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Doping with testosterone and androgenic/anabolic steroids: Impact on health, screening tools and medical care



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ABSTRACT

Doping in elite or amateur athletes with testosterone, androgens and anabolic steroids (A/AS) has as a main objective to develop muscle strength and mass to improve sports performance. Massive doping is a worldwide public health issue insufficiently known by physicians in general and by endocrinologists in particular. Yet, its prevalence, probably underestimated, would be between 1 and 5% at the international level. Numerous deleterious effects associated with A/AS abuse have been identified: inhibition of the gonadotropic axis responsible for hypogonadotropic hypogonadism and infertility in men, and masculinization (defeminization), hirsutism and anovulation in women. Metabolic (very low HDL cholesterol), hematological (polycythemia), psychiatric, cardiovascular and hepatic complications have also been documented. As a result, anti-doping agencies have developed increasingly effective techniques for detecting A/AS, both to identify and punish cheating athletes and to protect the health of the greatest number of them. These techniques use a combination of liquid and gas chromatographic methods coupled with mass spectrometry, known respectively by the acronyms LC-MS and GC-MS. These detection tools have a remarkable sensitivity and specificity to detect natural steroids and synthetic A/AS of known structure. Furthermore, by distinguishing isotopes, it is also possible to distinguish natural endogenous hormones, testosterone and androgenic precursors from those administered for doping purposes. For elite athletes, a “biological passport” has also been introduced. It consists of monitoring the evolution of steroids and their metabolites, as well as other biological parameters in the blood and urine over time after having established a basal state athlete signature, established, a priori, without doping. Better training of health professionals, general practitioners and specialists should be a priority for academic institutions and medical societies. It would provide them with better knowledge of the populations at risk and the clinical and biological semiology of male and female doping, including withdrawal syndrome associated with anxiety and depression following cessation of chronic A/AS use. The ultimate goal is to provide these physicians with the keys to treating these patients while combining medical rigor and empathy. These points will be addressed in this short manuscript.

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Doping with androgens and anabolic steroids (A/AS) as well as with substances aimed at increasing endogenous testosterone production is a real worldwide public health problem, unfortunately underestimated. Yet, this massive misuse can impact the health of men and women by triggering morbidities that can even increase mortality [1–3]. It is also a controversial field, very difficult to evaluate because of the use of substances outside of any medical and institutional control, most often in a clandestine/illicit setting [1–3] leading to a black market favored by major financial interests and conflicts of interest.

1. Epidemiology

The epidemiology of the use of A/AS in sports doping is very difficult to establish in a reliable way because of the intrinsic nature of the modes of acquisition and consumption of these products, which are almost always carried out in a clandestine and illegal context [1–3]. However, since the beginning of the 2000s, numerous attempts to evaluate the phenomenon, mainly using surveys based on questionnaires, have been implemented, particularly in the United States, in some European countries and in Australia [1–3]. In an attempt to mitigate underestimation biases linked to false declarations, more sophisticated methodologies have been implemented, especially questionnaires using “randomized responses techniques” [1–3]. These surveys have been aimed at populations of

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elite or amateur athletes as well as the general public [1–3]. From these surveys, a certain number of points seem to emerge [1–3]: among men in the general population, occasional or chronic use of A/AS would concern between 1 and 5% [1–3]. The use of these doping products is more frequent in men than in women with a sex ratio that could reach 50:1 [1–3]. Individuals who reported having used or using A/AS include occasional, short-term and chronic users. According to a survey among elite athletes, the prevalence of use could be close to 20% [1–3] but using questionnaires associating randomized responses techniques the use would be more important, comprised between 20 and 60% [1–3]. Important point, in most of the subjects having consumed A/AS the start of doping was during adolescence [1–3], which underlines the vulnerability of this age group.

2. Substances used

Historically, the use of A/AS began in the 1950s after the first chemical synthesis of testosterone by the German biochemist Johann Butenandt, which earned him the Nobel Prize in Chemistry in 1939 in association with the Croatian Lavoslav Ružička (<https://www.nobelprize.org/prizes/chemistry/1939/summary/>).

After this discovery and following the synthesis of many other chemical testosterone derivatives, use for doping purposes has spread, first among weightlifters, bodybuilders and then quickly among other categories of athletes [1–3].

The first ban in the Olympic Games was only introduced in 1968 in Mexico City. It is interesting to recall there that the use of A/AS became widespread while the dominant medical discourse at that time questioned or was skeptical about their effectiveness on sports performance [4]. It was not until 1996 that the first prospective randomized study was conducted that contradicted these unfounded medical opinions. This study was conducted by a group of university hospital endocrinologists led by Shalender Bhasin and published in the *New England Journal of Medicine*. This work, remarkable for its simplicity and methodological rigor, documented for the first time the effectiveness of testosterone used at supraphysiological doses on muscle volume and strength [5].

The most commonly used substances for doping are summarized in Table 1. They are often used in combination. These different molecules include natural testosterone, either unesterified (patches and gels) or esterified in position C17 with fatty acids of varying nature and length (enanthate, undecanoate, cypionate, etc.). These esterified forms are most often administered by

parenteral, intramuscular or subcutaneous route. Users may also ingest testosterone precursor steroids such as androstenedione and dehydroepiandrosterone (DHEA), which can be metabolized into testosterone [6].

Some athletes who practice doping may also self-administer very large doses of gonadotropins that stimulate testosterone secretion by testicular Leydig cells [7–9]. This is primarily chorionic gonadotropin, either extracted from the urine of pregnant women or synthesized in vitro (recombinant hCG) [7–9].

Other users use anti-estrogens or aromatase inhibitors [1–3,10,11]. These substances respectively prevent the action of endogenous estrogens at the nuclear estradiol receptor or cause a decrease in endogenous estradiol production by blocking the aromatization of aromatizable androgens [10,11]. The consequence is a suppression of the physiologic negative feedback of estradiol on pituitary gonadotropins secretion whose circulating concentration increases [1,2]. Finally, many doped subjects consume synthetic steroids, which have powerful androgenic and anabolic properties [1–3] (Table 1).

3. Side effects

Given the predominantly clandestine and uncontrolled use of doping agents, it is not surprising that data on their side effects are scarce and in general poorly documented, both quantitatively and qualitatively. Reported data is essentially based on clinical cases or small series and in the best of cases on a few case/control or cross-sectional studies [1–3]. Another difficulty is that the use of doping products is often multiple (cocktail effect) and can be associated with the use of other drugs or toxic non-anabolic products whose origin is also uncontrolled (counterfeiting and contamination of products purchased on the Internet) and with uncertain safety. The latter drugs can induce additional side effects that will potentially constitute confounding factors [1–3]. Moreover, as some surveys have shown, the practical use of doping products is very heterogeneous with a myriad of products, combinations (cocktails), dosage and duration, [1–3]. As a result, the available data have overall a low level of evidence, which should call for caution [1–3]. Despite these limitations, a number of side effects associated with the chronic use of androgenic and anabolic steroids have been reported.

4. Effects on the gonadotropin axis and testicular functions

The main and best-documented hormonal effect of very high dosage testosterone and A/AS is the inhibition of the gonadotrope

Table 1
Steroids drugs commonly used as androgens and anabolic agents/medications that increase endogenous testosterone levels.

Natural steroids	Synthetic steroids (non-exhaustive list)	Drugs that increase endogenous testosterone (indirect doping)
With intrinsic androgenic effect	Nandrolone analogues (synthetic, anabolic steroid analog of testosterone)	Selective estrogen receptor modulators (SERMs)
Testosterone	Oxandrolone	Clomiphene
Dihydrotestosterone	Trenbolone	Raloxifene
Boldenone (natural androgen secreted by some animals, developed for veterinary use particularly in horses, https://pubchem.ncbi.nlm.nih.gov/compound/Boldenone)	11 β -methyl-19-nortestosterone (11 β -MNT)	Aromatase inhibitors
Nandrolone (steroid analog of testosterone)	Oxymetholone	Exemestane
Testosterone precursors (pro-androgens)	Bolandiol	Letrozole
Androstenedione	Clostebol	Anastrozole
Dehydroepiandrosterone (DHEA)	Danazol	Gonadotropins that directly stimulate testosterone secretion by Leydig cells
	Drostanolone	Human chorionic gonadotropin (hCG)
	Tetrahydrogestrinone	Recombinant human LH
		Others
		Opioid antagonists, and neurotransmitters involved in regulation of endogenous LH and indirectly in testosterone secretion

Table 2

Effect on pituitary gonadotrophins and testicular hormones of chronic use of A/AS and indirect doping with drugs used to increase endogenous testosterone.

Compound used hormone ^a	Testosterone	FSH	LH	Inhibin B	INSL3 ^b
Testosterone	↑	↓	↓	↓	↓
Testosterone precursors ^c	↑	↓	↓	?	?
Non-testosterone A/AS	↓	↓	↓	↓	↓
hCG	↑	↓	↓	↓	↑ or –
Aromatase inhibitor ^d	↑	↑	↑	?	?
Clomiphene/Raloxifene ^d	↑	↑	↑	?	?

?: no data available.

^a Measured in serum.^b Insulin-like Peptide 3.^c High dosages of precursors (DHEA, androstenedione) required.^d Used alone.

axis in humans [12,13]. This pharmacological inhibition of pituitary gonadotropin secretion induces a decrease in endogenous testosterone and peptides of testicular origin such as inhibin B and INSL3 [12–15] (Table 2). Within a few months the profound drop in LH and FSH will lead to an inhibition of spermatogenesis, which will result in at least oligospermia and in the most severe cases azoospermia [1–3]. Inhibition of spermatogenesis is usually accompanied by a significant decrease in testicular volume [1–3]. Infertility and testicular hypotrophy are effects that may lead men taking high doses of testosterone and/or A/AS to consult care providers. Some doped athletes cleverly use A/AS in combination with chorionic gonadotropin (hCG), either alone or with FSH-containing preparations in an attempt to mitigate the testicular effects of gonadotrope inhibition [1–3,16]. Many doped athletes complain of loss of libido and/or erectile dysfunction [1–3]. When questioned, it is not always easy to determine whether these complaints are direct side effect due to A/AS impact on the central nervous system or due to estrogen deficiency when using A/AS in combination with non-aromatizable steroids as well as aromatase inhibitors or a consequence of withdrawal syndrome due to attempts to stop or reduce the dose of doping products. Sometimes, the medical consultation refers to simple attempts to obtain prescriptions from doctors in charge in order to continue with legal justification the chronic consumption of testosterone. The time required to recover the gonadotrope axis after stopping doping can take several months or even a year or more, depending on the length of the previous exposure period and the magnitude of the doses administered [17].

5. Neuro-psychiatric effects

The abuse of testosterone and A/AS has been associated with a range of deleterious psychiatric effects such as aggressive behavior that can trigger violent acts. The frequency of these behavioral effects is, as expected, very difficult to assess [1–3]. Furthermore, the interpretation of these disorders is not always unambiguous, and it is often a challenge to distinguish between personality disorders predisposing to doping and a causal effect of androgenic/anabolic steroids [1–3]. Anxiety disorders, impulsive behavior and even manic states have also been reported in A/AS doped subjects when using very high doses [18,19]. On the other hand, when attempts are made to reduce the dosage or to stop using doping agents, depressive states (with lethargy, loss of stamina, asthenia) and prolonged anxiety may occur [1–3,18,19]. These episodes, classified as withdrawal syndrome, are assumed to be caused by an addiction to anabolic androgens, which would explain the high risk of relapse [1–3]. They are possibly enhanced by the chronic decrease in circulating testosterone and estradiol after withdrawal of the doping agents as a result of prolonged inhibition of the gonadotrope axis.

6. Hepatotoxic effects

Hepatotoxic effects include cholestasis and transaminase abnormalities, peliosis hepatis, and hepatic tumors that are usually benign but sometimes malignant [1–3]. During occasional use, the biological damage to the liver may regress when the anabolic drugs are stopped.

Hepatic injuries have been described mainly during chronic use of orally ingested synthetic anabolics [1–3]. The main A/AS responsible were the 17 α -alkylated derivatives, widely used before the 1980s but less used since then. Testosterone and 1-methylated anabolics are reported to be less toxic to the liver [1,2].

7. Cardiovascular effects

The use of high doses of testosterone or A/AS may have deleterious cardiovascular effects by different potential mechanisms: (a) procoagulant and therefore prothrombotic effects that may be related or be increased by high hemoglobin and hematocrit levels [1–3]; (b) by vasospasm; (c) by direct cardiotoxicity altering particularly the systolic function. In the long term, A/AS can induce accelerated atherogenesis [1–3] as a consequence of metabolic abnormalities such as chronic and deep HDL cholesterol decrease [1–3]. At the outcome level, the associated consequences can be cardiomyopathy, which may be complicated by heart failure or sudden death and myocardial infarction. At the vascular level, deep vein thrombosis has been reported, which can be complicated by pulmonary embolism; arterial thrombosis has also been reported [1–3].

8. In women

The objective of female athletes using A/AS is similar to that of men [1–3]: to increase muscle strength and physical performance. Given the much lower post-pubertal physiological testosterone concentrations in women than in men [20,21], an increase in muscle mass and performance compared to non-doped women can theoretically be obtained with lower doses of A/AS. A randomized versus placebo study published in 2014 investigated the effect of intramuscularly administered testosterone ester in escalating doses, from low to clearly supraphysiologic in women previously hysterectomized with or without oophorectomy [22]. The authors showed that administration of clearly supraphysiologic doses (inducing serum testosterone levels > 2 ng/mL) to women resulted in an increase in lean body mass and muscle strength [22]. They also observed an increase in vitality, libido and sexual activity, as well as an increase in hematocrit and hirsutism [22]. With the exception of a few elite female athletes and body builders, women would rarely use such large doses of A/AS as reported in men [22,23]. The use of hCG in female athletes would also be marginal because of its low efficacy on increase in endogenous circulating androgen levels

Table 3

Main detection methods used for capture of direct and indirect testosterone and androgen-doping.

Substance	Detection method
Direct	
Synthetic androgens/anabolics	L/GC-MS
Testosterone/natural androgens	L/GC-MS, T/E, CIR-MS
Unknown androgens (designer and nutraceutical)	L/GC-MS (bioassay)
Indirect	
hCG (urinary extracted or recombinant)	hCG immunoassay or LC-MS
hLH (recombinant)	hLH immunoassay or LC-MS
Anti-estrogens	L/GC-MS

L: liquid chromatography; GC: gas chromatography; MS: mass spectrometry; CIR-MS: carbon isotope ratio measured by mass spectrometry.

[8]. The side effects of A/AS, already difficult to study in men, are even more difficult to evaluate in women because of a possible less frequent use [1–3]. Among the most reported side effects listed are the classic signs of hyperandrogenism such as acne, hirsutism, and menstrual cycle abnormalities due to anovulation which can also lead to infertility [22]. In the most severe cases of doping, alopecia, clitoral hypertrophy and loss of femininity (masculinization) with breast hypotrophy have been described [1–3,22]. It must be stressed that in women, acne, menstrual disturbances, and infertility, can be reversible. However virilization (associated with important hirsutism, malepattern balding, voice change, clitoral enlargement and breast atrophy) may be irreversible depending on the dose and duration of A/AS exposure [1–3].

Some studies suggest a higher likelihood of psychiatric disorders such as dietary restriction predisposing to A/AS use. Addiction in female A/AS users is also more frequent than in men doped athletes [23–25].

As metabolic consequences, a decrease in HDL cholesterol, sometimes very substantial, has been documented [22]. Of note, biochemical effects such as suppression of SHBG, lipid changes, and hepatotoxicity are equally prevalent in female than in male androgen abusers [1–3].

9. Screening

Detection and diagnosis of doping in exogenous testosterone, A/AS users as well as in users of compounds aimed to increase endogenous testosterone (indirect doping) involve a number of increasingly sophisticated methods to detect and measure these substances in urine and/or blood [1–3]. The most commonly method of detection performed is mass spectrometry (MS) preceded by chromatographic separation using either liquid chromatography (LC-MS) or gas chromatography (GC-MS) (Table 3). These techniques and their use in doping detection have been detailed in excellent reviews [1–3].

Detection of natural androgens (testosterone [T]), (dihydro-T [DHT]) or their precursors (the pro-androgens androstenedione and DHEA), always raises the issue of distinguishing between the exogenous and endogenous steroids. Exogenous testosterone administration can be detected by measuring in urine the ratio of testosterone to its 17 α -epimer epitestosterone, this being considered as a sensitive screening test. Because in males, both T and epitestosterone are co-secreted by Leydig cells and excreted in urine consistently so that the urine T/E is usually stable for any individual over time [1,2]. Administration of exogenous testosterone, which is not converted to epitestosterone, increases the urine T/epitestosterone ratio and, when it exceeds a specified threshold, it indicates administration of exogenous T [1,2].

However, the urine T/epitestosterone ratio is less considered as an effective screening test for exogenous T doping in females

[1–3,26,27]. Another difficulty is the establishment of reliable “pre-doping” normal values in elite athletes of both sexes for whom one can rarely be certain of the absence of taking illicit substances [1,26,27].

Administration of exogenous testosterone can also be identified by carbon isotope ratio measured by mass spectrometry (CIR-MS) that can distinguish endogenous from exogenous testosterone but also other exogenous natural androgens or pro-androgens (DHT, androstenedione, DHEA) according to the C13/C12 ratio detected in urine [1]. A significantly lowered C13/C12 ratio of urinary androgens relative to endogenous reference steroids indicates that urinary steroids originates at least partly from exogenous compounds [1].

With LC-MS and GC-MS, the detection of A/AS whose structure is known is relatively easy. Their sensitivity also allows sometimes the detection of certain synthetic products long time after their use has stopped [1–3].

A difficulty emerges if the structure of the A/AS is not identified as some molecules manufactured and marketed by non-approved producers [1–3]. These entities, often linked to illicit activities or even organized crime, distribute their products through unofficial channels (black market), on the Internet and in gyms, presenting them as nutritional supplements [28].

Since their prohibition, the anti-doping agencies in France, Agence française de lutte contre le dopage (AFLD), U.S. Anti-Doping Agency (USADA) among others and at the international level – World Anti-Doping Agency (WADA) have been updating the prohibited substances (<https://www.wada-ama.org/en/prohibited-list>) deploying screening that mainly focused on elite athletes [1]. These agencies make extensive use of mass spectrometry detection. They have also developed the so called athlete “biological passport” which consists in identifying an individual signature combining various circulating biomarkers, including hormones (and their metabolites) and non-hormonal markers (haematological for example). Each signature would vary only in a narrow corridor specific to the individual and would be stable over time [29–31]. According to the designers and users of this tool, longitudinal monitoring using Bayesian approaches of those signatures would make possible to detect any suspicious deviation that would trigger a more in-depth search for doping products [29–31]. This method was validated by the WADA in 2009 [1,2] but a number of limitations have been raised by some experts [3].

Finally, to detect androgen-doping use, some experts have proposed the use of alternative biological matrices combined with GC-MS [1,32,33]. Authors implementing this kind of approach propose to detect steroids in tissues as hair, skin and nails as well as in saliva or exhaled breath. One of the most reported alternative matrix is hair. Hair having the advantages of minimally invasive sampling and simple convenient storage with the potential for very long period of detection [1,32,33].

10. Role of physician

In medical practice, in front of a potentially doped patient the main objective is to prevent, treat and manage both the addiction and the harmful consequences of doping.

The main factor that makes both the diagnosis and care of doping difficult is the clandestine and illegal use of these products, which expose the athletes users to very severe sanctions (<https://www.ncbi.nlm.nih.gov/books/NBK305894/>). For this reason, a relationship of trust leading to spontaneous declaration of the use of these substances is exceptional, even in case of side effects or complications caused by their use and which have motivated a consultation with the endocrinologist or another specialist [1–3]. The physician must be attentive to any patient who practices

intense sports activity, whether amateur or professional. As this is a high-risk population, the possibility of a doping-related effect must be systematically raised alongside the usual differential diagnoses, and this whatever the reason for consultation. Another evocative situation is the complaint of withdrawal signs mentioned above which contrast with a developed musculature on clinical examination. In such patients, testosterone is usually low and gonadotropins are low or “normal” when the doping agent has been discontinued before the medical appointment.

Disclosure of interest

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