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Risks of Using Anabolic Androgenic Steroids (AAS) as Performance-Enhancing Drugs

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Abstract: In sports, using performance-enhancing drugs (PEDs) has become pervasive, and a serious problem is known as "doping". The use of PEDs refers to the manipulation of synthetic or endogenous substances with the intent of altering athletic performance. Overall, these drugs were recognized as potent image-enhancing drugs. The primary objective of the majority of substance abusers is to enhance their physical appearance. Common performance-enhancing drugs include anabolic-androgenic steroids (AAS), creatine, erythropoietin, beta-hydroxybeta-methylbutyrate, human growth hormone, amphetamines, diuretics, and other masking substances. AASs are constantly expanding class of synthetic androgens that are used both legally and illegally. The abuse of AASs has increased significantly. Numerous illegally available AAS substances are prescribed to treat medical conditions associated with low testosterone levels. AAS attracted great public health concern because of their negative effects on all organs, tissues, and bodily processes. AAS long-term toxicity affects the cardiovascular system and the reproductive system. The purpose of this article is to provide an overview of the most common PEDs and their potential repercussions on health.

Key words: Health · Athletics · Abuse · Ped · AAS

INTRODUCTION

Atheletic sports use various substances to gain an advantage in competition, and these substances are called Performance-enhancing drugs (PEDs) [1]. The use of PEDs, also known as "doping," has become a pervasive and serious problem in sports and health. PEDs include any synthetic or autologous substance that is used or manipulated to improve athletic performance [2], and these substances are used in attempts to enhance both physical performance and appearance [3]. Since the beginning of competitive sports, the idea of PEDs has been around. Ancient Greek Olympians and Roman gladiators both used certain wines, herbal teas, and mushrooms to help them enhance performance [4]. PEDs have evolved since then in response to advances in pharmaceutics [5]. The Tour de France was ruined in 1998 by a massive doping scandal, which prompted the establishment of the World Anti-Doping Agency (WADA), which is a hybrid organization with both public and private members, and its original goal was to "promote and coordinate the international fight against doping in sports"[6], and it is in charge of keeping a Prohibited List of substances and methods that athletes are not allowed to use [7]. For more than two decades, (WADA) has been the primary organization in charge of creating and coordinating anti-doping policies for international sports [8].

Any substance or method is deemed to be on the Prohibited List if it satisfies any two of the following three conditions:

1. The substance or procedure has the potential to increase or enhance sports performance, either alone

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or in conjunction with other substances or methods, according to medical or other scientific evidence, pharmacological effect, or experience.
2. Supported by pharmacological results, medical or other scientific evidence, or experience, the substance or method poses a real or prospective risk to the athlete's health.
3. In the World Anti-Doping Code's introduction, WADA's determination that the use of the substance or method violates the spirit of sport is described [9].

PEDs are often used by children and teens who want to improve their athletic skills. In turn, the use of all PEDs tends to rise with age during adolescence and is higher among athletes than among non-athletes [3]. Amphetamines and other stimulants, androgenic-anabolic steroids, synthetic peptide hormones (growth hormone releasers), beta 2 agonists, narcotics, and diuretics (masking agents) are all prohibited in and out of competition, according to the World Anti-Doping Agency's (WADA) most recent update for 2021[5].

When PEDs are used or abused, they can have several bad effects, which vary depending on the drug [10].

Athletes often use PEDs like anabolic-androgenic steroids (AAS), human growth hormone (hGH), creatine, erythropoietin (EPO), blood doping, amphetamines, stimulants, and beta-hydroxy-beta-methylbutyrate (HMB), which is a diuretic and a masking agent, and people are also worried about gene doping because technology is making it easier to do [2, 10].

The goals of this article review are to help get the word out about the dangers of the widespread use of performance-enhancing drugs by people from all walks of life, making this a public health issue, and to summarize some of the adverse effects of using anabolic androgenic steroids without a doctor's supervision (AASs).

Anabolic-Androgenic Steroids (AASs): Anabolic steroids (AASs) are synthetic testosterone derivatives that increase muscle mass and strength [11], and it belongs to the largest category of image and performance-enhancing drugs (IPEDs) and is widely used to achieve body image and sport performance objectives [12]. 1-3% of US residents are estimated to be AAS users and widespread use of anabolic androgenic steroids is attributable to their ability to enhance muscle growth for aesthetic and athletic purposes while minimizing androgenic effects [13]. 60% of AAS users are recreational, non-competitive, or non-athletic bodybuilders who use these drugs primarily for cosmetic purposes [14]. It is estimated that more than 98% of AAS users are male [15]. It is believed that an increasing societal emphasis on body image has contributed to a rise in male steroid abuse [16,17]. In addition, some factors are responsible for the persistence of this risky phenomenon, including the belief that the negative effects of these drugs are reversible and can be treated medically after sporting events. This belief is completely false, and numerous previous studies have demonstrated that this abuse frequently results in irreversible, severe adverse effects [18,19]. AAS usage is viewed as a public health risk due to the fact that these drugs have side effects that affect all of the body's organs, tissues, and functions, notably long-term impact on the cardiovascular and reproductive systems[13].

Anabolic androgenic steroids (AAS) are prescribed for low testosterone-related medical conditions, testosterone, and AAS are also used to treat renal failure, anemia, and hypothyroidism in the clinical setting, in children, growth retarded puberty, and in the case of certain chronic weaknesses, such as AIDS and cancer, and growth retarded [20].

Users follow dose patterns that incorporate multiple AASs in addition to other medicinal medications believed to enhance the intended physical effects or mitigate undesirable side effects [12]. Six to eighteen-week cycles are the most common period for AAS use. The purpose of this method is to develop muscle mass and strength throughout a cycle while allowing the body to recuperate between cycles [21].

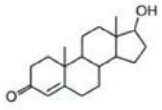
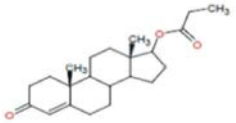
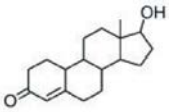
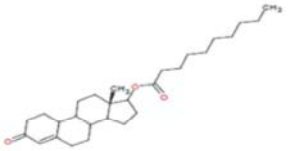
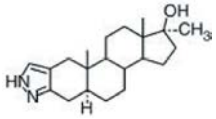
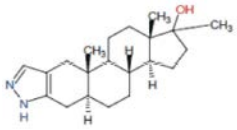
Indeed, with limited public health resources accessible to men who use AAS and general skepticism of clinicians among many of these patients, men frequently rely on other men who use AAS and online sites for information about usage and procurement [22].

Anabolic Androgenic Steroids (AAS) Structure: The main human androgen is testosterone. It is produced by the male testes, female ovaries, and female adrenal glands. Males and females produce 3 to 7 mg per day and 0.1 to 0.4 mg per day, respectively[23].

The human body naturally produces testosterone, an endogenous anabolic steroid that regulates the metabolism of muscle and bone as well as secondary sexual characteristics in men. The AAS are synthetic testosterone derivatives [24].

AASs are classified into three major classes based on the substitution of the base molecule.

Table 1: The chemical composition of testosterone and its popular metabolites

Class	Chemical Structure	Example
I		 Testosterone Propionate
II		 Nandrolone decanoate
III		 Stanozolol

1. Class I: those in which the 17-β-hydroxyl group has been esterified.
2. Class II: is associated with a C-19 demethylated group and may additionally have C-17 esters.
3. Class III: those that have the 17-α position alkylated [25, 26].

The androgens naturally produced and released by glands are C19 steroids [27]. These alterations make it possible for these compounds to have a physiological effect that lasts for several months. Therefore, any reported changes in the impact of AAS could be related to structural variations in the AAS molecules [28]. Table 1 provides the classification and some examples of anabolic steroids [29, 30]. It is believed that nandrolone (one of the AASs) esters have the highest ratio of anabolic to androgenic effects among all AAS [30].

Physiology: Anabolic steroid drugs increase protein consumption and activate protein synthesis which contribute to the development of muscle mass [31]. Furthermore, Athletes that use steroids will have a rise in aggression, which could lead to more intense training, which in turn would lead to greater muscle size and strength, and more aggressive performance in competition [32].

The biological activity varies among different androgens, and the most active molecules are testosterone and 5-dihydrotestosterone (DHT), both of which are distinguished by a 17-hydroxyl group [33].

As with other steroid hormones, AAS exerts its effects by binding to an intracellular protein called an androgen receptor (AR) in the target tissues (Fig. 1), forming an androgen receptor complex in the cell nucleus [34]. This complex then triggers a molecular cascade that produces androgenic and anabolic effects similar to those of testosterone [24]. Androgen receptors (ARs) are a class of nuclear receptors that have a role in controlling the expression of genes that contribute to muscle development and maintenance [35].

When the steroid-receptor complex gets into the nucleus, it binds to palindromic DNA sequences. They specifically attach to hexanucleotide halves organized as inverted repeats and separated by three nonconserved base pairs, known as hormone response elements (HRE) [35]. In order to promote gene transcription and the subsequent synthesis of messenger RNA from DNA in the cell nucleus to begin protein synthesis, this receptor complex travels to binding sites on the chromatin [2, 34, 36].

Thus, when supraphysiological dosages of testosterone are administered, oestradiol and DHT levels rise. High levels of oestradiol can cause some side effects, such as stimulating breast glandular tissue and stopping the body from making its LH and FSH. Dihydrotestosterone is mostly made in the skin, liver, and prostate, where 5-reductase activity is high, this could cause male pattern baldness and more hair on the body [24, 37].

Adverse Effects: The vast majority of studies on the harmful effects of anabolic androgenic steroids have been conducted on adult males. On the other hand, there is a paucity of information regarding the potentially

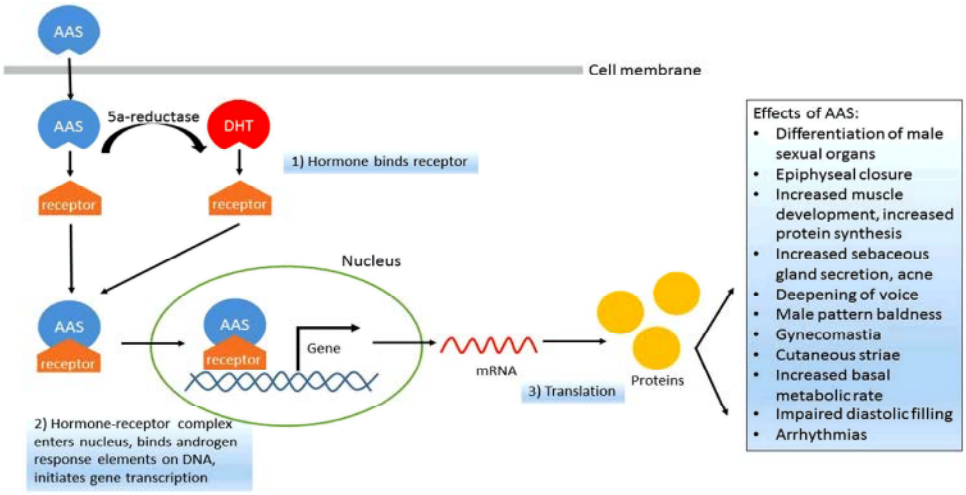


Fig. 1: The physiology of anabolic-androgenic steroids and the effects they have. DHT dihydrotestosterone, DNA deoxyribonucleic acid, mRNA messenger ribonucleic acid, AAS anabolic-androgenic steroids [2]

hazardous effects of anabolic androgenic steroid usage in females and adolescents, the two demographic categories where these drugs are most likely to cause harmful effects because they do not produce testosterone naturally [38].

The consequences that are linked with masculinization, such as a deepening of the voice and excessive hair growth, are the types of the most common changes that are commonly regarded as irreversible in females [39]. Acne is one of the common unfavorable outcomes that males often experience. In addition, the user may have hair loss, painful gynecomastia, and atrophy of the testicles, as well as other adverse effects that are difficult to identify by the users [40]. Abuse of anabolic steroids has been related to a variety of cardiovascular problems, including hypertension and malfunction of the left ventricle [41]. Furthermore, the use of anabolic androgenic steroids can result in severe liver damage [42], as well as endocrine abnormalities, mental issues, and neurologic repercussions [43]. Effects of androgens on the functioning of cells including toxicity, mutagenicity, genotoxicity, and carcinogenicity of sexual hormones are all caused by a mix of hereditary and epigenetic variables [44].

Liver Disorders: A previous study demonstrated that chronic use of supraphysiological doses of testosterone enanthate (doping dose) had a toxic effect on the rat liver, causing changes in normal histology, hypertrophy, and fibrosis at both histological and biochemical levels, potentially leading to the loss of its functions [45].

According to Bond *et al.* [46] hepatotoxicity is one of the most common negative effects of AAS misuse. Al-Aubody and AL-Diwan [47] found that Sustanon ® 250 injections affected the liver by raising ALT and AST while decreasing ALP. Additionally, Sustanon ® 250 injections influenced the lipid profile by increasing TG and VLDL while lowering HDL, LDL, and AI. Five months of AAS abuse can cause hepatocellular damage. Furthermore, AASs are linked to hepatic peliosis (proliferation of sinusoidal hepatic capillaries resulting in cystic blood-filled cavities), cholestatic jaundice, and rarely hepatic neoplasms [48]. DeVido [49] mentioned that 17 alkylation of steroids such as methyltestosterone, methandrostenolone, oxymetholone, oxandrolone, and stanozolol increased their oral bioavailability and consequently slowed their metabolism in the liver causing the drug to be exposed to hepatocytes and cholangiocytes for longer periods of time increasing its toxicity [50].

Al-abdaly *et al.* [51] concluded that a high dose of Sustanon increased oxidative stress, had induced macroscopic and microscopic pathological changes in the liver, such as the necrosis of hepatic cells and the infiltration of inflammatory cells. A previous study concluded that elevated liver transaminases, acute cholestatic syndrome, chronic vascular injury, hepatocellular carcinoma, toxicant-associated fatty liver disease, and other major alterations in lipoproteins are all indicators of hepatotoxicity. While many of these changes may settle, regain normality after stopping steroids adminstration, and others could be fatal [11].

One of the most popular AAS is stanozolol, which is an example of a 17-alkylated androgen, although this class of steroids is also associated with serious liver damage [53].

Cardiovascular Disorders: There is mounting evidence that anabolic androgenic steroid-related cardiovascular disease and thrombosis are linked to a cerebrovascular accident in young anabolic androgenic steroid users [54, 55], and increased erythropoiesis, hematocrit increase, hyperviscosity, and hypertension, whereas, may have a direct effect on the heart muscle and its function [56]. Moreover, AASs are increased myocardial ischemia risk during peak exercise[43].

The greater dose of Sustanon®250 (one of the AASs) resulted in a complete absence of the normal architecture of heart muscle, with atrophied cardiac myofibers [57]. Supraphysiological levels with long-term use of AASs may enhance the heart's vulnerability to cardiovascular problems such as hypertension and hypertrophy [58, 59].

In addition, androgens have receptors in the heart, and their activity directly impacts the heart by interacting directly with nuclear receptors and raising the production of mRNA, so stimulating cardiac protein synthesis and causing myocardial hypertrophy [60].

The research conducted by Achar *et al.* [41] revealed a correlation between AAS consumption and atrial fibrillation and ventricular arrhythmia. During long-term and high-dose anabolic androgenic steroid use, lipid abnormalities, cardiac deformation and dysfunction (especially in the left ventricle), and sudden mortality have been observed [61].

Kidney Disorders: Multiple studies have shown that prolonged androgen exposure harms the kidneys, particularly the glomerular cells, resulting in the accumulation of mesangial matrix, podocyte depletion, and structural adaptations [62].

Injectable anabolic androgenic steroids can harm the kidneys [42] the possibility of developing Wilm's tumor [63]. In addition, nephrocalcinosis and hypercalcemia have been recognized in AAS users who had not intramuscular injected oily solutions [64].

Nandrolone Decanoate (ND), one of the AAS, typically causes fibrosis and cell proliferation in the kidneys of users [40,65]. Glomerular and interstitial damage occurs in steroids users by glomerular hyperfiltration, direct renal toxicity, and hypercalcemia [66].

The study conducted by Al-Aubody and AL-Diwan [57] on male rats treated with high doses of Sustanon®250 (50, 100, and 150mg/Kg.bw) for three months revealed necrosis, degeneration in the epithelial lining of renal tubules, and the higher dose caused dilated Bowmans space and additional histological changes such as lyses of some glomeruli [67]. The study evaluated renal biopsies of ten AAS users with renal failure and recommended direct glomerular toxicity by AAS and glomerular hyperfiltration due to increased body mass (obesity) as harmful mechanisms.

Rats treated with testosterone had an increased bladder-to-body mass ratio and a decreased collagen-to-smooth muscle ratio, according to Shortliffe *et al.* [68]. Additionally, the ratio of kidney mass to body mass increased, despite a decrease in glomerular density in the testosterone-treated group. It has also been proven that exogenous testosterone accelerates the progression of existing metastatic prostate cancer [69].

Neuro-Psychiatric/Behavioral: An overdose of AAS can produce mental instability in the form of manic-depressive states, which are characterized by intense nervousness that cannot be controlled or severe sadness that may be accompanied by suicidal tendencies[51]. In point of fact, it has been proven that high doses of AASs that are beyond the physiological norm might cause neurotoxicity by being involved in the process of apoptosis and neurodegeneration [70]. Several central nervous system processes, including memory, aggression, anxiety, and depression, are influenced by supraphysiological concentrations of AASs, particularly in genetically susceptible persons [71]. Aggression, anxiety, impulsive behavior, hypomania, and less commonly mania are the symptoms that are most frequently seen in patients taking high dosages of AAS; nevertheless, psychotic reactions are also possible [72].

Reproductive System and Infertility: Addiction to anabolic steroids inhibits the development of sperm [73]. Direct injury to the testes is one way in which exogenous anabolic steroids impair a man's ability to reproduce [74]. Since the very first administration, AASs decrease reproductive function by altering the action of male sex hormones, as noted by [75]. Nandrolone Decanoate (ND) (one of the AASs) has the strongest negative effect on the hypothalamic-pituitary-gonadal axis decreasing luteinizing hormone (LH) and follicle-stimulating hormone (FSH), thus lowering testosterone levels [76].

The study of Ahmed [77] showed that toxic doses of Sustanon 250 had widespread adverse effects on the testicles of rats, and an analysis of the testicles' histology revealed severely distorted seminiferous tubules with a loss of their normal histological structure, and certain seminiferous tubules atrophied; dysregulation of the seminiferous tubules shows, and spermatogenesis is severely suppressed [77]. Histological analyses of the

testes of male animals showed that the use of AAS impaired spermatogenesis, as evidenced by a lack of advanced spermatids and a decrease in the quantity of spermatids [62, 63].

CONCLUSION

This review revealed that the long-term administration of AASs in high doses may lead to harmful consequences, such as cardiomyopathy and atherosclerotic disease, hypogonadism, testicular atrophy, severe liver disease, psychiatric disorders, and neurologic consequences. Additionally, in kidneys, several studies have highlighted the fact that prolonged androgen exposure has a direct toxic effect.

Education on the dangers and possible adverse effects on one's health that might result from the use of over-the-counter performance-enhancing drugs is an essential issue that should be taken into consideration.

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