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Damage and Morphometric Effects of Prohibited Substance Use as Doping on Tissues and Organs

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Abstract: Uncontrolled acute or chronic use of very high doses by athletes to enhance athletic performance, improve muscle strength and physical appearance (Pope et al, 2017; Gök et al 2016) Erythropoietin, methenolone Enanthate (rhEPO), Testosterone propionate, Testosterone phenylpropionate, Testosterone isocaproate, Testosterone decanoate (Özdemir & Yalçın, 2011; Bozkurt et al., 2011a-b; Özdemir, 2020), which are among the most common AAS used for doping purposes, can cause irreparable serious organ damage (Al-Otaibi, 2024). Prohibited substances are also widely used as pharmacological drug therapy in patients with chronic diseases to improve the quality of life by achieving the appropriate effects on the body (Handelsman, 2006). Despite their use in clinical treatments, banned substances have also been found to have some negative effects on patients and the health of external users (Mutalip et al 2013). Testosterone is used in drug therapy for chronic respiratory or heart failure, anemia due to bone marrow failure, increasing or decreasing erythropoietin in renal failure, and for muscle and bone healing in autoimmune diseases. The abuse of these substances is often used illegally in large doses for non-medical purposes, especially in strength sports and bodybuilding. In parallel with effective findings that reduce the abuse of banned substances in elite sports, there is a need to focus more attention on non-sporting cosmetic, recreational, exertional and occupational abuse (Handelsman, 2006). Athletes use banned substances to improve performance regardless of health risks (El-Gendy, et al., 2021). In studies conducted in various countries, the lifetime prevalence of banned substances used for exertion, physical appearance and performance enhancement in young men is reported at rates ranging from 3-12% (Gök et al., 2016). The use of banned substances has continued to increase in recent years and there is a need for more research on this subject. In this study, it is aimed to inform the society and especially the sports community about the damage caused by banned substances used as doping on tissues and organs.

Keywords: Doping, Organs, Tissues

Introduction

Anabolic-androgenic steroids (AAS) are synthetic compounds derived from testosterone and its related precursors. AAS are commonly used illegally, particularly among adolescents and athletes, to enhance muscle growth and achieve a lean body mass for aesthetic purposes. This illegal use can lead to serious health problems and various dysfunctions. Sudden cardiac death (SCD) is noted as the most common medical cause of death among athletes (Torrisi et al., 2020).

The misuse of anabolic-androgenic steroids (AAS) has become quite prevalent among both professional and recreational athletes. These steroids are used to quickly increase muscle mass and achieve an aesthetic

appearance. However, many of the adverse effects of AAS on testicular morphology, tissue redox state, and androgen receptor levels during training are not yet fully understood (Sretenovic et al., 2021).

Testosterone is a hormone produced through the interaction between the pituitary gland, hypothalamus, and testes. Pulsatile gonadotropin-releasing hormone (GnRH) secreted by the hypothalamus stimulates the release of luteinizing hormone (LH) from the anterior pituitary, which then interacts with Leydig cells in the testes to produce testosterone. More than 95% of circulating testosterone is produced in the testes (Şensoy, 2024).

It is evident that AAS used in clinical-therapeutic trials by medical doctors are not free of side effects. These side effects vary depending on the type and dosage of the steroids and include increases in liver enzyme levels, cholestatic jaundice, and peliosis hepatis (Maravelias et al., 2005). Additionally, effects such as stunted growth and thickening of the bone cortex have been observed (Özdemir and Yalçın, 2011; Bozkurt et al., 2011a-b).

Common side effects of AAS include increased water retention, liver dysfunction, edema, jaundice, increased cardiac workload, increased risk of benign and malignant liver tumors, increased blood pressure, kidney dysfunction, increased cholesterol levels, tumor growth stimulation, increased risk of cardiovascular disease, elevated blood sugar levels, pustulation, nosebleeds, muscle cramps and spasms, thyroid dysfunction, tendon damage or rupture, psychological disorders, euphoria, and aggression (Gök et al., 2016).

In women, the side effects of anabolic-androgenic steroids (AAS) include hirsutism, nymphomania, hair loss, menstrual irregularities or early menopause, reduced breast size, voice deepening, and clitoral enlargement. In prepubescent boys, side effects include premature epiphyseal closure and stunted growth. Additionally, AAS use can lead to hair loss, infertility, reduced production of male sex hormones, gynecomastia, decreased libido, testicular shrinkage, impotence, and reduced sperm production. Male sex hormones can cause the prostate gland to enlarge, lead to prostate cancer, reduce sperm production, and cause Wilms tumors and abnormal sperm (Livanelioğlu, 2010).

Furthermore, prolonged androgen use can reduce height growth in young individuals and lead to early epiphyseal closure in children and adolescents (Al-Ismail, 2002; Özdemir and Yalçın, 2011; Bozkurt et al., 2011a-b). Anabolic steroids can suppress the production of estrogen and testosterone (Kaşıkçıoğlu, 2009). Testosterone administration has been shown to reduce albumin and total serum protein levels ($p<0.05$), while increasing cholesterol, aminotransferase, and aspartate levels ($p<0.05$). Therefore, long-term testosterone administration during adolescence may lead to organ defects (Lök and Yalçın, 2010; El-Gendy et al., 2021).

Erythropoietin (EPO) is a glycoprotein hormone primarily synthesized in the kidneys and has a gene locus on the seventh chromosome (Glöckner et al., 1998). EPO's primary function is to stimulate the proliferation and maturation of erythroid cells in the bone marrow. Besides its use in treating anemia, EPO also has anti-inflammatory, antioxidant, anti-apoptotic, and angiogenic effects. However, this hormone is sometimes used by athletes for doping purposes.

Mitchell et al. (2005) and Kaşıkcıoğlu (2009) reported that bone loss occurs a few months after steroid use, with this loss being more prevalent in trabecular bone of the vertebrae and femoral head compared to cortical bone. A morphometric study on rats examining the effects of AAS on the humerus and femur found that AAS reduced cortical bone density in males (Özdemir and Yalçın, 2011; Bozkurt et al., 2011a, 2011b). Mitchell et al. (2005) and Kaşıkcıoğlu (2009) noted that weight-bearing exercises could reduce AAS-induced bone loss.
EPO is a hematopoietic growth factor that stimulates the formation of red blood cells and is known as a doping agent in high-performance sports, particularly cycling. It is used in clinical settings to treat anemia caused by insufficient endogenous EPO production, especially in chronic kidney failure. In recent years, the non-hematopoietic functions of EPO have also been extensively researched. These non-hematopoietic capabilities, including osteogenic and angiogenic potentials, are of particular interest to orthopedic and musculoskeletal engineering (Rölfing, 2014).

In clinical settings, EPO administered to anemic patients can increase the number of red blood cells by 35%, change the shape of cells, and enhance their oxygen-carrying capacity. Erythropoietin is an important hematopoietic growth factor necessary for erythropoiesis. This hormone is a glycoprotein composed of 165 amino acids and four carbohydrate chains, with a molecular weight of 30,400 kD (Koury et al., 1998; Wang et al., 1985).

This study comprehensively examined the biological and psychological effects of anabolic-androgenic steroids (AAS). The findings indicate that AAS use leads to serious health problems in both men and women. In men,

increased testosterone levels support the development of secondary sexual characteristics, while excessive use leads to testicular atrophy, reduced sperm production, and loss of libido. In women, AAS use causes side effects such as hirsutism, voice deepening, and menstrual irregularities. These findings clearly show that AAS negatively impacts sexual health and the reproductive system.

Effects on the Heart

One of the most affected systems by the side effects of anabolic-androgenic steroids (AAS) is the cardiovascular system. AAS use increases vascular resistance and blood pressure, raises levels of pro-inflammatory biomarkers, and leads directly to myocardial toxicity. To assess the relationship between AAS use and sudden cardiac death, it is crucial to focus on the organs where these side effects are most frequently observed (Torrisi et al., 2020).

A recent case study highlighted the cardiovascular risks associated with androgen use (Scarth and Bjørnebekk, 2021). Long-term AAS consumption has been shown to cause liver, heart, and vascular injuries in adolescent rats, along with increased serum CK-MB and AST activity (Lok, Tasgin, Demir, and Özdemir, 2010; Tasgin, Lok, and Demir, 2011). The abuse of erythropoietin and AAS can result in severe and irreversible organ damage (Al-Otaibi, 2024).

Even therapeutic use of AAS has been associated with adverse effects. Anabolic effects often manifest with numerous physical and physiological side effects. Reported side effects include acne, testicular atrophy, gynecomastia, hypertension, arrhythmia, myocardial infarction, depression, increased red blood cell count, impaired diastolic function, reduced sperm count, and increased mortality (Mutalip et al., 2013; Nascimento et al., 2016). Left ventricular hypertrophy has been observed in individuals engaging in resistance exercise and using high doses of AAS. Özdemir et al. (2013) found that the use of methenolone enanthate, an AAS, increased muscle hypertrophy and left ventricular heart rate in pubertal female rats.

The toxic effects of anabolic steroids on the heart and skeletal muscles of albino rats have been exacerbated by treatment with fenugreek seed extract and silymarin (Hassan et al., 2023). Abdollahi et al. (2016) reported that the combination of chronic nandrolone administration and long-term high-intensity swimming exercise increased the incidence of ventricular fibrillation in male rats. Sretenovic et al. (2016) reported that nandrolone administration increased left ventricular wall thickness in Wistar albino rats, with the thickening ranging from 6% (nandrolone only) to 30% (nandrolone with exercise) compared to the control group. Exercise alone also led to greater wall thickening (16%) compared to the control group. AAS use has been observed to have adverse and lasting effects on left ventricular function (Johnson et al., 2024). Chronic use of testosterone enanthate at doping doses has been found to cause hypertrophy and fibrosis in the heart muscle and liver of rats, leading to loss of organ function at both histological and biochemical levels (El-Gendy et al., 2021).

Effects on the Liver

The use of anabolic-androgenic steroids (AAS) can lead to various adverse effects, depending on the dosage. AAS, often used illegally in high doses by athletes, pose significant health risks. Supraphysiological and long-term use of AAS can result in cardiovascular, neurological, endocrine, gastrointestinal, renal, and hematological disorders (Petrovic et al., 2022). Hepatotoxicity, in particular, is one of the major concerns associated with AAS therapy and abuse. It has been shown that testosterone and its derivatives can induce specific cholestasis, peliosis hepatis, and the formation of benign and malignant hepatic tumors (Cunningham et al., 2013; Zelleroth et al., 2021). Prominent side effects of AAS therapy include elevated liver enzyme levels, cholestatic jaundice, peliosis hepatis, and various neoplastic lesions, all indicating hepatotoxicity (Nasrollah & Shahidi, 2001).

In recent years, the use of anabolic steroids among athletes and young individuals has significantly increased. This rise has particularly heightened the toxic effects of orally administered steroids on the liver (Boada et al., 1999). Even three months after discontinuing steroid use, destructive effects on liver cells persist. However, some of the negative impacts on liver enzymes have been observed to decrease significantly over time (Barbalho and Barreiros, 2015).

Studies by Parkinson and Evans (2006) found that bodybuilders who used steroid medications during exercise exhibited significantly increased liver enzymes and blood factors. Elevated ALT and AST levels indicate that liver and muscle enzymes have entered the bloodstream. The liver detoxifies various drugs or sends them to the

bile, converting steroid hormones not found in tissues into androsterone and dihydroepiandrosterone, which are then excreted through the bile or urine after sulfation. The damage to liver tissue from these drugs can vary depending on the type of drug, duration of use, and dosage (Robergs and Roberts, 2000).

The most common forms of tissue damage in the liver include vascular hyperemia, degeneration, inflammation, and an increase in cytoplasmic fat vacuoles. This condition leads to liver deformation and hardening, destroying liver tissue and replacing it with connective tissue. In some cases, this damage can lead to liver failure, encephalopathy, and ultimately death (Susan et al., 2007).

The increased use of anabolic steroids among athletes and young people has raised concerns, particularly about the hepatotoxicity of orally administered steroids. Various in vivo effects of AAS have been reported, including liver microsome damage in male rats. A five-week study in mice reported that AAS use increased markers of hepatic necrosis, centrilobular vessels, and collagen accumulation in liver parenchyma (Boada et al., 1999).

Anabolic-androgenic steroids (AAS) are used in medical settings for two primary purposes. Firstly, they are used in androgen replacement therapy for patients with androgen deficiency due to genetic disorders of the hypothalamus, pituitary gland, or testes. Secondly, AAS are applied as pharmacological androgen therapy (PAT) to improve the quality of life in patients with chronic diseases without androgen deficiency, aiming to achieve optimal testosterone effects. However, chronic use of testosterone enanthate at supraphysiological (doping) doses can lead to significant toxic effects. Research indicates that long-term administration of such doses can cause histological and biochemical changes in cardiac and hepatic tissues, resulting in hypertrophy, fibrosis, and potential loss of function. Understanding these effects is crucial for healthcare providers and patients considering AAS therapy (El-Gendy et al., 2021).

Effects on the Nervous System

The hippocampus is a region notable for its structural plasticity and its significant role in learning and memory. This has led to considerable interest in studies examining the effects of androgens on the brain. Animal studies have demonstrated that supraphysiological doses of androgens can lead to neurodegeneration, reduced levels of brain-derived neurotrophic factor (BDNF), increased inflammation, and decreased neuronal density. Data from human studies suggest that prolonged androgen use may result in similar behavioral and cognitive deficits (Scarth and Bjørnebekk, 2021).

Damio et al. (2021) investigated the effects of two different steroid treatments, testosterone cypionate and stanozolol, on neuronal density in the limbic, motor, and sensory cortical areas, as well as in the hippocampal CA1, CA2, and CA3 regions of both male and female mice. They found that both testosterone cypionate and stanozolol significantly reduced neuronal density in the limbic region in male mice, with stanozolol alone significantly reducing neuronal density in the CA1 region.

A study involving 99 weightlifters and 130 androgen users suggested that long-term androgen use may accelerate brain aging. The brain ages of androgen users were found to be higher than those of controls, and the longer the exposure to these substances, the more rapid the brain aging (Scarth and Bjørnebekk, 2021). Abuse of AAS may lead to neurotoxicity, activating cell necrosis (Bertozzi et al., 2018). This was observed as a significant reduction in neuronal density in animals supplemented with AAS compared to control and exercise groups (Corsini et al., 2022), indicating that similar neurotoxic processes may affect the nervous system in these animals.

Corsini et al. (2022) conducted a study examining the impact of physical exercise on neuronal body damage in the brains of male rats. They found that steroids influenced cell death mechanisms, leading to cell death that affected the nervous system, particularly impacting the locus coeruleus and causing significant neuron loss in this region. Behavioral disorders associated with AAS may reflect notable psychopathological comorbidities between drug addiction and neural circuit adaptations, including neurotrophic changes. There is a high expression of steroid receptors and enzymes involved in steroid synthesis and metabolism in brain regions implicated in the onset of anxiety and aggression associated with AAS abuse. Chronic administration of high-dose AAS has been shown to promote anxiety-like behaviors (Bertozzi et al., 2018). Long-term use of AAS negatively affects ERα or ERβ receptors in brain regions responsible for aggression control (Melloni and Ricci, 2010).

In conclusion, research on the effects of androgens on the brain examines how banned substances used for doping impact healthy brain function and behavior. These effects arise from various changes occurring in specific brain regions, such as the cerebral cortex, hippocampus, amygdala, and hypothalamus. High-dose androgen therapy has been associated with increased oxidative stress and impaired neuroplasticity. However, most of these findings are derived from animal studies, and their direct applicability to humans may not yield accurate results.

Effects on Body and Organ Weights

The primary aim of steroid use is to achieve rapid muscle mass gain and an aesthetic appearance. However, the adverse effects of combining anabolic-androgenic steroid (AAS) abuse with training on testicular morphology, tissue redox status, and androgen receptor levels are still not fully understood (Sretenovic et al., 2021). The androgenic and anabolic effects of testosterone can have significant impacts on body weight and various organs (Özdemir and Yalçın, 2011).

Experimental studies have shown that testosterone administration does not significantly alter body weight in rats but does lead to a significant reduction in testicular weight (Özdemir and Yalçın, 2011; Sretenovic et al., 2021). This reduction is attributed to decreased testosterone levels, leading to apoptosis in spermatogenic cells and affecting spermatogenesis, sperm count, morphology index, viability, progressive motility, and testicular injury (Al-Otaibi, 2024).

In a study by El-Gendy et al. (2021), a significant reduction in body weight was observed in the group treated with a doping dose of testosterone enanthate for 8 and 12 weeks compared to the control group. It is also known that mild hyperthermia conditions can reduce testicular weight, trigger apoptosis in germ cells, and cause damage to the seminiferous epithelium (Lue et al., 2000). In a four-week study by Chuffa et al. (2011), no significant weight loss was observed in the exercise group, while Nandrolone Decanoate showed a statistically insignificant decrease in body weight despite its anabolic effects in experimental animals.

The body weights of rats given anabolic steroids, protein supplements, and exercise were found to be the lowest among all groups. Testicular weight significantly decreased in the anabolic groups, and the groups that exercised had the lowest hematocrit values. All serological values remained within normal ranges, and no pathological changes were observed in tissues taken from specific "target organs" (Bauman et al., 1988).

In a study by Özdemir and Yalçın (2011), testosterone administration in male rats did not affect the weight of the heart, right kidney, or left kidney, but led to a slight decrease in spleen weight compared to the control group. Additionally, a significant reduction in liver weight and the weights of the right and left testes was observed in hormone-treated male rats. Blystone et al. (2007) reported that administering testosterone to adolescent male rats significantly reduced the weight of some organs. These findings align with Carson et al.'s (2002) report that nandrolone administration significantly decreased testicular weight in male rats. Balkaya et al. (2002) also observed a significant reduction in the weight of certain organs in male rats administered testosterone. In this study, the female rats in the experimental group showed only a quantitative decrease in heart, liver, and spleen weights compared to the control group, while the weight of the right kidney was statistically increased.

Effects of AAS on Sexual Behavior and the Reproductive System

Anabolic-androgenic steroids (AAS) are synthetic compounds derived from the testosterone molecule, naturally produced in the interstitial Leydig cells of the testes. AAS are typically used in two main medical scenarios: first, in androgen replacement therapy for patients with androgen deficiency due to genetic disorders of the hypothalamus, pituitary gland, or testes; and second, as pharmacological androgen therapy (PAT) to improve the quality of life in individuals with chronic diseases without androgen deficiency (Mutalip et al., 2013).

The effects of AAS on the reproductive system in men include decreased libido, sexual impotence, impaired spermatogenesis, and prostate hypertrophy. In women, observed effects include hirsutism, voice deepening, and menstrual irregularities (Mutalip et al., 2013). Experimental studies in rats have examined the effects of AAS on testicular morphology and histology, revealing significant reductions in the number and size of Leydig cells in the interstitial space (Naraghi et al., 2010).

In a study conducted by Grokett and colleagues (1992), rats treated with AAS showed weights of the testes, prostate gland, and seminal vesicles that were 69%, 50%, and 29% lower, respectively, compared to control groups. During a three-hour incubation period, testicular testosterone production in treated animals dropped to as low as 1.3% of control values. Additionally, serum levels of FSH (11.7% of control) and LH (undetectable) were significantly lower in treated animals compared to controls. Histological findings showed a cessation of late spermatid development and a marked decrease in Leydig cell populations in the interstitial area (Grokett et al., 1992; Naraghi et al., 2010). These findings suggest that treatment with oxandrolone in immature male rats can have profound and multi-level effects on the adult male reproductive system (Grokett et al., 1992).

The pathophysiological effects of AAS are not limited to the reproductive system; they are also associated with increased oxidative stress in the heart, liver, and kidneys (Frankenfeld et al., 2014). Previous studies have indicated that excessive production of reactive oxygen species (ROS) can lead to male infertility by disrupting steroidogenic activity in the testes and affecting the integrity of cell membrane macromolecules (Manna et al., 2003; Sretenovic et al., 2021).

It has been found that estrogens derived from androgens during early developmental stages significantly influence male sexual preferences. An increase in sexual preference for female stimuli among males exposed to supraphysiological testosterone levels around postnatal day 21 suggests that males exposed to high testosterone levels might experience disadvantages in reproductive success under natural conditions where competition among males is high. Conversely, males not exposed to testosterone may have a higher likelihood of approaching females, potentially enhancing their reproductive success (Domínguez et al., 2002; Henley et al., 2010).

In earlier studies, Beach and colleagues (1949) administered varying doses of testosterone propionate injections to castrated male rats daily. Doses below 50 micrograms did not produce significant changes in mating behavior, and treated animals showed a significantly lower likelihood of exhibiting sexual response to females compared to normal animals or castrated animals receiving higher testosterone doses. These results suggest that high early androgen levels play a role in bisexual social preferences rather than homosexual preferences (Hanley et al., 2010).

Research by Clemens et al. (1978) demonstrated that females developing between two males in utero exhibited more male-like sexual behavior in adulthood compared to females developing between two females. Prenatal treatment with anti-androgens prevented this effect. Neumann and colleagues' (1966) study showed that male offspring of mothers treated with anti-androgens during pregnancy exhibited feminized behaviors in adulthood. In another study by Pollak and Sachs (1975), females treated with testosterone during both prenatal and postnatal periods displayed more pronounced male-like sexual behavior in adulthood compared to those treated only postnatally.

Effects on Bone Tissue

The use of anabolic-androgenic steroids (AAS) can have various adverse effects on bone development, particularly during the growth period. One of the most significant side effects of AAS is the premature closure of the growth plates (epiphyseal plates), which can lead to stunted growth in animals, indicating that prolonged use of these substances can cause similar effects in humans (Özdemir & Yalçın, 2011). Additionally, some studies have reported that AAS use can negatively impact the healing of injuries, thus suggesting cautious use in clinical treatment (Arslan & Besoluk, 2023).

Methenolone Enanthate (ME) is used, particularly for the treatment of anemia due to bone marrow failure, wasting syndromes, osteoporosis, and sarcopenia (Tauchen et al., 2021). The administration of high doses of ME in rats can lead to early epiphyseal closure in the femur and humerus, halting bone growth and potentially adversely affecting bone development, especially in young athletes and sedentary individuals using AAS (Özdemir & Yalçın, 2011).

In a study by Bozkurt et al. (2011a-b), it was reported that intraperitoneal (IP) administration of Methenolone Enanthate at a dose of 5 mg/kg for four weeks, five days a week, in 40-day-old Sprague-Dawley male and female rats resulted in a decrease in femur length in males and an increase in females. A reduction in corpus thickness was observed in males, while an increase was noted in females. No difference in cavum medullare diameter was found in either gender, and no difference in cortex thickness was observed in males, while an increase occurred in females.

Another study by Lok and Yalçın (2010) found that the intraperitoneal administration of Nandrolone at a dose of 10 mg/kg for four weeks, five days a week, in 30-day-old male and female rats led to a reduction in femur length, with no differences found in femur corpus thickness, cavum medullare diameter, or cortex thickness. Additionally, subcutaneous administration of Testosterone at a dose of 5 mg/kg for ten weeks, five days a week, in 50-day-old Sprague-Dawley rats resulted in a reduction in femur length in males and an increase in females; a decrease in corpus thickness in males, with no effect observed in females; no difference in cavum medullare diameter in males, with narrowing observed in females; and no effect on cortex thickness in either gender (Özdemir & Yalçın, 2011).

In studies by Özdemir et al. (2020), the effects of Methenolone Enanthate on scapula height, width, and surface area in rats were found to be similar to other AAS, suppressing bone development in male pubescents while promoting bone development in females. It is emphasized that commonly used doping substances have negative effects on bones in males in the medium and long term.

Among the side effects of AAS observed in prepubescent males are the early ossification of cartilage and stunted growth (Özdemir & Yalçın, 2011). Testosterone and synthetic androgen analogs have been widely used in pharmacological androgen therapy (PAT) to produce androgenic effects on bone marrow, muscle, or bone. While PAT has increasingly been replaced by newer, more expensive drugs, androgens continue to play a significant role in many traditional applications due to their cost-effectiveness (Handelsman, 2006).

The effects of anabolic-androgenic steroids (AAS) on bone tissue have been extensively studied in both clinical and experimental settings. While AAS have been reported to have positive effects on bone density, it is also highlighted that long-term and high-dose use can lead to adverse outcomes on bone health. AAS have the potential to reduce bone fragility by increasing bone mineral density; however, their unbalanced use can lead to abnormal growth and deformities in bone structure (Bhasin et al., 2001).

In one study, the effects of nandrolone decanoate on bone mineral density (BMD) were investigated, and it was found that this steroid increased BMD but also caused an increase in bone marrow fat content. This could negatively affect the hematopoietic potential of the bone marrow, leading to impairments in bone marrow function (Van Brussel et al., 1999).

AAS use can also affect bone remodeling processes. Specifically, testosterone and other androgens have bone-forming effects; however, these effects can vary depending on the dose and duration of use. High-dose and long-term AAS use can increase bone resorption, leading to bone loss rather than net bone gain (Seeman, 2001). Moreover, the effects of AAS on bone tissue can differ based on age, gender, and physiological condition. For instance, while bone density-enhancing effects may be observed in young adults, increased bone fragility may occur in older individuals. Therefore, it is crucial to consider individual factors when assessing the effects of AAS on bone tissue (Clark et al., 1999).

Testosterone and synthetic androgen analogs have also been used in pharmacological androgen therapy (PAT) to produce androgenic effects on marrow, muscle, or bone. While PAT has been increasingly replaced by newer, more expensive drugs, androgens remain cost-effective in many traditional applications (Handelsman, 2006). In conclusion, the effects of anabolic-androgenic steroids (AAS) on bone tissue should be carefully evaluated, considering both positive and negative aspects. More comprehensive research is needed on the potential risks and benefits of AAS on bone health. Healthcare professionals should carefully manage the use of these substances, considering their effects on bone tissue. These assessments are critical for minimizing the long-term health impacts of AAS use and enhancing safety in treatment processes.

Psychological Effects

Research on the effects of anabolic-androgenic steroids (AAS) on brain development and behavioral outcomes has revealed extensive impacts on neurological and psychological health, including during adolescence. The influence of AAS on brain organization has been observed in both humans and animal models, showing significant alterations in neurotransmitter functions and neural structures (Cunningham et al., 2013). Adolescence is a critical period for brain development, and exposure to AAS during this time can disrupt the normal pattern of brain development, leading to long-term behavioral changes.

The effects of AAS on aggression have been extensively studied. Aggression is a behavioral effect frequently associated with AAS exposure, which can result from a combination of various factors. The chemical

composition of AAS, hormonal context, environmental conditions, physical provocation, and social interactions all play significant roles in the expression of aggression (Kanayama et al., 2010; Lumia et al., 2010). These factors can influence AAS users' tendencies to respond to social encounters with increased vigilance and enhanced motivation.

High doses of AAS used by athletes can have psychological and neurological side effects. It has been shown that high-dose AAS use increases the risk of emotional and psychotic syndromes, as well as psychological dependence (Bahrke et al., 1996; Zelleroth et al., 2021). Additionally, the phenomenon known as "roid rage" suggests that behavioral changes in AAS users are side effects of these substances (Lumia et al., 2010).

Endogenous androgens and estrogens affect the nervous system in both males and females, altering behavioral responses. However, the notion that AAS directly causes aggression has been re-evaluated by recent studies. It has been highlighted that men with AAS dependence are not typically more violent, but they are more likely to have a history of behavioral disorders and psychopathology (Kanayama et al., 2010).

In conclusion, studies on the effects of AAS on brain development and behavior indicate that the use of these substances can lead to a wide range of neurological and psychological effects. Exposure to AAS during adolescence can alter the normal course of brain development and increase vulnerability to psychopathological conditions and maladaptive behaviors. Therefore, further research on the neurological and psychological effects of AAS is essential, and healthcare professionals should carefully manage the use of these substances.

Evaluating the potential risks and benefits of AAS use requires comprehensive and ongoing research to understand and manage their health impacts. This research will be crucial in determining the long-term effects of AAS and in developing more informed approaches to their clinical use.

Conclusion

This study comprehensively examines the biological and psychological effects of anabolic-androgenic steroids (AAS). The findings demonstrate that AAS use can lead to significant health issues in both men and women. In men, increased testosterone levels support the development of secondary sexual characteristics; however, excessive use has been associated with testicular atrophy, reduced sperm production, and loss of libido. In women, AAS use has been linked to side effects such as hirsutism, voice deepening, and menstrual irregularities. These findings clearly indicate that AAS have detrimental effects on sexual health and the reproductive system.

Beyond biological effects, the psychological impacts of AAS use are also profound. Research indicates that AAS users show increased tendencies towards aggression and violent behavior, which are often associated with pre-existing psychopathology, behavioral disorders, and a history of drug addiction. The phenomenon known as "roid rage" suggests that AAS users attribute their behavioral changes to the side effects of AAS, such as psychosis or paranoia, which has even been used as a legal defense. This highlights that AAS use has implications not only for individual health but also for public safety and the legal system.

Long-term and high-dose AAS use leads to serious pathophysiological changes in vital organs such as the heart, liver, and kidneys. Effects such as myocardial hypertrophy, increased liver enzyme levels, and impaired kidney function indicate that AAS use causes systemic toxicity. Additionally, changes in muscle tissue and overall body composition negatively impact the general health status of AAS users. Psychologically, AAS use alters behavioral responses to sensory and social stimuli. Users often become more aggressive and active, negatively affecting social relationships and daily life. These findings suggest that AAS have broad impacts not only on physical health but also on psychosocial well-being.

In conclusion, the biological and psychological effects of AAS use result in significant health and behavioral impairments in users. Therefore, it is crucial to regulate AAS use and develop more effective policies to prevent the abuse of these substances. Awareness campaigns should be conducted to inform the public, especially young athletes, about the adverse effects of these substances. There should be collaboration among healthcare professionals, educators, and policymakers to develop comprehensive strategies to prevent AAS abuse. In this context, early intervention and treatment programs should be implemented to prevent AAS dependence.

Scientific Ethics Declaration

* The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

*This research's ethical approval was obtained from the Aydın Adnan Menderes University Social and Human Sciences Ethics Committee.

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