic markers and function of endothelial cell. AAS users generally possess higher body mass and blood pressure. Platelet count is higher whilst HDL-cholesterol was lower in AAS users contrasted to non-users. Amounts of high sensitive CRP (hs-CRP) were superior in AAS users. Compared with non-users, flow-mediated dilation is remarkably decreased in AAS users, whiles endothelium-independent function resembles in both groups. Besides, flow-mediated dilation is positively related to HDL-cholesterol levels. AAS users show significant changes in blood lipids in addition to in inflammatory markers, which are becoming with enhanced cardiovascular hazard. Moreover, this profile is accompanied by a decline in the endothelial function [91].

Weight was substantially greater among AAS users. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were both increased in AAS users. Hematocrit, hemoglobin, white blood count (WBC) and fibrinogen were not different between the groups. An increased platelet count was found in AAS users as well as an increase in hs-CRP. Stanozolol and nortestosterone (nandrolone) were the most commonly used substances. Flow-mediated dilation (FMD) was significantly reduced in AAS users compared with controls. On the other hand, groups did not differ regarding endothelium-independent vasodilation (EID). There was a significant and positive association between HDL-cholesterol and FMD. AAS-user athletes present reduced endothelial function, as indicated by FMD, compared with non-user athletes. In addition, AAS users also have important changes in atherothrombotic risk markers, such as elevated resting blood pressure, higher platelet count and hs-CRP levels accompanied by lower HDL-cholesterol levels. A relevant issue regarding steroid use/abuse is related to its impact on BP. Even though some studies failed to detect increased BP in AAS users, an elevation of either systolic or diastolic blood pressure has been described. Androgens usually cause sodium [92-94].

## Results and Discussion

The universal lifetime outbreak of AASs abuse is 6.4% for males and 1.6% for women. Many AASs, often take from the internet and suspicious origins, have not undergone appropriate testing and are consumed at extraordinarily high doses and in inconsequent combinations, as well as along with other drugs. Controlled clinical trials survey undesired side effects are missing because ethical limitations exclude exposing candidates to potentially toxic regimens, adumbrating a causal relation among AASs abuse and conceivable consequences. Unfortunately, AAS users seldom seek remedy, but this condition may alternate as the first large wave of illicit AAS users now reaches middle age and becomes the risk age for long-term cardiac, neuroendocrine, and psychiatric disorders from these drugs [1].

AAS abusers showed remarkably less plasma testosterone levels and higher frequencies of symptoms indicative of hypogonadism compare to healthy control group years subsequently AAS cessation. The key findings of this study were that AAS abusers represented notably lower free testosterone and plasma total, smaller testicular measurements, and featured a higher proportion of participants with depressive indications, fatigue, erectile dysfunction and reduced lipid profile compare to the control group more than two years after AAS cessation. These outcomes demonstrate that a remarkable proportion of AAS abusers displayed AAS-induced hypogonadism such as biochemical and functional hypogonadism, years afterward AAS cessation [64]. With respect to side effects of AAS usage, disorders in cardiovascular system, reproductive system, liver, pathological effects, endocrine dysfunction, and psychological aspects and behavioural changes, changes in the cholesterol levels, myocardial infarctions related to endothelial disorders, vasospasms or thrombosis and maybe also unexpected cardiac death have been observed in AAS user athletes [45,47]. It has been proven periodontal microbiological differences among systemically healthy non-smoker males obtaining AASs and non-AAS users and there were relationships among disease severity and use of AAS. It was established a repeated co-abuse of AAS and narcotics between youth taken into detention in order to criminal activity [48,56].

AAS are pertaining to offensive behaviours in men; however the underlying individuality traits of AAS abusers and attendant alcohol consumption may confuse this correlation. So, the risk of AAS consumption for the liver may be greater compare to the esthetic benefits, and illustrate the emphasis of AAS users screening for liver hurt [68,69]. It is strongly advised that there should be some concerns about possible supplement-induced changes in the laboratory exams for bodybuilders [70]. AAS abuse might enhance the skin lipids and increase the cutaneous microbial propagation. In addition,

statistically considerable differences were also observed in skin lesions between the AAS users and the non-AAS user athletes [78]. Detecting AASs misapplication *via* the control network of the World Anti-Doping Agency (WADA) not only helps to assurance fair situation for athletes, but also to support them from medical consequence of AASs misapplication. Several situations may be pertaining to male infertility such as AAS consumption, too [94]. It is conceivable that long-time misapplication of AAS will conduct to change in vitamin D situation [56].

We conclude increased information and understanding of side-effects due to AAS consumption is significant in order to discover measures for remedy and surveillance of these abusers. Because the potential benefits are not enough for consumers therefore, identification and prevention adverse effects on athletes taking these medications should be warned.

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