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## Anabolic-androgenic steroids. Mechanism of action and clinical effects

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### ABSTRACT

**Introduction and aim.** Anabolic-androgenic steroids (AAS) are used for the rapid enhancement of muscular mass and optimization of athletic performance. Their administration is frequently linked with a plethora of adverse health implications. The primary objective of this study is to provide a comprehensive analysis of multifaceted impacts of anabolic-androgenic steroids on the human body.

**Material and methods.** A review of literature was performed by searching PubMed and GoogleScholar databases using the following key words: anabolic-androgenic steroids, muscular hypertrophy, female masculinization.

**Analysis of the literature.** Anabolic-androgenic steroids are synthetically manufactured derivatives of testosterone. Given the widespread distribution of the androgen receptor, the effects of these steroids are broad, influencing almost all bodily functions. Their impacts include, promoting muscular hypertrophy including that of the cardiac muscle, premature epiphyseal closure, liver diseases, masculinization in females, feminization in males, and degradation in sperm quality.

**Conclusion.** AAS consumption is a significant public health problem. While they may appeal to users by enhancing their physical attractiveness they carry multiple health consequences. Patients should be educated about the adverse effects of taking AAS so they can make informed decision about starting or stopping their use.

**Keywords.** Anabolic-androgenic steroids; muscular hypertrophy; cardiovascular risk; acne; female masculinization.

## **Introduction**

Anabolic-androgenic steroids (AAS) are synthetic derivatives of the male sex hormone, testosterone. The term "anabolic" is derived from the Greek word "ἀναβολή," which means "to lift something quickly, to build quickly," while "androgenic" comes from the Greek "ἀνδρός" - "from a man" and "γενής" - "to be born." Androgens play a key role in the development of male sexual characteristics, e.g., prostate, penis, seminal vesicles, and epididymis. In addition, they determine the male phenotype, regulate reproductive abilities, and influence maturation, fertility, and male sexual functions. Anabolics, on the other hand, are responsible for stimulating muscle and bone growth. Among AAS, the most common are two groups -  $17\alpha$ -alkyl derivatives, e.g., oxandrolone, oxymetholone, and fluoxymesterone, and  $17\beta$ -ester derivatives, including testosterone cypionate, testosterone enanthate, testosterone heptylate, testosterone propionate, nandrolone decanoate, nandrolone phenpropionate, and dromostanolone. Nandrolone phenpropionate was one of the first AAS used by professional athletes as a form of doping. Its use was officially banned by the International Olympic Committee in 1974.<sup>1,2</sup>

## **Aim**

The aim of this paper is to present the cons and pros of AAS therapy but also general side effects of using AAS.

## **Material and methods**

A review of the available literature was performed by searching the PubMed and GoogleScholar databases using the following key words: Anabolic-androgenic steroids, muscular hypertrophy, epiphyseal closure, hirsutism, acne, female masculinization.

### **Analysis of the literature**

#### *Epidemiology*

It is estimated that 3-4 million people in the United States and tens of millions of people worldwide use AAS to enhance physical performance or increase physical attractiveness. About 98% of those are men.<sup>3,4</sup> In the 2019 report of the World Anti-Doping Agency (WADA), out of 278,047 samples taken from professional athletes, 2,701 tested positive for doping substances or their metabolites, of which 11% of cases had medical indications for their use.<sup>5</sup>

#### *Mechanism of Action*

Anabolic-androgenic steroids (AAS) are administered in various forms including oral medications, subcutaneous injections, and transdermal patches. However, oral tablets are the most common mode of administration<sup>6</sup>. The bioavailability of testosterone when given orally is relatively low, approximately 15%<sup>6</sup>. This can be attributed to the first-pass effect, which takes place in both the liver cells and the intestines<sup>7</sup>. In the plasma, testosterone and other sex steroids are primarily transported bound to proteins, specifically albumin, sex hormone-binding globulin (SHBG), corticosteroid-binding globulin (CBG), and orosomucoid<sup>8</sup>. It is estimated that around 53–55% of testosterone binds to albumin, 43–45% to SHBG, and the remaining 0.5-3% exists as the free fraction<sup>9,10</sup>. The free fraction, along with the fraction bound to albumin, unlike that bound to SHBG, can be readily utilized by tissues<sup>10</sup>. The roles of the fractions bound to CBG and orosomucoid remain unclear<sup>8</sup>. Upon reaching their target cells, AAS can directly interact with the androgen receptor, thereby influencing gene expression. They may also be converted by aromatase to estradiol or by 5 $\alpha$ -reductase to dihydrotestosterone (DHT)<sup>11</sup>.

#### *Striated Muscles*

AAS, like testosterone, increase the synthesis and accrual (growth occurring due to an increase in extracellular matrix mass, not due to an increase in cell quantity or size) of muscle proteins, increase the activation of satellite cells, and decrease catabolic pathways through genomic and non-genomic actions.<sup>12,13</sup> Testosterone and DHT induce muscle growth by promoting myogenic differentiation in mesenchymal pluripotent CD34 $\beta$  stem cells through a pathway mediated by the androgen receptor. In muscles, endogenous androgen receptors are

mainly expressed by satellite cell lineage cells, including satellite cells, myoblasts, and myocytes. Muscle hypertrophy induced by testosterone is associated with an increase in satellite cells. Androgen receptors are also detected in cells present in the muscle interstitial fluid, such as fibroblasts and endothelial cells.<sup>13,14</sup> AAS also stimulate the secretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1). Both GH and IGF-1 can stimulate the differentiation of satellite cells into mature myocytes, which may directly affect the increase in muscle mass.<sup>13</sup> Studies are not conclusive, but it seems that AAS have a greater impact on the increase of type I (slow twitch) muscle fibers than type II (fast twitch).<sup>15</sup>

### *Bones*

Linear bone growth occurs in growth plates located at each end of the bone shaft. These plates contain columns of dividing chondrocytes producing collagen. As the collagen layer thickens, older chondrocytes degenerate, and the cartilage calcifies. Bone elongation continues as long as the growth plate remains active. GH, IGF-1, and androgens control bone length growth by stimulating chondrocytes to grow and differentiate.<sup>16</sup> In the early phase of maturation, androgens and estrogens stimulate the intra-cartilage development of bones. Towards the end of maturation, estrogens, through the stimulation of the estrogen receptor, promote fusion and closure of growth plates. This process contributes not only to the irreversible depletion of chondrocyte precursors in the resting zone but also to the aging of the growth plate. This, in turn, is associated with a decrease in the rate of growth and proliferation, and the number and size of chondrocytes. During this stage of maturation, androgens are aromatized into estrogens.<sup>17,18</sup> The time between the onset of puberty and the cessation of growth is shorter in children receiving AAS.<sup>18</sup> The enlargement of the bone diameter and the increase in the cortical layer thickness occur through the deposition of bone matrix on the periosteal side by the action of osteoblasts. It was previously believed that such a pattern of periosteal accretion was characteristic of bone growth during male maturation. It was thought that stimulation of the androgen receptor promotes faster matrix accretion, while the presence of estrogens inhibits this process.<sup>19</sup> Recent studies involving men with low aromatase activity have proven that estrogens are essential for bone remodeling and achieving peak bone mass.<sup>20</sup> In light of this information, it can be concluded that AAS promote bone matrix accretion, thereby increasing bone mass.

### *Cardiovascular System*

Cardiovascular system diseases (CVS) are among the most severe side effects of taking steroid hormones.<sup>21,22</sup> The most common pathologies associated with the increased cardiovascular risk associated with AAS use include coronary heart disease, sudden cardiac

death, heart muscle damage, heart muscle hypertrophy, dilated cardiomyopathy, arrhythmias, atherosclerosis, calcification of blood vessels, hypertension, and thrombosis.<sup>23,24</sup> Autopsy studies performed on bodies of individuals whose death was associated with AAS use revealed extensive anatomical changes. Asymmetric hypertrophy of the left ventricle was noted, coronary artery atherosclerosis causing significant narrowing of its lumen, pulmonary thromboembolism, thrombi in the coronary vessels and heart chambers, and inflammatory infiltrates were identified.<sup>21</sup> Histopathological studies observed heart muscle damage characterized by myocardial hypertrophy, focal myocardial damage with loss of myofibrils, and interstitial fibrosis, mainly in the subpericardial area.<sup>21</sup> AAS bind to the androgen receptors of vessel walls increasing their calcification, which results in endothelial cell damage. In addition, AAS disturb lipid metabolism by lowering the level of high-density lipoproteins (HDL) and increasing the level of low-density lipoproteins (LDL), which increases the risk of coronary artery disease and cerebrovascular diseases.<sup>23,25</sup> In post-mortem histopathological studies on the hearts of animals undergoing AAS therapy, signs of myocardial apoptosis strongly correlated with the dose of AAS were demonstrated. It is suggested that androgens promote the influx of  $Ca^{2+}$  and mobilization of  $Ca^{2+}$  in the sarcoplasmic reticulum to increase mitochondrial permeability, leading to the release of apoptotic factors such as cytochrome C, apoptosis-inducing factor, and caspase, leading to apoptosis.<sup>23</sup> Necrotic foci, fibrosis, or hypertrophy of the heart muscle combined with physical exertion can cause life-threatening arrhythmia, which can ultimately lead to sudden cardiac death.<sup>24</sup>

### *Hepatotoxicity*

The liver is a parenchymal organ abundant in androgen receptors. It is estimated that about 8% of all drug-induced liver injuries are caused by AAS use.<sup>26</sup> Several pathophysiological mechanisms are suggested to explain the essence of AAS hepatotoxicity. By disrupting the intramitochondrial respiratory chain at the level of complexes I and III, AAS contribute to the formation and accumulation of reactive oxygen species, thereby causing oxidative stress. As a result, there is a disruption of the dynamics of the cellular potential of mitochondria, decreased energy production in cells, degeneration, and necrosis of hepatocytes.<sup>27,28</sup> AAS induce an inflammatory cell infiltrate into the liver parenchyma and activate Kupffer cells producing pro-inflammatory cytokines such as transforming growth factor-beta1 (TGF- $\beta$ 1), tumor necrosis factor-alpha (TNF $\alpha$ ), and interleukin-1B (IL-1B). Chronic inflammation induces the deposition of extracellular matrix and collagen, leading to liver fibrosis.<sup>27</sup> By stimulating androgen receptors, there is nodular growth of hepatocytes distorting the

parenchyma and mechanically blocking the vascular system, creating cystic changes filled with blood, called hepatic peliosis. Additionally, hepatocyte hyperplasia leads to the formation of liver tumors.<sup>27</sup> Activation of androgen receptors by AAS disrupts bile transporters, mediates intracellular microfilament damage, and increases the expression of genes responsible for bile transporter synthesis, leading to the accumulation of bile acids, cholestasis, and cholestatic jaundice.<sup>27,29</sup> From a clinical perspective, taking AAS may lead to the development of cholestatic jaundice, hepatic peliosis, fatty liver disease, hepatocellular hepatitis, spontaneous liver rupture, liver adenomas, hepatocellular cancer, or an increase in liver enzyme activity.<sup>29</sup>

### *Dermatoses*

Androgens play a crucial role in the proliferation and differentiation of sebaceous cells, contributing to an increase in sebum production.<sup>30</sup> Additionally, under the influence of androgens, there is a hyperproliferation of the epidermis of hair follicles, which in turn leads to sebum retention. The inflated hair follicles rupture and release pro-inflammatory substances into the dermis, stimulating an inflammatory response. Pathogens such as *Cutibacterium Acne*, *Staphylococcus Epidermis*, and *Malassezia Furfur* induce inflammatory states and proliferation of hair follicles' epidermis. As a result, a chronic inflammatory skin condition called acne vulgaris develops.<sup>31</sup> The use of AAS not only increases sebum production but also alters the skin microbiota, increasing the number of bacteria, particularly *Staphylococcus Aureus* and *Cutibacterium Acne* species.<sup>32</sup>

The activation of the androgen receptor shortens the anagen phase, which is the growth phase in the normal hair growth cycle. In the case of male pattern baldness, excessive activation by androgens leads to the miniaturization of hair follicles due to the shortening of the anagen phase, resulting in thinner and shorter hair follicles that may eventually not penetrate through the epidermis.<sup>33</sup> AAS, through activation of the androgen receptor on the scalp, contribute to male pattern baldness in both men and women.<sup>34</sup>

### *Female Reproductive System*

Physiologically, in women, testosterone is produced by the ovaries and the reticular layer of the adrenal cortex. Its production begins between the 8th and 9th year of life in girls. The peak testosterone concentration in women's blood occurs between the 3rd and 4th decade of life, after which it continuously decreases until the postmenopausal age. This decrease is not related to menopause, and the reasons for it remain unclear to this day.<sup>35,36</sup> In the ovarian cycle, high testosterone concentration coincides with the luteal phase and persists throughout the second half of the cycle.<sup>36</sup> It has been shown that women's sexual functions are associated

with the occurrence of testosterone and its derivatives. It has been observed that endogenous testosterone is associated with the frequency of masturbation, sexual desire, and arousal, and its derivative, dehydroepiandrosterone, is positively correlated with the frequency and desire for masturbation.<sup>35</sup> For this reason, local testosterone therapy in postmenopausal women is being considered to increase sexual drive. However, due to safety concerns, research in this area is highly limited, and the therapy itself is considered too risky.<sup>36,37</sup> During the use of AAS, a significant decrease in gonadotropin (LH and FSH) concentrations is observed, as well as a decrease in the concentration of endogenous testosterone. After discontinuing the use of AAS, the level of gonadotropins gradually returns to normal, while the testosterone concentration, compared to its concentration before the period of AAS use, remains lower - this applies to both sexes.<sup>38</sup> Women who take AAS show signs of masculinization. The most noticeable include a thickening of the vocal cords, leading to a lowering of voice pitch with accompanying hoarseness, and enlargement of the clitoris. Additionally, increased sexual desire, hirsutism, menstrual cycle disorders, cessation of menstruation, and decreased fertility appear.<sup>38</sup>

#### *Male Reproductive System*

During the intake of AAS, a series of hormonal changes occur in the male body. There is a decrease in the concentrations of gonadotropins and SHBG, and an increase in the concentrations of testosterone, its derivatives and estrogens.<sup>38,39</sup> As a result of these changes, there may be disturbances in erection and a decrease in sexual desire (19% and 31% of reported cases respectively).<sup>39</sup> The number of sperm cells in semen decreases and their morphology changes. The quality of sperm deteriorates and this continues up to the 30th week after discontinuation of AAS.<sup>39,40</sup> Although, subsequently, sperm parameters improve, impaired testicular function may persist, leading to decreased fertility.<sup>41</sup> Due to supraphysiological concentrations of testosterone in individuals taking AAS, some testosterone is aromatized in adipose tissue to estrogens. This contributes to the development of gynecomastia in men.<sup>41</sup> Additionally, men taking AAS experience testicular atrophy, Leydig cell tumors, prostate cancer, and benign prostate hyperplasia.<sup>42</sup>

#### **Conclusion**

The intake of AAS is a significant public health problem. The main recipients are men seeking to enhance the attractiveness of their physique or to improve sports performance. AAS therapy increases muscle mass, causes bone thickness gain, and in combination with physical exercises, allows for better sports performance. However, it carries multiple health consequences, from temporary elevation of liver enzymes, lipid metabolism disorders, or

decreased sperm quality, to permanent changes in the morphology of the heart muscle, feminization in men with testicular atrophy, and masculinization in women. Patients should be educated about the adverse effects of taking AAS so they can make an informed decision about starting or stopping their use.

### **Declarations**

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Not applicable

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#### ***Author's contributions***

Conceptualisation, D.M.; Methodology, D.M.; Software, M.S.; Validation, N.I.; Formal Analysis L.A.; Investigation, P.Z.; Resources, M.S.; Data Curation, D.M.; Writing – Original Draft Preparation, D.M.; Writing – Review & Editing, D.M., M.S.; Visualisation, P.Z.; Supervision, N.I.; Project Administration: N.I., L.A.

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Authors have no conflicts of interest to declare.

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