

# The Uses of Anabolic Androgenic Steroids Among Athletes; Its Positive and Negative Aspects- A Literature Review

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**Abstract:** The use of anabolic androgenic steroids (AAS) for strength training and muscle building is a widespread practice among athletes and young individuals. Athletes and bodybuilders are using these substances for various purposes, such as enhancing muscle mass, strengthening their bodies, and enhancing their performances. AAS exert a wide range of physiological effects that result in the activation of central signaling, resulting in adverse effects. Moreover, excessive use of AAS which can be categorized as AAS abuse; is linked to biological and psychological pathologies, which can lead to mortality. Complications arising from steroid abuse involve both cellular and physiological complications. Cellular complications arise when activation of signaling proteins like mTOR, Akt, etc. leads to alteration in protein synthesis pathways, cell cycle, oxidative stress, and apoptosis, contributing to damage at the cellular level. Physiological complications are evident with cardiovascular pathologies, including an altered lipid profile, cardiac hypertrophy, hypogonadism after discontinuation of AAS, and modulation of GABA receptors in the brain, all contributed by the androgen receptor signaling. Clinical complications budding from these altered physiological processes lead to clinical effects like testicular dysfunction, acne, gynecomastia, and neuropsychiatric disorders. Despite potential therapeutic benefits, AAS use is prohibited by the World Anti-Doping Agency (WADA) due to concerns over adverse health effects. This review highlights the molecular mechanisms, physiological processes, and clinical complications arising from the excessive use of AAS among athletes.

**Keywords:** androgenic steroids, mTOR pathway, AKT pathway, steroids abuse

## Introduction

The world of sports has long been a stage for human achievement, where athletes push their physical and mental limits to attain greatness. In this pursuit, the use of performance-enhancing substances has remained a contentious issue, with anabolic androgenic steroids (AAS) emerging as one of the most widely debated substances in sports circles.<sup>1</sup> Anabolic androgenic steroids, derived from the male sex hormone testosterone, have garnered attention due to their potential to significantly alter an athlete's physical capabilities.<sup>2</sup> This literature review delves into the multifaceted landscape of AAS use among athletes, examining both its positive and negative aspects, shedding light on the motivations behind their use, and the subsequent physiological and psychological consequences.

Anabolic androgenic steroids, originally developed for medical purposes such as treating hormone deficiencies and muscle-wasting diseases, have found a different path in the realm of sports.<sup>3</sup> Athletes often seek their effects, which include increased muscle mass, strength, and endurance, with the aim of gaining a competitive edge. The allure of improved performance and the desire to achieve remarkable athletic feats has led to the illicit use of AAS by athletes across various disciplines.<sup>4</sup>

The allure of AAS for athletes predominantly lies in the potential positive impacts on performance. The heightened ability to build lean muscle mass and increase strength can contribute to enhanced athletic performance.<sup>5</sup> AAS can accelerate recovery from intense training, enabling athletes to train more frequently and intensely. This heightened

training capacity can translate to improved skill development and performance outcomes.<sup>6</sup> Moreover, the psychological boost resulting from these physical improvements can enhance an athlete's self-confidence and self-esteem, which are crucial for optimal performance under pressure.<sup>7</sup>

While the potential benefits of AAS are enticing, the negative aspects of their use cannot be overlooked. The misuse of AAS in sports can lead to a range of adverse health effects.<sup>8</sup> Physiologically, AAS can disrupt the body's natural hormone balance, leading to a plethora of complications such as cardiovascular issues, liver damage, and reproductive system abnormalities.<sup>9</sup> Moreover, the misuse of AAS can also impact an athlete's credibility and tarnish the integrity of sports. The unlevel playing field created by doping can undermine the principles of fair competition, eroding the essence of sportsmanship.<sup>10</sup>

Athletes turn to AAS for a variety of reasons, often influenced by the intense pressures to succeed in a hyper-competitive sporting landscape.<sup>11</sup> The pursuit of fame, financial rewards, and national pride can push athletes to seek shortcuts to greatness. Additionally, the fear of falling behind peers who might be using AAS can create a sense of necessity, fuelling the prevalence of their misuse. The use of AAS in sports raises significant ethical and legal dilemmas.<sup>12</sup> The breach of fair play and the inherent risks associated with AAS consumption challenge the integrity of sports. Organizations such as the World Anti-Doping Agency (WADA) have established stringent regulations and testing protocols to curb the misuse of AAS and maintain a level playing field.<sup>13</sup> Athletes found to be using AAS face not only disqualification but also damage to their reputation and potential legal consequences.<sup>14,15</sup>

The issue of AAS use among athletes is a complex matter with far-reaching consequence.<sup>16</sup> While the allure of enhanced performance through AAS is undeniable, the potential detrimental effects on health, integrity, and fairness within sports cannot be understated.<sup>17</sup> This literature review will delve into the nuanced layers of AAS use among athletes, dissecting the motivations that drive their use and the subsequent impact on physiological and psychological well-being. By comprehensively understanding the multifaceted nature of AAS use, stakeholders in the world of sports can make informed decisions to preserve the authenticity and sanctity of athletic competition while safeguarding the health and dignity of athletes.<sup>18</sup>

## Anabolic Steroids

Athletes use anabolic steroids to increase their strength and muscular mass. These substances are also known as anabolic-androgenic steroids.<sup>19</sup> Despite their negative reputation, anabolic steroids may be used therapeutically. These drugs might lower the damage that happens to muscles during a hard workout. That could help athletes bounce back faster from a workout. They might be able to exercise harder and more often.<sup>20</sup> Anabolic-androgenic steroids, sometimes known as "steroids" or "androgens", are the most abused Performance Enhancing Drugs (PEDs).<sup>21,22</sup> These compounds are synthetic analogs of the male sex hormone testosterone. In both males and females, they increase the growth of skeletal muscle (anabolic effects) and the development of male sexual traits (androgenic effects).<sup>23</sup> The steroids are generally formed biologically from cholesterol and then interconverted, as shown in [Figure 1](#). Besides naturally occurring steroids, synthetic steroids do exist and are widely used among athletes.<sup>24</sup>

Anabolic steroids are classified as controlled substances in numerous countries, including Australia, Argentina, Brazil, Canada, the United Kingdom, and the United States.<sup>26</sup> Despite this, there remains a readily accessible global supply of steroids for non-medicinal use. This accessibility is because, in many countries, anabolic steroids can be legally purchased without a prescription.<sup>27,28</sup> Consequently, foreign distributors often operate within the legal framework of their nations when supplying these substances to international customers via online platforms and email orders. The majority of hormone products circulating in the European market originate from countries within the European Union and Russia, with occasional contributions from Thailand, Turkey, Egypt, India, and Pakistan.<sup>29–31</sup> Similarly, significant volumes of anabolic steroids in the United States are sourced from Mexico, Russia, Romania, and Greece.<sup>32</sup>

In the United Kingdom, the Misuse of Drugs Act classifies anabolic steroids under Schedule IV Part 2.<sup>24</sup> This includes most anabolic steroids as well as clenbuterol (an adrenoreceptor stimulant) and human growth hormone.<sup>33</sup> While there are no restrictions on possessing these substances within medicinal products for self-administration, individuals have faced intent-to-supply charges for possessing large quantities without a prescription. Importing and exporting anabolic steroids requires a Home Office license, with exceptions for small quantities for legitimate purposes.<sup>34</sup>



findings linked to anabolic steroids.<sup>35</sup> Frequent steroids include testosterone, nandrolone, stanozolol, and methandienone. Detecting testosterone use is complex due to its endogenous production. The urge for success drives competitors to enhance performance despite the risk of penalties, even though some claim WADA's statistics do not fully reflect steroid doping in top-level athletics.<sup>34,43,44</sup>

Anabolic steroids' chemical structures and activity have undergone modifications to amplify anabolic effects and minimize androgenic ones.<sup>45</sup> While some steroids have been withdrawn in several countries, they remain available in others for medical use, such as methandienone, methyltestosterone, oxandrolone, and stanozolol. In the United Kingdom, licensed products include testosterone and its esters, nandrolone (as the decanoate ester), mesterolone, and oxymetholone (restricted to named patients). Some countries limit boldenone and trenbolone to veterinary purposes, yet athletes and bodybuilders sometimes administer these anabolic steroids.<sup>34</sup>

Methenolone acetate, methandrostenolone, oxandrolone, oxymetholone, and stanozolol are some of the orally administered steroids in use among athletes. Some intramuscularly used steroids are boldenone undecenoate, methenolone acetate, nandrolone decanoate, Sustanon 250<sup>®</sup>, testosterone enanthate, and testosterone cypionate.<sup>46</sup> Anabolic-androgenic steroids are the best-studied class of PEDs that can boost a user's confidence and strength, leading users to overlook the severe, long-lasting, and in some cases, irreversible damage they can cause.<sup>47</sup>

## Population Burden of AAS Abuse

Anabolic androgenic abuse gained popularity due to its impact on physique and performance in sports like bodybuilding, weightlifting, baseball, football, cycling, wrestling, and many others to improve their performance.<sup>48</sup> The gain in muscle mass and strength contributes to aesthetic appeal and therefore use of androgenic anabolic steroids paved the way to the events of abuse. Among Americans with ages ranging from 13 to 50 years, 2.9–4.0 million people have reported using AAS. Almost 1 million people utilizing AAS within this community have reportedly developed AAS dependence.<sup>49</sup> The use of AAS is likely to be observed in gym members practicing weightlifting followed by the number of people working in the private sector and beyond 25 years of age. AAS abuse is more evident in Western regions as compared to Africa and Asia. The report explains that this high likelihood of AAS abuse can be attributed to the concept of “muscularity” in those culture.<sup>50,51</sup> However, other than the cultural norms, factors that are associated with AAS abuse, especially in gym members include weightlifting, the use of supplementary vitamins, special diets, and social exposure to people who regularly use AAS for similar purposes.<sup>52</sup> Accurate estimation of steroid-associated gynecomastia is crucial for effective healthcare planning and tailored treatment approaches. The studies identify indicators of steroid usage, assesses responses to surgical and nonsurgical management, and compares preoperative and intraoperative data between different groups. The results highlight the significance of monitoring steroid consumption in gynecomastia cases, which often goes underestimated due to social stigma and misdiagnosis.<sup>53,54</sup> The use of AAS not only impacts sports performance but also poses significant health risks and psychological consequences, highlighting the importance of comprehensive education, awareness, and intervention strategies to address the widespread issue of AAS abuse.<sup>8</sup>

## Uses and Recommendations of AAS

Since use of drugs is generally regulated, AAS has also been subject to approval from FDA,<sup>55</sup> where it has been indicated for primary hypogonadism, delayed puberty in boys, hypogonadotropic hypogonadism, gonadotropin and luteinizing hormone-releasing hormone (LHRH) deficiency, pituitary-hypothalamic axis (HPA-axis) dysfunction originating from various tumors.<sup>56</sup> AAS is also used for the treatment of physiological deficits arising from anatomical abnormalities like cryptorchidism, orchitis, testicular torsion, vanishing testis syndrome. Patients with a history of orchiectomy, Klinefelter syndrome, or ongoing therapy with chemotherapeutic agents, alcohol abuse, and heavy metal poisoning are also treated with AAS.<sup>57</sup>

Testosterone is also used as an adjunct treatment for certain malignant conditions bone marrow stimulation in leukemia and aplastic anemia, however, these treatments are non-FDA approved.<sup>58</sup> Similarly, kidney failure, growth failure, stimulation of appetite, muscle mass in malignancy, and acquired immunodeficiency syndrome are also treated with AAS.<sup>59</sup> Furthermore, it's important to note that while AAS has legitimate medical uses as mentioned, its potential for misuse and abuse, along with the associated health risks, underscores the critical necessity for responsible medical supervision and comprehensive patient education regarding the proper and safe use of these substances.<sup>60</sup>

## Molecular Mechanisms of AAS

Increased size and muscle strength are desirable for aesthetic appeal however, at a cellular level, the use of AAS will lead to activation of multiple pathways that result in the increase in size of muscles and strength. Since these pathways have different outcomes in other types of cells, they may, therefore, elicit a different outcome response.<sup>61</sup> Androgens increase both the size and strength of skeletal muscle via diverse mechanisms. AAS binds to and activates androgen receptors in nuclei resulting in transcription of the associated genes.<sup>62,63</sup> These genes include transcription factors specific to muscles, structural proteins, microRNAs, and enzymes. Activation of these proteins also results in cellular cross-talk with other signaling molecules as well which include Akt, myostatin, IGF-I, and Notch signaling.<sup>62</sup> Akt is a central signaling molecule therefore, its activation can also lead to unwanted physiological effects. The metabolic effects of anabolic androgen are reflected by their effect on muscles where they increase  $\text{Ca}^{2+}$  uptake and modulate kinase activities.<sup>62</sup> While IGF-1 signaling is responsible for cellular growth functions, its receptor, IGFR, is a tyrosine kinase receptor and activates common downstream signaling molecules including Akt, leading to the activation of S6K1, which translates into protein synthesis and growth. The cellular growth and strength are therefore contributed by both activation of downstream Akt and S6K1 and activation of nuclear receptors.<sup>64</sup>

Anabolic androgenic steroids (AAS) are synthetic derivatives of testosterone that are commonly used to enhance athletic performance and promote muscle growth. These compounds exert their effects primarily by binding to androgen receptors within cells, leading to various physiological responses.<sup>65</sup> The molecular mechanisms of AAS involve interactions at the cellular and molecular levels, influencing gene expression, protein synthesis, and cellular signaling pathways.<sup>66</sup> Several studies have investigated the molecular mechanisms of AAS. For instance, research has shown that AAS usage can induce changes in gene expression in muscle cells, contributing to muscle growth and potentially muscle memory. This suggests that AAS might lead to the retention of myonuclei in muscle tissue, which could contribute to long-term muscle adaptations.<sup>66,67</sup>

AAS has also been found to influence cardiac function and the central nervous system.<sup>68</sup> Chronic use of AAS has been associated with ventricular repolarization disturbances and disruptions in areas of the central nervous system, leading to behavioral changes.<sup>69</sup> The precise molecular mechanisms underlying these effects are still being studied, and more research is needed to fully understand these complexities. At the cellular level, AAS impacts protein synthesis by upregulating the expression of various genes related to muscle growth and repair. Additionally, AAS may modulate calcium homeostasis and cardiac contraction in heart cells, potentially affecting cardiac function.<sup>70</sup>

## Physiological Mechanisms of AAS

### Effects on Muscles

The growth effects of AAS are exerted by the promotion of protein synthesis through gene transcription as described earlier. The binding of AAS to its receptor results in the displacement of glucocorticoids from their receptors.<sup>71</sup> Consequently, protein degradation is inhibited as glucocorticoids are responsible for the degradation of protein in the cell.<sup>72</sup> Among these anabolic steroids, stanozolol's mechanism of action has been hypothesized to be influenced by a significant increase in type I muscle fiber size which provides enough strength for the athletes to exercise longer, consequently resulting in type II fiber hypertrophy.<sup>73</sup> Testosterone injections of 600 mg dose on the other hand have shown a greater increase in fat-free mass in individuals who were not exposed to exercise intervention as compared with those who did resistance exercise with placebo treatment.<sup>74</sup> These effects are demonstrated for the increase in muscle mass mainly while no such effects have been observed in muscle concentrations of creatine.

Contrary to these findings, AAS doping in athletes in a dose-dependent manner has exhibited an increase in capillary density, muscle fiber area, myonuclei density, and lean body mass, thereby leading to the conclusion that AAS supplementation increases lean leg mass, muscle fiber size and improvement in muscle strength.<sup>75</sup> These studies showing long-term administration of AAS's enhancement effects in human skeletal muscle morphology and physical performance.<sup>76</sup> The effects of anabolic androgenic steroids (AAS) on muscle growth involve intricate physiological mechanisms. AAS promotes protein synthesis through gene transcription and inhibits protein degradation by displacing glucocorticoids from their receptors.<sup>77</sup> Notably, distinct AAS like stanozolol may influence type I muscle fiber size,

enhancing endurance, while testosterone injections exhibit differential fat-free mass increases based on exercise exposure.<sup>78</sup> Despite debates, AAS supplementation demonstrates the potential to augment muscle mass, fiber size, and overall strength, particularly in physically demanding sports; however, misuse without clinical guidance remains a concern.

## Effects on Liver

As with most other drugs, the frequency and severity of hepatic adverse effects from AAS arise from several factors including formulation of the drug, route of administration, dosage, duration, and idiosyncratic responses.<sup>79</sup> Hepatotoxic effects of testosterone occur due to slower clearance of anabolic steroids like testosterone. These adverse effects are likely to arise from 17- $\alpha$ -alkylation modification, which makes their use desirable for oral intake.<sup>66</sup> Moreover, such substitutions facilitate the potency and duration of action of these anabolic steroids. Hepatotoxic events are related to elevated liver transaminases, translating into acute cholestatic syndrome. Testosterone and its derivatives especially have been frequently employed as a causative factor in a specific form of cholestasis called peliosis hepatis, benign and malignant hepatic tumors.<sup>80</sup> Other than that, chronic vascular injury, fatty liver diseases associated with toxicants like alcohol, and significant lipoprotein alterations have been observed with the use of AAS. Usually, these modifications are reversible with cessation of steroid use, however, some of them can pose life-threatening conditions.<sup>81</sup> Overall, the hepatotoxic mechanisms currently unveiled in AAS-related hepatotoxicity include disturbance of antioxidative factors, upregulation of bile acid synthesis, and induction of hepatocyte hyperplasia.<sup>71</sup> The AAS-induced hepatotoxic effects result from various factors, encompassing drug formulation, administration route, dosage, duration, and individual responses. Hepatotoxicity, often linked to elevated liver transaminases and acute cholestatic syndrome, can stem from the 17- $\alpha$ -alkylation modification in AAS, which enhances their oral availability and effectiveness.<sup>82</sup> Additionally, AAS usage has been associated with intricate hepatic conditions like peliosis hepatis, benign and malignant tumors, vascular injuries, fatty liver disorders, and disrupted lipoprotein profiles.<sup>61</sup> While many alterations are reversible upon discontinuation, certain consequences may escalate into severe, life-threatening scenarios.

## Effects on Bones

The mechanism of androgens in the skeletal system is to inhibit bone resorption through osteoclastic activity. This results in the increase of androgen receptor-mediated bone formation.<sup>83</sup> The increase in bone formation is associated with longitudinal and periosteal bone growth and an increase in bone mass. In various conditions, including ovariectomized and orchietomized rats, AAS exhibit anti-catabolic effects by reducing trabecular bone resorption, while also demonstrating the potential to enhance cortical bone strength, providing insights for addressing established osteoporosis related to aging.<sup>84,85</sup> In the ovariectomized and orchietomized rats, AAS have shown decreased trabecular bone resorption which further elaborates their anti-catabolic effects in bone.<sup>86</sup> In particular, an increase in the mechanical strength of cortical bone was observed in ovariectomized rats with AAS use, a finding that led to the development of AAS as a potential lead for treating established osteoporosis associated with aging.<sup>87</sup> AAS has shown stimulation of endosteal bone formation. These findings have provided recommendations for AAS use particularly ND and nandrolone in estrogen-deficient conditions.<sup>88</sup> Administration of ND and nandrolone have revealed their significant effects in increasing bone mass in osteoporotic men and women. The bone gain with AAS use in such patients is almost 3% per annum, however, maximal effects are observed in the initial months of treatment.<sup>89</sup> This bone gain is associated with stimulation of bone formation, increase in serum albumin, and fat-free skinfold thickness.<sup>90</sup> Research using cellular models like SaOS-2 cells has also shown promising results for AAS use by promoting osteogenic commitment in these osteoblasts.<sup>91</sup> Despite their positive effects on bone growth, AAS use has shown a paradoxical effect on tendons and ligaments. Contrary to their anabolic effects on bone formation and bone growth, rupture of biceps and quadriceps tendons has been reported in athletes using AAS.<sup>92</sup> Conclusively, despite their deleterious effects on other organs, AAS have desirable effects on bone formation and growth, which calls for more cellular and clinical studies deciphering their effects on bone-related disorders.

## Effects on Fat Metabolism

Alteration in fat metabolism due to AA use has shown a decrease in sphingolipids and glycerolipids with palmitic, palmitoleic, stearic, and oleic acids. These lipids serve as a building block in the formation of membrane-bound structures in cells and therefore, play a key role in the wear-and-tear mechanism of cellular growth.<sup>93</sup> Lipid profiling in individuals with AAS abuse revealed an increased amount of free fatty acids and glycerophospholipids. This increase is associated with odd-numbered chain fatty acids and/or arachidonic acid.<sup>94</sup> Notably, AAS influences HDL-cholesterol dynamics by enhancing hepatic lipase activity, which plays a pivotal role in HDL particle size conversion from HDL2 to HDL3, with even relatively low AAS dosages contributing to significant reductions in HDL-cholesterol level.<sup>95</sup> Administration of a low dosage of almost 6 mg per day of AAS compound for 2 weeks has shown a reduction of up to 20% in HDL-cholesterol levels in HL deficiency.<sup>61</sup> Reduction in HDL and increase in LDL and triglyceride levels have shown a predisposition to adverse cardiovascular events, thereby reflecting its adverse effects on the cardiovascular system.

## Cardiovascular Risks Associated with AAS Abuse

Adverse events associated with AAS use are widely studied for the cardiovascular system. In general, cardiomyopathy, myocardial infarction, and fatal arrhythmias have been reported with AAS use.<sup>96</sup> An increase in Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio has been implemented in the pathophysiology of ventricular arrhythmias caused by AAS use, with reports of sudden death.<sup>97</sup> Cardiomyopathy in response to AAS use is also contributed by the increase of heart chamber diameters, changes in ventricular relaxation via altered diastolic function, and alterations in left ventricular contractility at the subclinical level.<sup>98,99</sup>

Neurohumoral responses from AAS include a transient increase in blood pressure, yet, clinically significant hypertension is still to be established. The mechanism postulated to be involved in alteration in neurohumoral response includes an increase in systolic blood pressure with a decrease in plasma MR-proANP levels.<sup>100</sup> On the other hand, suppression of testosterone in men has shown an increase in NY-proBNP levels, which were restored by testosterone replacement, thereby formulating the role of testosterone in circulating natriuretic peptide levels.<sup>101</sup> Also, there have been reports of a link between AAS abuse and aortic stiffness that can be partly explained by their effects on platelet function and neurohumoral responses together.<sup>102</sup>

Platelet function in response to AAS abuse involves a pronounced pro-thrombotic state, reflected by the increase in platelet aggregation.<sup>103</sup> Parallel coagulatory responses from the humoral regulation lead to a more complex pro-coagulator state characterized by the activation of pro-coagulatory and fibrinolytic pathways. Among these AAS, nandrolone specifically has shown a tendency to accelerate clot development and firmness in Wistar rats.<sup>104</sup> This might explain evident alterations in endothelial-dependent or independent vasodilation resulting in clot formation.<sup>105</sup>

Additionally, the altered lipid metabolism, as discussed above, sets a foundation for the development of atherosclerosis and hypertension,<sup>106</sup> alongside an accelerated coagulation cascade, further exacerbating the condition. Persistent use of AAS therefore shows an association with myocardial dysfunction and accelerated coronary atherosclerosis. Such adverse events associated with AAS abuse are wreaking havoc on the current prevalence of cardiovascular events, without the recognition of AAS abuse as a public health concern.<sup>107</sup>

## Effects on Kidney

Effects of AAS on kidneys have been categorized as either direct or indirect effects.<sup>108</sup> While indirect effects are linked to cardiovascular or muscular abnormalities discussed above, direct effects refer to focal segmental glomerulosclerosis, acute kidney injury, and predisposition to chronic kidney injury.<sup>109</sup> Creatinine is a biochemical marker of kidney functioning and AAS use has shown transient small increases in serum creatinine concentrations (1.05 mg/dl to 1.11 mg/dl) however, this increase remained clinically insignificant and returned to baseline after discontinuation of AAS use.<sup>110</sup> Comparatively, a larger increase in serum creatinine levels was observed in a placebo-controlled trial for a 4-week long duration, with resistance-trained men. These subjects were randomized to either a daily dose of 330 mg of oral prohormone 3 $\beta$ -hydroxy-5 $\alpha$ -androst-1-en-17-one (1-androsterone) or placebo,<sup>111</sup> thereby reflecting alteration in renal function. Nandrolone decanoate abuse can cause aldosterone and electrolyte imbalance in the body which could be

a serious risk factor for cardiovascular-related disorders.<sup>112</sup> The impact of AAS on kidneys has been categorized into direct and indirect effects, with indirect effects being linked to the cardiovascular or muscular abnormalities discussed earlier, and direct effects encompassing conditions like focal segmental glomerulosclerosis, acute kidney injury, and susceptibility to chronic kidney injury.<sup>5</sup>

## Effects of AAS Abuse on Sexual Functions

Testosterone, a reproductive hormone in males is known to be involved in metabolism where it enhances basal metabolic rate (BMR) at pharmacological doses.<sup>113</sup> As discussed earlier, it also has an impact on fat metabolism, thereby exerting its direct effects on the metabolism of reproductive hormones as well. Supraphysiological doses of AAS downregulate testosterone production.<sup>114</sup> Also, the external administration of testosterone in turn suppresses the hypothalamic-pituitary axis. It consequently translates into erectile dysfunction, violent tendencies, and decreased libido. Sexual dysfunction resulting from AAS abuse involves anabolic steroid-induced hypogonadism which includes azoospermia and testicular atrophy.<sup>115</sup> In males with  $\leq 1$  year of AAS abuse, withdrawal of AAS may suffice to normalize testosterone levels, but for abuse exceeding one year, additional therapy with clomiphene or gonadotropin may be needed to restore spermatogenesis.<sup>107</sup>

## Effects on Brain

AAs work by activating dopamine pathways in the brain. Specifically, testosterone acts through the mesolimbic dopamine system, which serves as a common platform in the brain for dependence on drugs of abuse.<sup>116</sup> Instead, testosterone resembles other mild reinforcers, such as caffeine, nicotine, or benzodiazepines. The potential for androgen addiction remains to be determined. These pathways are known for reward mechanisms in the brain, making them prone to developing dependence.<sup>117</sup> Also, AAS has been linked to modification in some indirect pathways including serotonergic, glutamatergic, and dopaminergic pathways in the lateral-anterior hypothalamus, translating into aggressive behavior.<sup>118,119</sup> AAS dependence arises from androgen reinforcement in the brain, which is comparatively lower than that of cocaine or heroin.<sup>120</sup> Reinforcements induced by caffeine, nicotine, or benzodiazepines instead are comparable to those induced by AAS.<sup>121</sup> Yet the AAS dependence requires further probing due to the adverse events associated with it. AAS dependence in males has exhibited thinning in the brain-wide cortical regions, in particular the pre-frontal cortex which is responsible for inhibitory control and emotional regulation.<sup>122</sup> Increased anxiety associated with chronic AAS use involves a direct amygdala-fugal pathway which forms the connection between the central nucleus of the amygdala and brainstem. In normal conditions, this pathway is responsible for cognitive-emotive and homeostatic processes. Among AAS, nalbuphine has shown some degree of dependence predisposing it as a drug of abuse among athletes. Consequently, nalbuphine's scheduling status has been recommended for re-evaluation.<sup>123</sup>

## Psychological Complications Arising from AAS Abuse

Psychological complications with the use of AAS have brought about an area of concern that needs to be addressed with rising global mental health challenges. AAS use has been shown to cause an increase in aggression and hostility.<sup>124,125</sup> Some studies report mood disturbance about the type and dosage of AAS.<sup>126</sup> The AAS abuse population at risk of psychopathic traits includes bodybuilders with a prior history of AAS use. Also, sexual and substance use risk-taking behaviors and anger problems, are widely observed in bodybuilders with AAS use history as compared with non-users.<sup>127</sup> Since AAS use enhances aesthetic appeal by increasing muscle strength, withdrawal brings about concerns related to the body image of a person, resulting in social physique anxiety, however, this effect has been observed in more severe symptoms of AAS abuse including depression and withdrawal.<sup>128</sup> Yet, AAS dependence or withdrawal symptoms like depressed mood have been observed in a small number of AAS users. Also, reverse anorexia syndrome may develop with a dissatisfied body image and low self-esteem in the individuals using AAS, which predisposes such persons to resume the use of AAS.<sup>129</sup> So far, only 37.12% of people have shown interest in seeking support from physicians regarding AAS dependence which calls for the need to appreciate seeking help regarding AAS dependence.<sup>130</sup> They can lead to early heart attacks, strokes, liver tumors, kidney failure, and psychiatric problems. In addition, stopping use can cause depression, often leading to resumption of use.



## Conclusion

Cellular and metabolic complications arising from anabolic steroid misuse have raised a recent public health concern. Health complications arising from anabolic steroid misuse have unveiled an occult cause of metabolic derangements in the younger population. Most studies have deciphered mechanisms where AAS activates common downstream signaling molecules like Akt, explaining unwanted events arising from AA abuse. AAS abuse has shown critical damage to cardiovascular, excretory, reproductive, muscular, hepatic, and nervous systems. Studies on AAS-related adverse effects have also brought about a connection with psychiatric disorders, thereby opening an area of interest for the causative factors of psychiatric disorders. Much is yet to be explored on how overt or occult AAS abuse defines certain behaviors in a normal individual. Can AAS play a role in defining behaviors that are generally attributed to a person's own choice of behavior or are they influenced by such drugs of abuse needs to be explored to better understand male psychology. Moreover, health complications arising from AAS abuse like gynecomastia, acne, etc. also raise concern over AAS's potential as a useful drug. While AAS abuse has been linked to many disorders affecting different organs in the body, it is interesting to observe that the effects of AAS have remained largely positive on bone growth. Reports on damage to tendons or ligaments exist, yet the effects of AAS remain largely beneficial for the skeletal system. Further probing into its mechanisms of action on bone growth may be useful for understanding the reason for its limited adverse effects on them. Moreover, clinical studies utilizing AAS for enhancing fracture repair in different ages and different kinds of fractures may provide useful insight into its clinical use. Conclusively, while AAS abuse has proven to be associated with many health complications, its effectiveness in treating skeletal disorders is largely unexplored. Probing its effectiveness for bone-related disorders with careful monitoring may offer a new mode of treatment for accelerated healing from complicated skeletal disorders.

## Acknowledgments

The authors are thankful to Dr Noor Bahadar for reviewing the manuscript and suggesting grammatical corrections.

## Disclosure

The authors report no conflicts of interest in this work.

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