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Brief review

Testosterone and anabolic androgenic steroids: Impact on acute kidney injury

Testosterona y esteroides androgénicos anabolizantes: impacto en la lesión renal aguda

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ABSTRACT

The synthesis of testosterone and its modifications have allowed its use in treating medical conditions of hormonal deficiency. Currently, the most common use of anabolic-androgenic steroids (AAS)—synthetic testosterone derivatives—is for purposes other than medical treatment. Various complications have been reported among AAS users, with cardiovascular and hepatic complications being the best documented; direct renal toxicity is less well understood. AAS-associated acute kidney injury (AKI-AAS) is an emerging entity, resulting from the increased number of reported cases and greater use of these agents, although its true prevalence is unknown. Analysis of clinical cases suggests that the main mechanisms involved in AKI-AAS are indirect. This review examines the main mechanisms of kidney injury in users of these agents.

Palabras clave:
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Rabdomiólisis
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RESUMEN

La síntesis de testosterona y sus modificaciones, han permitido utilizarla para tratar situaciones médicas de deficiencia hormonal. Actualmente, el uso más común de los esteroides androgénicos anabolizantes (EAA) —derivados sintéticos de testosterona— es con fines diferentes al tratamiento médico. Entre los usuarios de EAA se han reportado diversas complicaciones, siendo las cardiovasculares y hepáticas las mejor documentadas; la toxicidad renal directa es menos conocida. La lesión renal aguda asociada a EAA (LRA-EAA) es una entidad emergente, a raíz del mayor número de casos comunicados, y mayor consumo de estos agentes, aunque su prevalencia real es desconocida. Del análisis de casos clínicos, se deduce que los principales mecanismos involucrados en LRA-EAA son indirectos. En esta revisión, se estudian los principales mecanismos de lesión renal, en usuarios de estos agentes.

Introduction

Testosterone was first synthesized in the 1930s, independently by Croatian Leopold Ruzicka and German Adolf Butenandt. The pharmacokinetic characteristics of this hormone limited its clinical utility. Once the original testosterone molecule was synthesized, the pharmaceutical industry made various modifications, leading to the development of anabolic androgenic steroids (AAS).[1] These began to be used in sporting competitions in the 1950s and 1960s.[1] During that same period, the scientific literature already documented some experiences with the therapeutic use of AAS in severe renal failure[2] and in acute kidney injury (AKI).[3] However, in recent years, with the development of various molecules and their widespread use in the general population—often without medical supervision—the adverse effects of these agents have increasingly come to light.[1,4]

The increase in serum creatinine levels—a widely used biomarker for defining AKI syndrome[5]—has limitations in users of these agents[6]: on the one hand, it may reflect an increase in muscle mass inherent to the AAS effect per se—rather than renal dysfunction—or, conversely, delay the diagnosis of acute kidney injury (AKI) by rising only once glomerular filtration rate has already declined. Considering that structural renal injury may precede functional injury, and with the aforementioned limitations of serum creatinine in AKI,[5,6] this review analyzes the impact on AKI of testosterone supplementation, as well as that of AAS use (AAS-AKI).

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Testosterone

Testosterone, the main male sex hormone, is a key hormone in the body, with actions not only in the reproductive system but also responsible for systemic health—both physical and mental.[7] Its production takes place primarily in the testicular Leydig cells, under hormonal influence of the hypothalamic-pituitary axis: specifically, every 90 min the hypothalamus generates pulses of gonadotropin-releasing hormone; the action of this on the anterior pituitary produces luteinizing hormone, released into the systemic circulation. This hormone, acting on the testis, produces testosterone.[8] Plasma testosterone levels are maintained within the normal range (300–800 ng/dL) through negative feedback with the hypothalamic-pituitary axis, thereby preventing testosterone excess in the body.[8] Apart from the testes, testosterone production has also been reported in the adrenal cortex, liver, kidney, muscle tissue, and adipose tissue, albeit in smaller amounts.[9]

Main biological actions of testosterone

The actions of testosterone extend beyond its role in male sexual and reproductive function. Maintaining normal testosterone levels involves actions on the cardiovascular system (promoting vasodilation and reducing atherosclerotic plaque formation); it contributes to increased muscle mass—through enhanced muscle protein synthesis—; participates in body fat distribution and in the maintenance of bone mass.[7] It also plays a relevant role in erythropoiesis. This hormone is likewise key for cognitive function and mood. To exert these actions, testosterone binds to the sole identified androgen receptor, whose gene is located on the X chromosome.[7]

Renal effects of testosterone

In experimental models of renal ischemia/reperfusion injury in rats, a decrease in plasma testosterone is observed. Patil et al. demonstrated that administration of low-dose testosterone (20 μg/kg) to male rats 3 h post-reperfusion protected against ischemia/reperfusion-induced AKI, due to its anti-inflammatory effect by reducing T-cell infiltration in the kidney.[10]

The vasodilatory effect of testosterone on the afferent arteriole has been demonstrated in animal models.[11] In humans, studies suggest that androgen deprivation therapy used in prostate cancer could antagonize this vasodilatory effect of testosterone on renal vessels and predispose to AKI development.[12–14] Thus, discontinuation of androgen deprivation therapy, with recovery of testosterone levels, could favor improvement of renal function.[12]

Conversely, in experimental animal models of unilateral ureteral obstruction, Metcalfe et al. reported that endogenous testosterone production in male rats and in oophorectomized female rats administered exogenous testosterone resulted in increased tumor necrosis factor-alpha (TNF-α), leading to increased tubulointerstitial fibrosis and renal damage.[15]

Relationship between chronic kidney disease and testosterone

In the body, testosterone synthesis and regulation may be compromised in various ways: in addition to endocrine processes, such as diseases affecting the testis (primary hypogonadism) or the hypothalamic-pituitary-gonadal axis (secondary hypogonadism), systemic diseases may also lead to hormonal dysregulation resulting in testosterone deficiency.[7] Among the latter, chronic kidney disease (CKD) produces a functional hypogonadism, potentially reversible, in which the hypothalamic-pituitary-gonadal axis is affected by external factors[7]: accumulation of uremic toxins—related to reduced clearance—, chronic inflammation, nutritional deficiencies, erythropoietin therapy for renal anemia, and alterations in sex hormone-binding globulin metabolism may lead to testosterone deficiency in CKD, as reported in a recent study.[16] Furthermore, this condition confers a worse prognosis in certain groups, such as patients on hemodialysis.[17]

Testosterone supplementation

Testosterone supplementation may be necessary in certain clinical situations. First, it should be noted that from the third decade of life, testosterone levels progressively decline with age.[8] Also, in certain endocrinological diseases such as primary or secondary hypogonadism, testosterone levels are reduced.[7] In some of these clinical situations, testosterone supplementation may improve symptoms. However, due to the potential adverse effects of supplementation, its medical use is limited to specific indications, primarily in men older than 50 years with overt hypogonadism; it is contraindicated in patients with cardiovascular disease and prostate cancer, and few studies have analyzed its long-term effectiveness.[8] Regarding the effects of testosterone supplementation on AKI, studies show contradictory results: Greenberg et al. indicate an increased risk of AKI in patients receiving this therapy (RR: 1.53);[18] conversely, Bonnet et al. conclude that this treatment, in diabetic men with hypogonadism, was associated with reductions in AKI (HR: 0.93) as well as in renal failure requiring renal replacement therapy (HR: 0.81).[19]

Anabolic androgenic steroids

Definitions

Testosterone has a short half-life of approximately 10 min—due primarily to the hepatic first-pass effect—which is why it has limited clinical utility.[1,4] Modifications of this molecule by pharmaceutical companies have allowed its therapeutic use.[1,4]

Currently, the use of AAS—synthetic testosterone derivatives—often without medical supervision, represents a public health problem, mainly due to their potential consequences, which are often underestimated or unknown to users of these agents.[4,20] Increased muscle mass and physical performance, as well as improved physical appearance, are among the goals pursued by regular users of these substances. Moreover, the ease of obtaining these molecules through various channels (the internet, gyms, veterinary products, etc.), at supraphysiological doses and with the perception of being safe among the population, are additional reasons for healthcare professionals to be alert to possible cases of AAS abuse and to implement educational measures to prevent potentially serious consequences.[4]

The modifications made to the original molecule allow different routes of administration (oral/parenteral): changes to the testosterone ring allow use by either oral or parenteral routes; esterification of the 17β-hydroxyl group allows parenteral application, while alkylation of the 17α-methyl group produces orally administered derivatives.[1,4] Formulations for use in gel or skin patches also exist.

Prevalence of anabolic androgenic steroid use

The true prevalence of use of these substances is difficult to establish: in addition to social aspects—lack of acknowledgment of use among regular consumers—legal issues are compounded, as these are illicit substances when used outside medical indication and are prohibited in competitive sports. In 2014, a large meta-analysis including 187 studies reported a worldwide lifetime prevalence of AAS use of 3.3%, with a higher prevalence among males (6.4%) compared to females (1.6%).[21] However, a more recent meta-analysis focused on the female population describes an increase in female prevalence to 4%, with female bodybuilders representing a higher-

prevalence subgroup (16.8%) compared to athletes/gym users (4.4%) or the general population (1.6%).[22] Therefore, the lack of acknowledgment of use, along with the heterogeneity of studies regarding agent type, dose, and period of use, combined with methodological limitations, means that the true prevalence of use is likely underestimated.

Adverse effects associated with anabolic androgenic steroid use

The existence of a single androgen receptor may contribute to adverse side effects from AAS abuse.[7] Under normal conditions, testosterone is converted to estradiol by the aromatase enzyme. Estradiol promotes water retention, breast tissue proliferation, and body fat accumulation. Excess free testosterone, as a consequence of supraphysiological AAS doses, results in increased estradiol, contributing to dyslipidemia and atherogenesis.[23]

The beneficial effects of increased muscle mass, improved performance and physical appearance, are primarily sought by these users. However, the existence of a single androgen receptor means that these substances, in addition to anabolic—'desirable'—actions, are not free of androgenic—'undesirable'—actions, which attempts have been made to avoid or minimize during the synthesis of these molecules.[1] Among the side effects associated with AAS use, the following are described: effects on the genital and reproductive system (exogenous testosterone supplementation acts as negative feedback on the hypothalamic-pituitary axis, leading to hypogonadism, with subsequent consequences of erectile dysfunction, testicular atrophy, spermatogenesis alterations, and infertility); cutaneous alterations (alopecia, acne, or hirsutism); hematological alterations (increased erythropoiesis and high risk of thrombosis), and alterations in mood and behavior.[24]

However, among the major systemic complications—cardiovascular and hepatic—there is more consistent evidence, compared to renal complications, where the evidence is more limited.

Cardiovascular diseases associated with AAS abuse are well documented.[23,25] The use of supraphysiological doses of AAS implies the appearance of a high cardiovascular risk scenario, which may be reached through several pathophysiological mechanisms: hypertension—often uncontrolled—; dyslipidemia and atherothrombosis; arterial stiffness and endothelial dysfunction; alterations in cardiac muscle, with development of left ventricular hypertrophy and severe myocardial dysfunction, which may predispose to cardiac arrhythmias; or development of thrombotic events such as myocardial infarction, stroke, deep vein thrombosis, or thromboembolism. For all these reasons, AAS abuse has been linked to increased mortality and even sudden death compared to the non-using population.[23] The study by Horwitz et al. describes a 3-fold higher mortality risk in AAS users.[26] Similarly, the recent study by Windfeld-Mathiasen et al. reached an analogous conclusion, with an HR of 2.8 times higher among Danish men sanctioned for 2 years for doping, compared to a control group of non-users, considering both natural and non-natural causes of death.[27] Cardiovascular events have been reported among the causes of mortality. In the Danish cohort of Windfeld-Mathiasen et al., an increased risk of acute myocardial infarction, need for percutaneous coronary interventions, venous thromboembolism, arrhythmias, cardiomyopathy, and heart failure is noted.[25]

Hepatotoxicity related to AAS is also well recognized.[28,29] The advantage of using 17α-alkylated steroids orally, compared to other intramuscular preparations, has been associated with increased direct hepatotoxicity, given the shorter interval between exposure and hepatic damage, as well as a dose-dependent relationship.[30] It has been speculated that these testosterone derivatives might retain bile salts within hepatocytes, causing hepatocellular damage.[29] Another potential mechanism suggested is the role of these hormones in influencing the expression and function of canalicular ABC transporters, resulting in impaired conjugated bilirubin excretion, leading to the development of cholestasis.[29] It is in these latter cholestatic forms where generally higher bilirubin levels are detected, compared to hepatocellular damage.[29] Other hepatic disorders detected in both animals and humans include the development of hepatic peliosis, adenomas, and even hepatocarcinomas.[30]

Adverse renal effects associated with anabolic androgenic steroid use

The greatest available evidence of multiple potential pathways for renal damage by AAS comes from experimental animal studies.[6] However, in humans, it is more difficult to establish a direct association between use and renal toxicity, due to the existence of limiting factors, including: simultaneous use of several AAS, combination with other 'nutritional' supplements and vitamins—without regulatory oversight by health authorities—, concomitant use with other non-androgenic anabolic hormones—such as insulin or growth hormone—, polypharmacy (diuretics, non-steroidal anti-inflammatory drugs, etc.), and even use of other recreational substances such as cannabis, cocaine, or alcohol.[6,31]

The main direct nephrotoxicity linked to AAS abuse that is emerging in humans is podocyte toxicity, based on reported cases of focal segmental glomerulosclerosis (FSGS) among chronic users.[32] In addition to this direct renal toxicity, the increased body muscle mass of these patients, together with high-protein diets—particularly in the presence of pre-existing renal dysfunction—would indirectly contribute to renal damage through adaptive changes in glomeruli resulting from glomerular hyperfiltration.[32]

Furthermore, excess androgens (due to supraphysiological AAS doses) maintained over the long term can cause CKD through several pathways: activation of the renin-angiotensin-aldosterone system (with consequent increase in blood pressure and tubular water and sodium retention); increased endothelin (renal arteriole vasoconstriction); increased oxidative stress and pro-inflammatory cytokines, among other factors.[6]

Impact of sexual dimorphism on acute kidney injury

The incidence of AKI is higher in males compared to females.[33] The meta-analysis by Lima-Posada et al., including 83 studies involving 240 million patients, provides evidence for this finding.[34] Specifically, the role of sex hormones is linked to AKI. Although elements such as the renin-angiotensin-aldosterone system, oxidative stress, inflammatory markers, and apoptosis are involved in renal injury, sex hormones (testosterone and estrogens) regulate how these factors participate in the development of renal failure: estrogens exert a renoprotective effect by promoting renal vasodilation and reducing inflammation, oxidative stress, and apoptosis, while testosterone exerts opposing actions that promote renal failure.[34]

Impact of anabolic androgenic steroids on acute kidney injury

The evidence for direct renal toxicity from AAS is limited and is primarily related to podocyte damage.[31,35]

Prevalence of acute kidney injury associated with anabolic androgenic steroids

The lack of consistent prospective studies, as well as specific registries focused on AAS-AKI, means that the true prevalence of this complication among AAS users is unknown. Nevertheless, indirectly, we can infer a continuously growing public health problem.

Until relatively recently, AKI related to AAS use was considered a rare complication.[36] However, the widespread use of these substances in different population groups has led to increasingly frequent

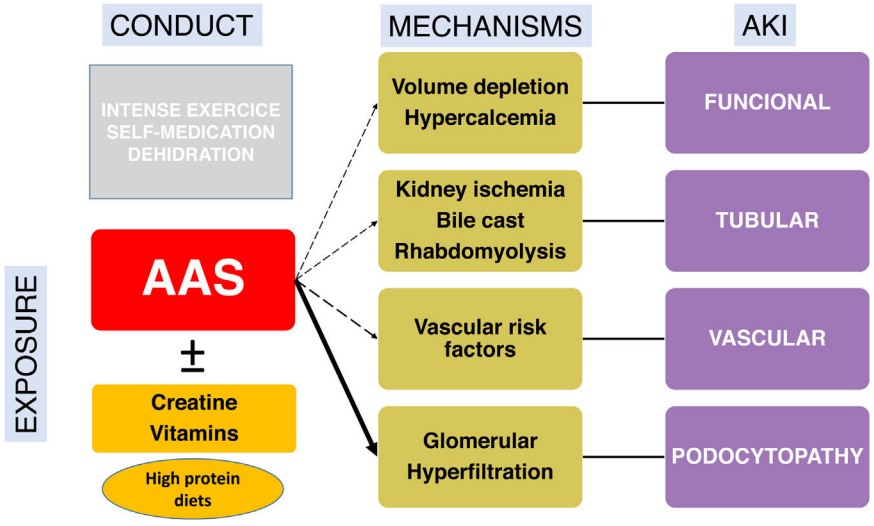

Figure 1. Summary of the main pathophysiological mechanisms involved in the pathogenesis of acute kidney injury. AAS: anabolic androgenic steroids.

detection in clinical practice, with a growing number of reported cases in the medical literature.[37–41]

In the Spanish and Latin American Registry of Drug-Induced Liver Injury (DILI), hepatic damage from AAS use increased from 1% (5 cases in the period 2001–2009) to 8% (15 cases over 4 years from 2010 to 2013), suggesting that a similarly growing prevalence of AAS-AKI cases could be extrapolated.[29] In this DILI Registry, of the 20 cases reported from AAS use, only 6 patients developed concurrent renal dysfunction along with hepatic failure, with peak total bilirubin and cholestatic damage being indirect risk factors for renal dysfunction.[29] Analysis of the profile of patients with AAS-related hepatic failure reveals males with a mean age of 32 years, with stanozolol alone or in combination with other AAS being the main AAS implicated in this hepatic damage.

Therefore, the growing prevalence of use of these substances (likely underestimated), combined with the increasing number of AKI cases described in the scientific literature, suggests a rising prevalence of AAS-AKI, which remains currently unknown.

Potential mechanisms of anabolic androgenic steroids in acute kidney injury

Analysis of clinical cases or case series of AAS-AKI reported in the medical literature[35–41] suggests that it is primarily indirect mechanisms, rather than direct toxicity per se (for which there is less scientific evidence), that may contribute to AKI in AAS users. Different types of AKI have been described according to the underlying causative factors, summarized in Fig. 1. Table 1 presents cases with different potential mechanisms involved in AAS-AKI.

AKI associated with functional causative factors

Several causes have been linked to the development of prerenal or functional AKI in these patients: On one hand, hypovolemia due to surreptitious diuretic use—as part of the strategy employed by AAS users to improve physical appearance—can lead to the development of prerenal AKI.[6]

Table 1
Analysis of cases with potential mechanisms of acute kidney injury associated with anabolic androgenic steroid use.

Case	Sex, age/activity	AAS involved	Dose/duration	Cause of AKI
Yoshida et al., 1994[37]	Male, 26 years, athlete	Stanozolol	125 mg, intramuscular, twice/week for 1 month before symptoms.	Cholestasis/acute tubular necrosis
Habscheid et al., 1999[38]	Male, 28 years, bodybuilder	Methandienone/ Stanozolol	10–50 mg/day PO/50 mg IM every 2 days/80 days	Cholestasis, bilirubin 77.9 mg/dl
Luciano et al., 2014[39]	Male, 41 years, bodybuilder	Nandrolone/ Testosterone/ metandrostenolone	Injection of: nandrolone 400 mg, 2/ week; testosterone, 400 mg, 1/week; Oral: metandrostenolone 60 mg daily/ 6 weeks before	Cholemic nephrosis
Flores et al., 2016[40]	Male, 31 years	Different ingredients	Dietary supplements (+AAS)/16 weeks before	Cholestasis, bilirubin 53 mg/dL
Gnanapandithan et al., 2019[35]	Male, 33 years	Trenbolone	2 injections the week before	Rhabdomyolysis (CK > 100,000 μ/l)
Machado Luchi et al., 2015[42]	Male, 21 years	Calcium supplements/ vitamins A, D/nandrolone	25 mg/mL weekly, months	Hypercalcemia/nephrocalcinosis
Bento C et al., 2015[43]	Male, 31 years, bodybuilder	AAS+/Veterinary multivitamin A, D, E/ Mineral oil IM	4 years; Monthly/Two years	Volume depletion (vomiting) + hypercalcemia
Unai et al., 2013[46]	Male, 42 years	Testosterone complexes	Years	Multiorgan failure
Leminski et al., 2022[44]	Male, 34 years	Testosterone/Stanozolol	Variable use, months	Bilateral renal infarction

AAS: anabolic androgenic steroids; IM: intramuscular; AKI: acute kidney injury; PO: per os (oral).

AAS users also tend to use other components, including vitamin complexes. A veterinary compound (containing vitamins A, D, and E), used to treat vitamin deficiencies and infections in animals, has been used by bodybuilders.[6] Generally, the vitamin doses used as AAS supplements exceed physiological limits and can produce chronic hypercalcemia. Thus, both volume depletion—due to gastrointestinal symptoms (nausea and vomiting)—and renal vasoconstriction caused by hypercalcemia can produce functional AKI. However, Machado Luchi et al. describe the case of a 21-year-old male with nephrocalcinosis who presented AKI secondary to hypercalcemia, but in this case the reported daily intake of a caloric supplement with calcium and vitamins (A and D) contained doses close to the recommended levels, which did not in themselves justify the degree of hypercalcemia presented (total calcium 14 mg/dL), suggesting the potential role of the AAS used (weekly intramuscular injections of nandrolone decanoate 25 mg) as a potential mechanism in the genesis of hypercalcemia.[42] Bento et al. describe the case of a 30-year-old bodybuilder who had been consuming for more than 4 years the vitamin complex: vitamin A (2,100,000 IU), D (ergocalciferol: 60,000 IU), and E (55 IU) monthly, in addition to AAS.[43]

Chronic AAS consumption and the associated vascular risk factors —such as hypertension, dyslipidemia, prothrombotic states—can lead to cardiac dysfunction through alterations in cardiac structure, particularly with the development of left ventricular hypertrophy and myocardial dysfunction.[23,25] These alterations may result in reduced renal perfusion, causing functional AKI in the context of cardiorenal syndrome.

AKI due to causative factors with potential parenchymal damage

Sustained renal vasoconstriction over time, from chronic high-dose vitamin use or other substances such as ephedrine, may be associated with the development of parenchymal AKI due to renal ischemia, with both acute tubular necrosis and acute interstitial nephropathy described.[28]

Bile acid nephropathy, or cholemic nephrosis, is a well-recognized entity in patients with severe cholestatic liver disease and is also present among AAS users.[39,40] As a consequence of hepatic damage, biliary transport is reduced, producing cholestasis with elevated bilirubin and bile acid levels that indirectly damage renal tubules.[30] Among the mechanisms involved in renal damage in cholemic nephrosis, in addition to reduced renal perfusion, there is increased tubular reabsorption of the high filtered load of bile acids, as well as formation of bile casts that obstruct tubules, leading to tubular damage.[39] Bilirubin levels above 21 mg/dL have been reported to contribute to renal damage.[29] In 1994, Yoshida et al. reported the first case of acute tubular necrosis, confirmed by renal biopsy, related to stanozolol abuse in a 26-year-old male.[37] Since then, additional cases of bile salt nephropathy have been published.[39]

Rhabdomyolysis is another indirect mechanism of tubular damage that can develop in AAS users. Specifically, the combination of significant muscle mass, moderate-to-intense exercise, and intramuscular AAS administration carries a risk of developing rhabdomyolysis.[35,41] As a consequence, the release of myocyte components into the systemic circulation ultimately damages the tubules through obstruction and direct tubular toxicity.

AKI due to vascular causative factors

High-dose AAS consumption has been associated with alterations in lipid metabolism (reduction of HDL cholesterol and increase of LDL cholesterol, decrease of apolipoprotein A1), increased hematopoiesis and alterations in platelet aggregation, as well as a greater risk of hypertension.[23,25] In this context, Leminski et al. report an exceptional case of bilateral renal artery thrombosis in a 34-year-old bodybuilder with chronic testosterone and stanozolol supplementation.[44]

AKI due to other potential mechanisms

Regular intramuscular administration of AAS can lead to abscess formation at the injection site, a complication that can progress to septic shock and adult respiratory distress syndrome, as described in the case reported by Herr et al.[45] It has also been speculated that AKI could be associated with multi-organ dysfunction, in the context of a possible immunomodulatory role of AAS, as described in the case by Unai et al.,[46] in which a healthy AAS user presented with multi-organ dysfunction. However, the role of AAS in the immune response in humans is not well understood, and no relevant studies are available; the evidence is limited to specific studies with small sample sizes[47,48] or isolated case reports.[49]

Diagnostic approach to acute kidney injury associated with anabolic androgenic steroids

Medical history

The illicit use of AAS for purposes other than therapeutic, obtained illegally, without guarantees regarding the final composition of the product, and without medical supervision, makes users reluctant to acknowledge their use: AKI in these individuals can pose a diagnostic challenge. In a specific profile of subjects with significant musculature, athletes or young people who regularly attend gyms, presenting with AKI of unknown etiology, the initial diagnostic suspicion should focus on taking a careful and directed medical history, explicitly asking about the use of these substances, frequency and dose used, duration of exposure, and whether there is combination with other types of substances (nutritional or recreational supplements). On physical examination, in addition to significant muscular development, the presence of reduced adipose tissue or testicular atrophy may be relevant, as well as the finding of unacknowledged hypertension. In cases of AKI with atypical evolution or without a clear cause, after careful initial evaluation, it may be necessary to perform a diagnostic renal biopsy.

Assessment of renal function with serum creatinine

Serum creatinine is a skeletal muscle derivative used as a marker of renal function.[5,6] Although various biomarkers in blood and urine have been identified that allow early identification of AKI, they are not routinely used in clinical practice. In contrast, serum creatinine remains the primary biomarker most commonly used, with the disadvantage that its elevation occurs after renal injury, which may delay the diagnosis of AKI.

Furthermore, serum creatinine also reflects muscle mass: an elevation of plasma creatinine in AAS users may reflect muscular hypertrophy or, conversely, renal damage. In these patients, a 24-h urine creatinine clearance can be used to estimate glomerular filtration rate.

In addition to serum creatinine, another biomarker unaffected by muscle mass is cystatin C.[6] Some authors recommend estimating glomerular filtration rate using a combination of these 2 biomarkers.[20]

Treatment of renal disease associated with anabolic androgenic steroid use

Prevention

The main known complications associated with AAS use could be avoided through the application of prevention and risk awareness strategies, which implies that, as healthcare professionals, health education measures should be implemented in populations particu-

larly vulnerable to and at risk of AAS abuse, such as young people and athletes.

General measures

When a complication related to AAS use is diagnosed, the first measure is its definitive discontinuation. However, this measure may be difficult to achieve in certain users, since chronic use can generate dependence and relapse into use.[31] Likewise, other substances that may be implicated should be suspended, and nutritional measures should be reviewed, limiting high protein intake, particularly if pre-existing renal dysfunction is present.[6]

Hydration should be adequate, avoiding dehydration states, which are favored by diuretic use without medical supervision.[6]

Other general health recommendations include weight loss, as well as avoidance of strenuous physical exercise.[31]

Vascular risk factors, generally present as side effects of AAS use, should be controlled: hypertension with renin-angiotensin-aldosterone system inhibitors—for their antiproteinuric effect—, dyslipidemia with lipid-lowering agents, and in thrombotic states, antiplatelet or anticoagulant agents should be considered.[23,25,31]

Regarding specific complications, hypercalcemia can be treated with vigorous hydration with 0.9% saline solution, furosemide, or bisphosphonates, with the prior prerequisite of suspending all exogenous calcium or vitamin supplements; in some cases, corticosteroids may also be necessary.[42,43] Corticosteroids can also be used in cases of associated acute tubulointerstitial nephropathy.[28]

In the case of cholemic nephrosis: treatment of this nephropathy involves identifying and treating reversible causes of cholestatic liver disease.[39] In specific cases, the use of plasmapheresis has been described as a measure to reduce the circulating burden of bile acids and thereby alleviate refractory pruritus symptoms.[40]

Regarding the treatment of rhabdomyolysis, intensive hydration, urinary alkalinization, and forced diuresis are fundamental pillars to apply regardless of the causative etiology.[35,41]

In cases of anuria, uremic symptoms, or electrolyte alterations that do not respond to medical treatment, renal support therapy with hemodialysis may be necessary.

Future research directions

The long-term medical consequences of AAS use are not fully understood. In view of the growing prevalence of use of these testosterone derivatives and their potential complications, it appears necessary to conduct studies to improve knowledge. In particular, studies evaluating dose-response relationships, reversibility of renal function after cessation of use, as well as the creation of specific registries to determine the true magnitude of the problem and improve the characterization of an emerging entity, are needed.

In conclusion, the increasing number of cases of AAS-associated acute kidney injury suggests a growing trend of this complication, although its true prevalence remains unknown; from the analysis of documented cases, it can be deduced that the main potential mechanisms of acute kidney injury with these agents are indirect.

Ethical considerations

This work does not include experimentation on humans or animals. The ethical standards applicable to the publication of scientific work are respected.

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