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REVIEW

Doping and sports endocrinology: anabolic-androgenic steroids

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Abstract The use of anabolic steroids affects not only professional athletes but also the general population (bodybuilders, gym clients, and adolescents). In the first case, its use is prohibited and sanctioned by the World Anti-Doping Agency and Olympic committees. For the other users, it is difficult to establish its prevalence since many obtain the products via the internet. The reasons for its use are varied and different forms of use and other types of users have been described. Among the side effects of steroid use, hypogonadism is the most frequent cause for endocrinological consultation. After a general introduction to doping, this review describes the historical background of anabolic–androgenic steroids, their classification, forms of use, physiological effects, adverse effects on different organs and systems, treatment of hypogonadism, as well as detection methods.

PALABRAS CLAVE
Anabolizantes;
Andrógenos;
Dopaje;
Atletas;
Gimnasio

Endocrinología del dopaje y los deportes: andrógenos anabolizantes

Resumen El consumo de anabolizantes hormonales afecta no solamente a atletas profesionales sino también a la población general (culturistas, clientes de gimnasios y adolescentes entre otros). En el primer caso su uso está prohibido y sancionado por la Agencia Mundial Anti-Dopaje y los comités olímpicos. Para los segundos es difícil establecer la prevalencia ya que muchos obtienen los productos a través de compras por Internet. Los motivos para su uso son diversos y se han descrito distintas formas de uso, así como diferentes tipologías de consumidores. Entre los efectos secundarios, el hipogonadismo es la causa más frecuente de consulta endocrinológica. En esta revisión se describen, tras una introducción general al dopaje, los

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antecedentes históricos de los andrógenos anabolizantes, su clasificación, las formas de uso, los efectos fisiológicos, los efectos adversos en diferentes órganos y sistemas, el tratamiento del hipogonadismo, así como los métodos de detección.

Doping is defined as ''the administration of drugs or stimulant substances to artificially boost the body's performance that is sometimes dangerous to health.''[1] It is not limited to competitive or elite athletes, which is the visible part of a vast iceberg and what often appears on the news, but rather there is a large underwater, hidden part that involves amateur athletes, trainers, and gym clients.

As there is generally only concern about legal problems in competition, its health effects are ignored; there is a false perception that it is a safe practice and that the side effects are insignificant and easily treated. Substances to boost physical performance are consumed at supraphysiological doses and various substances are often combined. This may cause complications that affect many organs and systems (such as the neuropsychiatric, cardiovascular, metabolic, endocrine, hepatic, or renal system, etc.) and can even cause death.[2]

The term ''doping'' was used for the first time in England in 1889 when opium extracts were used to treat racehorses. Egyptian wrestlers believed that animal testicles and penises had curative properties and were useful for fighting; the Indian physician Sushruta recommended eating them to increase virility. Greek and Roman athletes consumed plant extracts, mushrooms, and wine mixtures to compete in the Olympics.[3,4] In Latin America, stimulants such as cocaine and caffeine were widely consumed.

The trick is as old as mankind and thus has also been present in sports. Indeed, the International Olympic Committee established the first list of prohibited substances in 1967 and the World Anti-Doping Agency (WADA) was founded in 1999.[5]

The criteria for prohibition are based on the substance increasing physical performance but entailing a risk or adverse effect to health or going against good sportsmanship. The Olympic and Paralympic Committees of various countries as well as sports federations have accepted this list of prohibitions. Table 1 summarizes the substances prohibited by WADA in its most recent update in 2022. Up to 70 substances are listed among the anabolic agents.

According to the WADA, use of a prohibited substance is only allowed if the athlete needs it for therapeutic use for a documented disease, for example a physiological dose of an androgen or human chorionic gonadotropin (hCG) in previously diagnosed and well documented hypogonadism. This is called a therapeutic use exemption.

Many cases of doping have scandalized society and filled hundreds of pages of newsprint. The English cyclist Arthur Linton died in the middle of a race in 1886 after an overdose of trimethyl (a caffeine compound). Another cyclist, Tom Simpson, died with high levels of amphetamines in his blood while climbing Mont Ventoux in the 1967 Tour de France. Usain Bolt, considered the fastest man in the world, had to return his gold medal from the 2008 Beijing Olympic Games after one member of the Jamaican 4 × 100-meter relay team was found guilty of doping.[4]

Other cases have recently been reported in cyclists, such as Alberto Contador's use of clenbuterol, a sympathomimetic with an anabolic effect, or Lance Edward Armstrong, the seven-time consecutive Tour de France winner (1999–2005) who was stripped of the seven victories by the United States Anti-Doping Agency in 2012 when he confessed to doping with erythropoietin.

Skill-based sports require concentration, coordination, and quick reflexes and could benefit from drugs that reduce anxiety, tremor, and fatigue. Sports based on strength and muscle development are the target of anabolic-androgenic steroids. Sports that require endurance benefit from substances such as erythropoietin, transfusion, and mimetics. Lastly, those that require quick recovery benefit most of all from remodeling agents, such as growth hormone and growth factors.[6]

Most positive results on tests are due to hormone preparations and, in most cases, due to anabolic-androgenic steroids.

Hormone anabolic steroids

History

For more than 6,000 years, farmers have known that castrating animals facilitates their domestication.[7] In 1786, John Hunter performed the first testicular transplant from a rooster to a chicken. In the mid-19th century, experiments by Berthold also demonstrated that some substance in the testes was responsible for the growth of the comb and feathers in roosters, promoted their interest in the chickens, and increased their aggression toward other males. These characteristics were lost following castration only to be recovered after reimplantation of testicles onto the capons and even after a testicular transplant from another male.

Although the testicle is a testosterone-producing organ, it does not store it, unlike other endocrine glands such as the thyroids or pancreas. In addition, testosterone is inactivated by the liver when taken orally. Nevertheless, the consumption of testicles or extracts of it have been recommended since ancient times and in various cultures.

In contrast, castration—not taking to account social (eunuchs, slaves, harem guards), religious (*castrati*, or singing boys who were castrated to conserve the high ranges of a child's voice, but with the lung power of an adult), or punitive reasons—was recommended as a treatment for var-

Table 1 Substances prohibited by the World Anti-Doping Agency (WADA) in 2022.

A. Prohibited at all times (in competition and out of competition)
S0 Non-approved substances
Non-approved pharmacological substances or those which have no therapeutic indication or those only for veterinary use
S1 Anabolic agents
1. Anabolic-androgenic steroids
2. Other anabolic agents (clenbuterol, osilodrostat, SARMs, and others)
S2 Peptide hormones, growth factors, related substances, and mimetics
1. Erythropoietin and agents that affect erythropoiesis
2. Peptide hormones and their releasing factors:
2.1 Human chorionic gonadotropins (hCG), luteinizing hormone, and their releasing factors in males, e.g. buserelin, deslorelin, gonadorelin, goserelin, leuprorelin, nafarelin, and triptorelin
2.2 Corticotropin (ACTH) and their releasing factors, corticorelin
2.3 Growth hormone (GH), its analogs, and fragments
2.4 GH-releasing hormone (GHRH) and its analogs; GH secretagogs and mimetics (ghrelin, etc.), GH-releasing peptides (GHRP)
3. Growth factors and growth factor modulators
IGF-1 and analogues, FGF, PDGF, VEGF, etc.
S3 β-2 agonists
(There are exceptions for salbutamol, formoterol, and salmeterol, inhaled for therapeutic use depending on the dose/24 h and urine concentration)
S4 Hormone and metabolic modulators
1. Aromatase inhibitors
Androstenol, aminoglutethimide, anastrozole, testolactone, letrozole, etc.
2. Antiestrogens and selective estrogen receptor modulators (SERMs)
Clomifene, raloxifene, tamoxifen, raloxifene, fulvestrant, etc.
3. Agents preventing activin receptor activation
Myostatin inhibitors and neutralizing antibodies
4. Metabolic modulators, activators of the AMP-K, PPAR-δ agonists, insulins and insulin-mimetics, meldonium, and trimetazidine
S5 Diuretics and masking agents
Desmopressin, probenecid, plasma expanders such as dextran, mannitol, intravenous albumin; all diuretics and vaptans
There are exceptions for drospirenone and pamabrom as well as topical ophthalmic administration of carbonic anhydrase inhibitors (dorzolamide, brinzolamide) as well as for local administration of felypressin in dental anesthesia
M1 Manipulation of blood and blood components
M2 Chemical and physical manipulation
This refers to the manipulation of samples for control and intravenous infusions
M3 Gene and cell doping
Use of nucleic acids or analogues that may alter genome sequences or gene expression and the use of normal or modified cells
B. Prohibited in competition
S6 Stimulants
They are divided into *non-specified and specified stimulants*
They exclude clonidine, imidazole derivatives and adrenaline for ophthalmic or nasal use, and anesthetics such as bupropion, caffeine, nicotine, phenylephrine, pipradrol, synephrine, and phenylpropanolamine. Ephedrine, methylephedrine, pseudoephedrine, and norpseudoephedrine depend on urine concentrations
S7 Narcotics
Morphine and derivatives, methadone, oxycodone, fentanyl, pentazocine, pethidine, etc.
S8 Cannabinoids
Natural (hashish, marijuana) and synthetic, except cannabidiol
S9 Glucocorticoids
Administered through injectable, oral, or rectal route of administration
C. Prohibited only in particular sports
P1 Beta-blockers
Only in competition in automobile, billiards, darts, golf, skiing, and underwater sports. Also prohibited out of competition in shooting and archery

ious diseases such as lunacy, epilepsy, gout, priapism, and leprosy.

Brown Séquard (1817–1894), through his organ therapy, used extracts from the testes of pigs and dogs. Although his elixir contained truly homeopathic concentrations, he reported that it increased strength, mental capacity, and appetite. In addition, he stated that it cured constipation and, most of all, increased the length of the urinary stream. His product was a great commercial success, which led to various criticisms such as that of Harvey Cushing, who defined this practice as ''endocriminology.''[8] Oscar Zoth, winner of the Nobel Prize in Chemistry, together with his colleague Fritz Pregl were the first to use hormone extracts in athletes in 1869.

In 1929, the German Adolf Butenandt isolated the first sex hormone, estrone, and later the first androgen, androsterone, in the urine of a pregnant woman. He shared the 1939 Nobel Prize in Chemistry with Leopold Ružička. In 1935, Erns Laqueur and his collaborators isolated testosterone.

In 1950, athletes and body builders started to use testosterone and afterwards, in the 1952 and 1956 Olympic Games, the German and Soviet Union teams did. The magnificent results obtained by the German Democratic Republic after the 1960s, especially in women, notably attracted the public's attention and, after demonstrating their link to anabolic steroids, the International Olympic Committee prohibited them in 1974.[9,10] The most famous case of anabolic steroid abuse was that of Ben Johnson, who lost the gold medal he won after beating Carl Lewis the 100-meter dash finals in the 1988 Seoul Olympic Games for testing positive for stanozolol, a synthetic androgen.[11]

Since they have become commercially available, androgens, in addition to their use as replacement therapy in cases of hypogonadism, have demonstrated their benefit in some diseases such as anemia (before the introduction of erythropoietin), burns, growth with Turner syndrome, and wasting syndrome in HIV disease.[12] At present, the main indication of androgen treatment is replacement therapy in organic male hypogonadism (hypothalamic hypogonadism, Kallman syndrome and variants, hypogonadotropic hypogonadism, primary hypogonadism, genetic-Klinefelter syndrome, etc.) and in transgender hormone therapy.

However, in recent years, testosterone prescriptions have multiplied in relation to the diagnosis of functional hypogonadism, which is linked to the concept of late-onset hypogonadism. Its use in this disease is doubtful and, what's more, entails the possibility of androgenic dependence.[13] A low testosterone level with proportionally low sex hormone-binding globulin levels together with normal follicle-stimulating hormone and luteinizing hormone values is characteristic of pseudohypogonadism, which occurs in obesity. Functional hypogonadism is not a disease and treatment with testosterone is not justified unless there is evidence of its safety and efficacy is shown in clinical trials.[14]

Epidemiology

It is difficult to establish the frequency of use of androgens in the general population. Estimates vary widely (between 1% and 15%)[15] depending, logically, on the population studied; the rate is not the same when comparing students and body builders. At present, only 20% of users are professional athletes.[16]

Indeed, 68% of short- and long-distance runners in the 1976 Olympic Games of Montreal who were asked recognized having trained with anabolic steroids for the 1972 Olympic Games of Munich, which took place before their prohibition; in another study, all the weightlifters did.[17]

A survey of university students in the USA and various European countries revealed a rate of anabolic steroid use between 1% and 5%.[18] Another study on 6,000 Swedish adolescents revealed a figure of 2.8%–3.6% in males versus no cases in women.[19] A meta-analysis of various studies in different countries indicated a prevalence of 6.4% in men and 1.6% in women,[20] but there may have been overrepresentation of body builders, athletes, gymnasts, and prisoners in the sample.

In a German study, 13.5% of gym clients admitted to having taken anabolic steroids at some point, of which 3.9% were women.[21] In another Iranian study, the percentage of body builders who had used some type of substance to enhance physical performance was 51.7% and of these, 79.4% used anabolic-androgenic steroids.[22] A more recent study in a similar population found a rate of 36.2%.[23]

This disparity in results is due to the fact that many consumers hide their use either intentionally or out of ignorance.[20] On the opposite end, false positives may be due to mistaking anabolic steroids with corticosteroids or dietary products.[24]

The main reason for using androgens is to increase muscle mass and strength and, in subjects who do not compete, to improve physical appearance or body image, or what is known as vigorexia.[25] Users' expectations of results are based on the recommendations of friends, trainers, or information on the internet. Those who purchase products on the internet do not know exactly what they are buying, as it may not contain any of these substances or be a dangerous product. The countries where the use of anabolic steroids is most frequent are the USA, Brazil, Australia, and the Nordic countries of Europe. However, use is much lower in China, Korea, and Japan, where culturally, a muscular appearance is must less valued in men.

Several specific types of anabolic steroid users have been described.[26] Athletes have been consulted in various surveys about whether they would take a prohibited substance if it were not detected in order to win an Olympic medal (what is known as Goldman's dilemma), and a high percentage responded affirmatively.[27]

Generally, athletes administer anabolic steroids by stacking, or progressively increasing the dose over 6–12 weeks in order to then decrease it in the second part of the cycle. Various anabolic steroids tend to be used simultaneously, reaching doses that are 40–100 times higher than physiological levels. We have even observed recommended regimens for gymnasts in which the only weekly change was in the brand name.

Another form of administration is cycling, which involves periods of use and rest. In the rest period, many use tamoxifen and hCG to try to recover or restore testicular function.[13] Despite a lack of evidence, users believe these patterns of use lead to fewer undesirable effects and greater benefits.[10,11]

Types of anabolic steroids

Although the substances used should ideally only act as anabolic steroids and not have any androgenic or virilizing effect, the reality is that all exert both actions to a greater or lesser extent. In future developments in selective androgen receptor modulators (SARMs), the effects may be selectively modified, as has occurred with selective estrogen receptor modulators (SERMs).[28]

Androgens can be administered as transdermal testosterone in gel or patches. Their half-life is short. Therefore, testosterone esters in the 17 ®-hydroxyl group are administered in oil form through the parenteral route of administration (propionate, enantate, cypionate, undecanoate) in order to prolong their activity.

The elimination of the methyl group in position 19 gave rise to 19-nortestosterone and derivatives (nandrolone decanoate and phenpropionate) with a greater anabolizing effect than virilizing effect. These directly bind to androgen receptors and, after aromatization to estrone and estradiol, also to estrogen receptors.[29] A third type are alkylated compounds in the C-17-⟨, which are administered orally. They include, among others, oxymetholone, oxandrolone, metenolone, methandrostenolone, and stanozolol, which generate a slow hepatic metabolism that explains their greater toxicity.

Another form of increasing the rate of circulating androgens is through the administration of drugs that increase their endogenous production. This group includes gonadotropins (luteinizing hormone and hCG), aromatase inhibitors (anastrozole, letrozole, exemestane), SERMs (clomiphene, tamoxifen, raloxifene, bazedoxifene, fulvestrant, etc.), and lastly testosterone precursors (4-androstenedione, 4-androstenediol, 5-androstenediol, and dehydroepiandrosterone) or precursors of the synthetic androgen nandrolone (norandrostenedione, 4-norandrostenediol, and 5-norandrostenediol).

The most commonly used androgens in the population are testosterone and boldenone or trenbolone. The latter are only indicated for veterinary use. Among the doping substances most commonly detected by WADA in competitive athletes are testosterone, stanozolol, and nandrolone, especially among weightlifters and boxers.[2]

Many users often combine various doping substances in what is truly polypharmacy: for example, anabolic steroids are combined with growth hormone and aromatase inhibitors or SERMs to avoid side effects such as gynecomastia; thyroid hormones to lose weight are combined with diuretics that also serve to prevent its detection. What's more, others are used with opioids and alcohol.[30]

Effects of androgens

The main effect of androgens is muscle hypertrophy due to an increase in both type i and type ii muscle fiber thickness, the number of capillaries, and the number of myocyte nuclei per fiber, which could produce an increase in muscle strength.[31] The increase in protein synthesis with a positive nitrogen balance produces a gain of up to 37% when combining testosterone and exercise and only 10% with testosterone without exercise.[32]

Table 2 Adverse effects of anabolizing androgens.

Cardiovascular	Dyslipidemic arteriosclerotic disease
	Cardiomyopathy
	Arrhythmias
	Coagulation disorders
	Polycythemia
	Hypertension
Neuroendocrine	Hypogonadism due to suppression of the hypothalamic–pituitary axis
	Gynecomastia
	Prostatic hyperplasia and prostate cancer
	Virilizing effects in women (hirsutism, etc.)
Neuropsychiatric	Major mood disorders (depression, mania)
	Violence, aggression
	Dependence
	Neuronal apoptosis. Cognitive impairment
Hepatic	Inflammation and cholestasis
	Hepatic peliosis (rare)
	Tumors (rare)
Musculoskeletal	Epiphyseal closure in adolescents
	Tendon rupture
Renal	Renal failure secondary to rhabdomyolysis
	Focal segmental glomerulosclerosis
Immunological	Immunosuppressive effect
Dermatological	Acne
	Stretch marks

This dose-dependent muscle hypertrophy is manifested more in the muscles of the neck, shoulders, thorax, and arms due to a greater number of receptors; they return to their initial size after 12 weeks of suspension. The increase in muscle strength is not unanimously accepted by the scientific community[33] and is truly small and variable. Studies show conflicting results. In addition, there are few studies in women. Results in endurance sports, such as cycling, have also not been demonstrated.

Adverse effects

Table 2 summarizes the adverse effects due to consumption of anabolic-androgenic hormones. Most data have been obtained from case-control studies and, given the aforementioned polypharmacy, cannot always be attributed to androgens.

Cardiovascular effects

Arteriosclerotic disease is linked to dyslipidemia and characterized by a decrease in high-density lipoprotein (HDL) of between 30% and 50%, especially due to alkylated oral agents such as stanozolol[34] and an elevation of low-density lipoprotein (LDL cholesterol) with an increase is hepatic lipase activity.[10]

Cases of myocardial infarction and sudden death have been reported, with post-mortem studies that show ven-

tricular hypertrophy with fibrosis and cardiac myofibrillar dysfunction.[35] One work showed an increase in atheroma plaque with a decrease in ejection fraction after two years of using anabolic steroids compared to controls.[36] It has also been associated with a greater possibility of arrhythmias due to autonomic dysfunction.[37] Polycythemia together with abnormalities in coagulation factors as well as endothelial reactivity explain the greater incidence in thrombosis.[38]

Before the introduction of androgens, athletes had a greater risk of diabetes and coronary disease, but this has changed. A study in 62 Finnish weightlifters with a 12-year follow-up period showed a mortality rate of 12.9% (mean age 43 years) compared to 3.1% in the 1,094 people in the control group. Myocardial infarction and suicide were the most common causes of mortality.[39]

Neuropsychiatric effects

Many people who use anabolic steroids to improve their body image have previous neuropsychiatric problems. Studies confirm problems in impulse control, anxiety, mania, irritability, aggressiveness, and sometimes psychotic symptoms. These were most common among those who used supraphysiological doses, equivalent to more than 1 g of testosterone weekly.[2,40]

Exaggerated aggressiveness in the home setting and violent behavior, including attempts or cases of murder, have also been detected.[41] All of these psychiatric disorders are related to abnormalities in neurotransmitters such as serotonin and gamma-aminobutyric acid.[42] Supraphysiological doses of anabolic steroids exert a neurotoxic effect, with neuronal apoptosis and the possibility of developing cognitive impairment.[43]

Another aspect that must be considered is withdrawal syndrome, manifested in up to 30% of users and which has similar characteristics to opioid and alcohol withdrawal syndrome.[44]

Effects on the endocrine system

The administration of androgens suppresses the hypothalamic–pituitary–adrenal axis and, if use is prolonged, the resulting hypogonadism can last for months and years after suspending treatment,[45] with symptoms such as erectile dysfunction and decreased libido.[46] Atrophy of the seminiferous tubules and a decrease in testicular size occurs, which leads to infertility, with a decrease in sperm count of 73% and changes in spermatogenesis that are sometimes irreversible.[47]

Gynecomastia can occur, especially with androgens that aromatize to estrogens. Therefore, many add tamoxifen or aromatase inhibitors to prevent it or hCG to prevent testicular atrophy. Other effects include priapism and prostatic hypertrophy with a possible greater risk of cancer, with occasional cases reported in the literature.[2]

In women, amenorrhea or oligomenorrhea; mammary and uterine atrophy; and signs of virilization such as clitoromegaly, hirsutism, and androgenetic alopecia occur. Androgens can also be teratogenic.[48]

Treatment of hypogonadism. If the patient has been taking supraphysiological doses, a prudent measure would be to prescribe a dose that is two times as high as the physiological dose or a replacement dose for several weeks to progressively decrease the dose. This prevents withdrawal symptoms.[16,49] The use of estrogen-modulating agents can maintain erectile function after the suspension of testosterone.[50]

To treat infertility, clomiphene or hCG can be used.[51] The habitual dose tends to begin with 25 mg every two days, increasing by 25 mg every week until reaching a dose of 100 mg twice per week. The hCG dose is usually 1,000 to 3,000 IU two or three times per week. Spermatogenesis can also be recovered with a combination of a selective estrogen receptor modulator (SERM), hCG, aromatase inhibitor, and recombinant follicle stimulating hormone.[52]

Finally, supraphysiological doses can displace the cortisol from its receptors, inhibiting its catalytic effects.[15] In the thyroids, which have androgen receptors, they can alter function, with a decrease in total thyroxine and triiodothyronine and in the transporter globulin. In addition, gonadal steroids are the biggest regulator of the somatotropic axis, stimulating growth hormone secretion and the formation of IGF-1.[53]

Effects on the liver

Various hepatic abnormalities have been described, which range from mild, temporary increases in transaminases to severe, permanent forms depending on the doses, time of administration, and most of all the type; alkylated compounds are particularly hepatotoxic, although it can occur with any androgen.

Hyperplasia and cholestasis can occur with an elevation in bilirubin, alkaline phosphatase, and LDH with dose-dependent jaundice, and can yield upon stopping use. Adenomas and, more rarely, hepatocellular carcinomas have also been described, although a review has not demonstrated increased incidence.[9,54]

A typical complication with alkylated agents is hepatic peliosis, characterized by the formation of cystic cavities that can produce liver failure and internal bleeding.[10,55]

Other toxic effects

By increasing subcutaneous fat, androgens may contribute to acne in up to 50% of users. This skin complication is sometimes severe when it occurs the form of cystic acne and acne fulminans,[56] which is more often located on the torso. Curiously, it worsens with vitamin B supplements.[57] It can also form keloid scars, stretch marks, and skin marks from injections.

In adolescents, androgens produce premature epiphyseal closure that will lead to a shorter final height.

Prolonged androgen use has been associated with tendon ruptures in the upper limbs, which is a paradoxical effect to the anabolic effect and may be due to dysplasia of the collagen fibers.[16,58]

Rhabdomyolysis has been described in weightlifters who take anabolic steroids, with an elevation in CPK, creatinine, and myoglobinuria.[59] Some cases of focal segmental glomerulosclerosis have also been reported.[60]

As indicated above, androgens stimulate erythropoiesis, producing an increase in hematocrit and hemoglobin due to greater sensitivity to erythropoietin and suppression of hepcidin transcription.[61]

Finally, there is an increased risk of transmissible infections (hepatitis B and C, AIDS, etc.) arising from poor injection practices and hygiene. An online survey found that 13% of bodybuilders were exposed to these complications through sharing or reusing syringes or needles.[2] Bacterial or mycotic abscesses can form for this reason.[62]

Detection of anabolic-androgenic steroid doping

Anabolic steroid use may be suspected due to clinical signs (muscle development, acne, sexual dysfunction, and gynecomastia in men; androgenetic alopecia and hirsutism in women) and analytical data (suppression of gonadotropins, high testosterone levels, decrease in HDL cholesterol).

The implementation of Athlete Biological Passports by the WADA in 2009 was an important step for control, as it guarantees updated confirmation that the athlete has not consumed prohibited substances.[63,64]

For cases of legal use due to previous hypogonadism (therapeutic use exemption), it must be taken into account that the minimum washout period is two weeks for transdermal or gel testosterone, four weeks for oral undecanoate, eight weeks for intermediate-duration esters (enanthate cypionate) and 26 weeks for prolonged-action esters (injectable undecanoate), and up to 40 weeks for subcutaneous testosterone pellets. These periods tend to be longer if the doses are greater than physiological doses.[65]

The testosterone:epitestosterone ratio has also been used to detect doping. Epitestosterone is an isomer that segregates jointly with testosterone and is inactive. There is no conversion from testosterone to epitestosterone or vice-versa. The normal value of the testosterone:epitestosterone ratio is close to 1:1. A value greater than 6:1 is indicative of exogenous administration. The result can be masked with the simultaneous administration of epitestosterone.

The testosterone:epitestosterone ratio is also not valid in women because in women, androgens come from the ovaries and adrenal glands.[66] Therefore, other detection methods are needed, such as mass spectrometry and bioassays, which are easier and more economical, though they have the limitation of their standardization.[6,12] Another possibility is the use of biological matrices such as the hair, skin, saliva, or nails.[67]

Finally, regarding doping with indirect androgens, the following can be used: 1) testosterone precursors such as dehydroepiandrosterone and androstenedione; 2) gonadotropins; and 3) estrogen receptor antagonists and aromatase inhibitors.

Androstenedione is produced in the gonads and adrenal glands from dehydroepiandrosterone and is converted to testosterone via 17®- hydroxysteroid-dehydrogenase. Both androgens elevate testosterone levels and increase the testosterone:epitestosterone ratio. It can also be detected via mass spectrometry. The effect on muscle strength that gonadotropins produce is scarce. Recombinant luteinizing hormone and hCG require injectable administration several times a week and are expensive. Both can be detected via immunoassay or mass spectrometry,[68] although it is not valid to investigate hCG in women due to ethical reasons, given that it increases physiologically in pregnancy.

The described side effects of hCG are hyperglycemia and insulin resistance, decrease in thyroid function, adrenal insufficiency, carpal tunnel syndrome, arthralgia, myopathy, pancreatitis, hepatotoxicity, and possibility of neoplasms.[48]

The use of antiestrogens and aromatase inhibitors is based on the fact that estrogens are much more potent in inhibiting the gonadal axis. All of these have been prohibited by WADA since 2008, as are new SARMs. These modulating agents with specific action on different androgenic receptors are a field for future research in the development of new molecules indicated for various diseases[12] in which possible toxicity must be evaluated.[69]

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Conflicts of interest

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