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# Anabolic androgenic steroids and doping in sport

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**Abstract**. Anabolic steroids, technically known as anabolic-androgenic steroids (AAS), are synthetic derivatives of testosterone, modified to enhance its anabolic actions (promotion of protein synthesis and muscle growth). They are used by athletes (weightlifters, shot, hammer, discus or javelin throwers, rugby and American football players, swimmers and runners) to increase muscular mass and athletic performance and by bodybuilders to improve size and cosmetic appearance. AAS were the first identified doping agents that have ergogenic effects and are on the International Olympic Committee's list of banned substances.
The most popular AS used as doping substances are: *oximetolone, oxandrolone, testosterone undecanoate, nandrolone decanoate, nandrolone undercanoate, methandrostenolone.* To reach high dosages and rapid effects, steroid users practice a method known as "staking" which consist in the intake of two or more steroids in high dosages. Another method, called "pyramiding" provides a progressive increase of steroids dosage. The pyramid protocol is alternated with drug-free, process defined as "cycle". AAS abuse causes significant side effect: infertility, azoospermia, testicular atrophy, and gynecomastia in men and in women may develop excessive body hair growth, menstrual irregularity, hypertrophy of sebaceous glands, acne. Other side effects are: premature cease of growth caused by premature epiphysis closure; Alteration of cardiovascular function; increase of platelet aggregation and plasmatic levels of low density lipoproteins (LDL); liver damage; euphoria, aggressiveness and psychosis. Their action in central neuron system involves the dopaminergic neurotransmission and produces amphetamine-like activity. Therefore, the use of AAS should be banned from the sport, making a work of supervision and accountability of the sports centers and authorities in this field.
**Key words**: *anabolic androgenic steroid; doping; endocrinology; testosterone*.

## Generality information about doping

Sports are a considerable importance both for the physiological end ethic benefits, not only by improving the performance conditions of an athlete but also for the positive influence on the character and personality of a person (1,2).
In addition, sports activity, at any level, remains a competition and emulation in respect of the other competitors and towards ourselves (3).
Therefore, since the ancient times, were researched illicit systems that could artificially improve the athletic performance, in addition to training and physical preparation; in ancient Greece for example, during the carrying out of the Olympic Games, the athletes used to assume an infusion of herbs and mushrooms in order to increase their performance (4).
More recently, at the early nineties, marathon runners assumed alcohol during the race and the American athletes began the use pharmacological practices by assuming a stimulant of popular diffusion called strychnine (5,6).
With the years gone by and the pharmacological progress, the use of drugs by athletes became more intense reaching a point of international phenomenon known as "*doping"*.
The word *doping* has an uncertain etymology. Probably, it originates from the English verb *to dope* which means "administer stimulants" and the subject *dope* by the mean of "stimulant substance" (4).
Many athletes use drugs especially AAS and in sports medicine, *doping* is "the assumption of substances or the recourse at particular methods which are able to artificially increase

an athlete's performance during a sports competition, contrary to sports morals and despite physical and psychological health" (6).

Drugs, substances biologically and pharmacologically active and medical practices, which their application is considered doping, are divided, in compliance with the provisions of the Strasbourg Convention and under the indications of the International Olympic Committee (IOC) and other international organizations responsible in the sports sector, in classes, according to their chemical and pharmacological character and their corresponding effect (4,7)

WADA significantly modified the Prohibited List of the IOC Medical Commission, binding from the end of 2003 (Table I). Since that moment the list has been regularly updated, and all changes, based mainly on scientific research, have been preceded by numerous consultations with representatives of the sport and medicine. By publishing a new version of the Prohibited List every year (Table II) and by enlisting numerous examples of prohibited substances WADA fulfilled partly the need of publishing a complete list of prohibited substances. In spite of the examples of prohibited substances or methods in particular groups, some additional substances, which are not located on the list but are characterized by "a similar chemical structure or similar biological effect(s)", can be considered as doping (7).

The empowerment effect and the sense of euphoria, induced by the use of doping substances, are related biological and/or organic malfunctions and alterations, which may not always be reversible (5-6). For such reason, doping should be considered not only an offense towards sports, but also a crime against health (6). Therefore, in Italy the necessity of updated rules for the protection of health in sports activities and for the fight against doping, it has been configured in the recent Law 14.12.2000 n* 376 through which, having become doping a criminal offence, the ordinary Judiciary at work in a territory that was once prerogative of Sports Justice (6). The first paragraph of the Article 9 of this Law includes the definition of the crime of Doping, which is committed by "whoever procures to others, administers, assumes or encourages by any mean the use of drugs or substances pharmacologically active including substances of hematologic and endocrinology nature, that are considered doping substances, that are not legitimated by pathologic conditions and are able to modify the psychophysical or biological conditions of the human organism, in order to affect the agonistic performance of an athlete, or are intended to modify the results of anti-doping test on the use of such drugs or substances" (6-7).

**Table** I. Prohibited classes of substances and prohibited methods, for the years 2001-2002 publisched by the IOC Medical Commission (Olympic Movement Anti-Doping Code, 2001).

| | |
|---|---|
| **I.** | **Prohibited classes of substance** |
| A. | Stimulants |
| B. | Narcotics |
| C. | Anabolic agents |
| D. | Diuretics |
| E. | Peptide hormones, mimetics and analogues |
| **II.** | **Prohibited methods** |
| A. | Blood doping |
| B. | Administering artificial oxygen carriers or plasma expanders |
| C. | Pharmacological, chemical and physical manipulation |
| **III.** | **Classes of prohibited substances in certain circumstance** |
| A. | Alcohol |
| B. | Cannabinoides |
| C. | Local anaesthetics |
| D. | Glucocorticosteroids |
| E. | Beta-blockers |

**Table II.** The WADA prohibeted list for 2010.

| |
|---|
| **Substances and methods prohibited at all times (in- and out-of-competition)*** |
| S1. Anabolic agents |
| S2. Peptide hormones, growth factors and related substances |
| S3. Beta-2 agonists |
| S4. Hormone antagonists and modulators |
| S5. Diuretics and other masking agents |
| M1. Enhancement of oxygen transfer |
| M2. Chemical and physical manipulation |
| M3. Gene doping |
| **Substances and methods prohibited in competition** |
| In addition to the categories S1 to S5 and M1 to M3 defined above, the following categories are prohibited in competition: |
| S6. Stimulants |
| S7. Narcotics |
| S8. Cannabinoids |
| S9. Glucocorticosteroids |
| **Substances prohibited in particular sports** |
| P1. Alcohol |
| P2. Beta-blockers |

## Epidemiologic notes

The restless evolution and multiplication of doping methods and substances, the fear by athletes of harsh sports and legal sanctions as well as the inadequacy of the identification techniques for illegal substances, contribute to make a not accurate evaluation of the prevalence of the Doping Phenomenon (6).

To estimate the use of prohibited drugs and other forms of doping in sports fields, in 1998 the National Italian Olympic Committee (CONI) and the National Research Council (CNR), appointed an independent committee designed to conduct a survey to ascertain the knowledge and opinions of the Italian athletes on doping practices (8). 1015 athletes and 216 sports professionals where interviewed during the survey. In total, 30% of athletes, coaches and sports managers and 21% of doctors stated that the athletic performance can be improved by using drugs or other doping techniques. In particular, more than 10% of athletes expressed the opinion that amphetamines and anabolic steroids are frequently used in national and international level.

Moreover, the percentage of athletes and sports professionals that retain harmful the use of doping methods and prohibited drugs was higher than the percentage that considered their use effective (8) (Table III).

A current meta-analysis, which concentrates and summarize the results of over 29 epidemiological researches, estimated the prevalence of doping from 3% to 5% in children, up to 15%-25% in adults that practice a sport at a competitive level (9).

A study conducted in Norway from 1977 to 1995 on 15208 athletes has demonstrated that, despite the low prevalence in registered athletes or athletes affiliated with sports societies (1,2% to 1,4%), the use of doping substances can assume worrying values in non professional athletes or amateurs (20 to 24%) (10). These results seem to be due to the difficulty to submit targeted control athletes who do not participate in official competitions. To finish, still remain obscure data on the prevalence of doping in East European athletes before the fall of the Berlin Wall.

**Table III.** Knowledge and evaluation of the benefit/risk ratio related to the various practices of doping by athletes and technicians (Lancet 1990; 336: 1048-50).

| | **Athletes** | | | **Technicians** | |
|---|---|---|---|---|---|
| | **Information about pratices** | **Efficacious** | **Dangerous** | **Efficacious** | **Dangerous** |
| Amphetamines | 92 | 42 | 79 | 56 | 95 |
| Anabolic steroids | 92 | 60 | 80 | 67 | 94 |
| Beta-blockers | 25 | 7 | 19 | 36 | 69 |
| Diuretics | 57 | 17 | 30 | 29 | 63 |
| Vasodilators | 40 | 14 | 26 | 28 | 64 |
| Analgesic Narcotics | 76 | 39 | 48 | 43 | 67 |
| Blood doping | 55 | 32 | 31 | 50 | 61 |

## Anabolic steroids

Anabolic steroids (AS) are a class of compounds studied and synthesized to stimulate body and muscular growth (anabolic effect). Some authors use the term "steroids" to refer both to androgens and to anabolic steroids, since both have the same basic chemical structure. The anabolic effect is determined by a local nitrogen (azotes) increment with an increase of new formed proteins, by the rise in glycogen, phosphorus content and phosphorus compounds of high energy potential, by an accentuated oxygen consumption on muscular level and by an increased water content in muscle mass (11). The use of AS for therapeutic reasons has always been rare and limited: in the '60, for example, before the Growth Hormone in recombinant form was available, Oxandrolone was use for the treatment of short stature in Turner Syndrome (12). Currently, such drugs are mainly employed for the treatment of delayed puberty, particular forms of anemia and particularly hypogonadism in children and adolescences and for the treatment of hereditary angioedema, hypogonadism, aplactic anemia, breast cancer and senior men osteoporosis in adults (6).

Drugs bases on the AS effects have been listed by the IOC (International Olympic Committee) as substances assumed for doping purpose (4). More specifically, a wide use of AS is registered in sports in which is required a significant muscle mass(weight lifting, box, fight, gymnastics, shot put) as well as in sports where the increment of muscle mass allows an increase in speed potential of an athlete (American football, speed races and high jump) (13). Furthermore, other categories of athletes using AS are Bodybuilders, which may not participate in competitive events but their target is to reach a particular physical appearance.

In addition to their ability to promote the muscular growth and strength , AS are able to reduce the time of physical recovery after intense and protracted physical activity and to stimulate aggressive and determined attitude, basic requisites in sports where is required physical contact with the opponent (14). AS are regularly used by men even if since 1990 the use of AS by women has undergone a significant increase. In 1997, in fact, according to the American statistics, about 175.000 female adolescences have admitted to assume AS with a 100% increase since 1991. As for male adolescences, according to current American, there are 325.000 consumers with over one million of adolescences who have not used AS at the age 12 to 17. The percentage of youth assuming these drugs without medical prescription rises above the 6% according to an American estimation for the year 1993 (14). This percentage rises to over 50% if only adult male bodybuilders are assessed.

The statement of the *American College of Sport Medicine* related to the use of AS is the following: 1) the use of anabolic steroids during training in association with an adequate diet may contribute to increase body weight, especially on behalf of lean body mass; 2) in some individuals the use of anabolic steroids develop the effects induced by training in muscular strength if associated with an high-protein diet; 3) anabolic steroids are not able to modify the aerobic power and ability; 4) the use

of AS can cause serious damage at liver and cardiovascular level, reproductive system and psychological disorders even on therapeutic doses; 5) the use of AS among athletes is against the rules and the ethical principles of sports.

**Chemical characteristics**

Anabolic-androgenic steroids (AAS) are synthetic derivatives of testosterone, originally designed to provide enhanced anabolic (tissue-building) potency with negligible androgenic (masculinizing) effects (Table IV). In men, testosterone is the principal secreted androgen and the Leydig cells synthesize the majority of testosterone. In women, testosterone also is probably the principal androgen and is synthesized both in the corpus luteum and the adrenal cortex by similar pathway. The testosterone precursors androstenedione and dehydroepiandrosterone are weak androgens that can be converted peripherally to testosterone. Approximately, 60 different AAS are available that vary in their chemical structure and thus in their metabolic fate and physiological effects (13-15). All AAS are thought to have some androgenic activity, and the androgen receptor binding properties of several of these compounds have been characterized in brain tissue (16).

However, natural testosterone is rapidly degraded by the liver so the plasmatic level required for the accomplishment of his anabolic effect, are not reached. Therefore, in order to have drugs with low or none androgenic activity (deprived of the male sex hormone effect responsible for the secondary and primary characteristics such as reproductive organs, hair system, voice tone etc) but with high anabolic activity, changes were made in the chemical structure of testosterone in three different positions (called by type A, B, C). It has been proved an increase of efficiency after these changes. The modifications made are represented by the etherification of group 17 β-hydroxyl (type A), the alkylation of the position 17 α (type B) and the modification of the ring of the ring of the steroid structure (type C) (13, 16).

From the Chemical point of view (11), AS are classified as:

- *Androstan derivatives* composed by 19 carbon atoms (androisossazolo, androstanolone, dimetazina, mestanolone, oxandrolone, quimetolone, quindolone, stanazolo, etc)
- *Androstane derivates* composed by 19 carbon atoms as well (bolesterone, 4-cloro-testosterone, fluossimesterone, metandrostenolone, metanolone, ossimesterone, quindemione, tiomesterone, etc)
- *Estranged and extrinsic derivates* that are 19- nosteroidi composed by 18 carbon atoms, from the elimination of the angular methyl in C10 (4-cloro-19-nortestosterone)etilestrenolo, nandrolone, nordoletone, noretandrolone, oxabolone, etc)

Each one of these 3 groups is further divided in 3 subgroups: in the subgroup I are included steroids which action is relatively brief and are administered by injection ( they generally have a β- OH and a H in C 17); the subgroup II molecules with short action as well, but they are administered orally (they usually have a β- OH and a methyl type of alkyl group, ethyl or ethynyl or an ether in C17 the results more efficient if assumed orally); finally, the subgroup III, includes steroids with long action and administered by injection (the 17 β-H group is esterificated; if the etherification is made with sulfuric acid, with glycine and hemisuccinate acid, we obtain soluble compound, with rapid assimilation and quick elimination; if, the esterification is made with acetic, phenylpropionic, cyclopenthyl or decanoic acid etc, we have liposoluble compound, with slow assimilation and slow elimination (11).

Anabolic steroids 17-alkylated by a methyl, ethyl or ethynyl group (etilestradiolo, metiltestosterone, noretandrolone, oxandrolone, ossimesterone, stanazololo, ossimetolone, etc) develop an irreversible binding and consequently follow metabolic pathways other than those for natural steroids; this implies a possible alteration of liver functionality as well as positive jaundiced liver disease; on the other hand 17- esterification (ex. quindolone) favorites the development of a reversible binding and a physiological metabolism in 17-ketosteroid, not influencing both liver functionality and jaundiced signs.

Screening procedures for AAS in World Anti-Doping Agency accredited laboratories are comprehensive and sensitive and are based mainly on gas chromatography-mass spectrometry, although liquid chromatography-mass spectrometry is becoming increasingly more valuable. The use of carbon isotope mass spectrometry is also of increasing importance in

the detection of natural androgen administration, particularly to detect testosterone administration (17).

**Table IV.** Biological Effects of Testosterone

| |
|---|
| **VIRILIZING EFFECTS** |
| ➢ Adjustment of the hypothalamic-pituitary-testicular |
| ➢ Regulation of spermatogenesis |
| ➢ Organization and development of sexual characteristics |
| ➢ Role in pubertal development |
| ➢ Facilitate the development of sebaceous glands |
| ➢ Adjustment of sexual behavior in adults (libido) |
| ➢ Effect on general behavior (aggression) |
| **ANABOLIC EFFECTS OF PROTEIN** |
| ➢ Increased bone density |
| ➢ Stimulation of osteoblastic |
| ➢ Ossification of the epiphyseal growth |
| ➢ Increased muscle mass (increased muscle performance) |
| ➢ anabolic effect on bone marrow, liver, kidney and heart |
| ➢ Stimulation of erythropoiesis |

## Action of mechanism

AS exert their pharmacological effects by binding to a cytoplasmatic receptor and moving into the nucleus incrementing RNA polymerase activity and synthesis of RNA and specific proteins (11). They are characterized by a lipophilic structure that allows their diffusion through the cytoplasmatic membrane. At intracellular lever, they binds to specific receptors that are composed of a single polypeptide chain contain two domains: the dimerization and hormone binding domain (localized COOH-terminal end of the receptor protein) and DNA-binding domain. Within these domains, each receptor has a binding site for the inhibiting proteins Heat Shock Proteins, the sequence of nuclear translocation, both placed in COOH-terminal position compared to DNA binding region, and the sites of interaction with the transcriptional system proteins, called AF-1 and AF-2 located respectively at the end of the $NH_2$-terminal and within the hormone binding domain. Intracellular receptors in the absence of specific activation signals are associated to *Heat Shock Proteins*, which block the DNA-binding domain functions by steric obstruction. When the AS enter the cytoplasm and bind to the receptor, there is a conformational change of the receptor molecule, which causes the dissociation of inhibitory proteins, the interaction with a second receptor molecule and the formation of a dimmer with high affinity towards specific sequences of DNA located in the promoter of target genes. These sequences are denominated «hormone-responsive

sequences (or HRE, by Hormone Responsive Elements). The receptor-ligand complex, once bound the responsive sequence to the hormone, recruits transcriptional apparatus proteins or co activators (proteins that facilitate its interaction with the initiation transcriptional complex) facilitating the synthesis of the primary transcript (18). Therefore, AS can stimulate the transcription of specific gene sequences and the synthesis of mRNA, its translation in ribosome, protein synthesis, which alter the function of the target cell.

The anabolic actions of AS have been recognized in skeletal muscle, in which these hormones promote the incorporation of amino acids in proteins and the activity of RNA-polymerase enzyme. AS antagonize the catabolic effect of glucocorticoids. During high stressed periods and intense training, the plasmatic concentration of cortisol increases, leading to a negative nitrogen balance and the inception of muscle fatigue; the AS reverse this catabolic effect by displacing cortisol from its receptor, inhibiting protein degradation and allowing athletes to sustain intense training.

AS also stimulate cell regeneration and repairing procedures, they promote erythropoiesis, are able to reactivate the adrenal steroid genesis and modulate catecholaminergic responsiveness (inhibition of the catecholamine reuptake) (11).

## Pharmacokinetic of anabolic steroids

AS are administered orally or by injection. Those ingested orally (danazol, fluoximesterone, methyl testosterone, oxandrolone, stanazolol) are absorbed from the stomach and, considering their short half-life are rapidly eliminated; in the liver they result more toxic than steroid administered by injection, and they are more effective. Inject able steroids (testosterone propionate, testosterone enanthate, testosterone cypionate) are characterized by: a) a delayed metabolism, reduced elimination and a longer permanence in the organism (a characteristic that increases the chances of detection with the anti-doping test); b)they imply less liver toxicity; c) a lower

activity than orally administered steroids. The injections can be determined up to one month after administration, whereas oral only up to a maximum of two weeks when administered intermittently (11, 18).

**Way of administration**

Athletes, using AS, assume them during their whole sporting careers. Typically, to achieve high doses and rapid effects is used a method called "stacking," which involves the concurrent use of two or more steroids in high doses (16).The use of such association is based on the assumption that each steroid has a different physiological action. The assumption involves the gradual increase in dose ("pyramiding"); athletes, in fact, begin with low-doses, reach the peak and then slowly decrease the dose for a period of time which can range from 4 to 18 weeks. The “pyramid” protocol consists in alternating steroid assumption with periods of suspension, process defined as "cycling". The dose (50-200 mg daily) used in this procedure is 200 times higher than the recommended dosage employed for therapeutic reasons (5-20 mg/day) (16,18). The dose is reduced gradually during the months preceding the competition, to reduce the chances of failing the anti-doping test before the race. Table V includes the main AS used as doping substances and their dosage. Cyclical AS recruitment keeps up to the competitive period. Many athletes use the method called "periodization" to obtain maximum performance during the race. The goal of periodization is to optimize the intensity, the load of work, the frequency and the period of rest, to avoid stress and overtraining syndrome; in fact, as the competition period approaches, the training load is reduces and the intensity is increases (19). With the "periodization", the annual program of training of the athlete (macro cycle), is divided in three months phases (mesocycle) and the use of steroids coincides with mesocycle in order to gain the maximum strength during the competition. Off season, the use of steroids differs considerably from pre-competitive cycles for the type of treatment and dosage. For example, for a bodybuilder, a cycle of 18 weeks out of season, includes the intake of 4 steroids at higher doses than during the first week, followed by a cycle of 6-8 weeks during which the 'athlete takes chorionic gonadotropin (HCG) and clomiphene citrate to increase the concentration of testosterone (16).

This treatment, associated with the exercise, causes an increase of lean body mass. Afterwards, it follows, a new 20 weeks cycle, in which steroids are used in different assays. Often, along with the drug cocktail, are given high doses of compounds rich in protein among with a diet that including herbal tea designed to increase the anabolic effect (16, 19).

To check whether athletes are using steroids, we measure the ratio of urinary testosterone and luteinizing hormone (T/LH), or the relationship between testosterone and epitestosterone (T/E). Recently, it was determined that a ratio T/LH greater than or equal to 30 represents a more sensitive marker of the use of AS compared to a T/E ratio greater than or equal to 6 (19).

**Table** V. The main AS used as doping substances and their dosage.

| STteroid- Chemical Name | Markated drugs | Terapeutic dosage | Doping dosage* |
|---|---|---|---|
| oxymetholone | Anadrol | 25-50 mg/die per os. | 50-150 mg/die os. |
| Oxandrolone | Oxandril | 2.5-5 mg/die per os. | 15-20 mg/die os. |
| Testosterone Undecanoato | Andriol | 40-60 mg/die per os. | 200 mg/die os. |
| Nandrolone decanoate | Deca-Durabolin | 50 mg/ settimana i.m. | 200-400 mg/week i.m. |
| Nandrolone Undecanoate | Dynabolon | 80.5 mg/settimana i.m. | 170-340 mg/week i.m. |
| Methandrostenolone | Dianabol,Nerobol,Stenolon | 15-30 mg/die per os. | 50-250 mg/die os. |

* Assay values are only indicative, derived from plasma assays performed during doping controls on the basis of self-declared or occasional. Some experts are extremely underestimated.

## Side Effects

Prolonged use of high doses of AS, especially if taken orally, it causes significant side effects leading to serious health risks (Table VI).

There are a few reports on the endocrinological and pathological changers in AAS abusers (20).

*Effects on reproductive function*. The AS in men can lead to disorders in the endocrine function of testosterone, in fact, taking AS depresses the secretion of pituitary luteinizing hormone (LH), which inhibits the release of endogenous testosterone. Therefore, infertility, azoospermia, testicular atrophy, is possible consequences of the abuse of steroids (21). Other side effects in men are associated with increased plasma concentrations of estradiol up to 7 times higher than the physiological concentration. These levels of estradiol, similar to those normally found in women, may explain the phenomenon of gynecomastia, which occurs in men who use these substances. In addition, high concentrations of AS may lead to a prostate hypertrophy (in its extra sphincter portion which is sensitive to androgens), with slight urination disorders (22) and may increase the risk of a malignant tumour (carcinoma) of the gland.

Epidemiological data, infact, relate the inception of prostate cancer to specific hormonal profiles. In prostate cancer were found elevated plasma concentrations of androstenedione, estrogens, or both; estrogens produced by the aromatization of androstenedione, promote tumour inception. Therefore, the hormonal imbalance induced by the AS could lead to the onset of cancer (*23*).

In women, assuming AS occur lower voice tune, increased hair growth on face and body, and menstrual disorders. The use of AS during pregnancy can lead to serious risks for the foetus (pseudohermaphroditism, delayed growth, intrauterine foetal death) (12,13). In addition, in both males and females, AS use can lead to acne development, sebaceous glands hypertrophy hair loss and alopecia (22).

Regarding growth effects, the administration of AS to adolescents may result in virilisation, gynecomastia, and premature ossification of the extra epiphysial cartilage with stunted height (24).

**Table** VI. Effects and Side effects of AS.

| |
|---|
| **Proven Effects** |
| Increase in fat-free mass, and body weight<br>Increase in arm girth, leg girth<br>Increase in bench press and squat scores<br>Increase in libido |
| **Disproven Effects** |
| No effect on endurance exercise, males on treadmill, VO2max in rats |
| **Side Effects** |
| Hepatocellular damage, HDL (57 ◊ 42)<br>Cardiovascular disease (stroke, MI)<br>Psychological disturbance<br>Decr LH, FSH, SHBG<br>Decr sperm count and fertility index<br>No change liver/prostate US, hematological indices |
| **Men** |
| gynecomasty (development of breasts), atrophy of the testicles, diminished libido, reduced fertility and impotence |
| **Adolescents** |
| Interrupted growth |
| **Women** |
| hirsutism (excessive hair growth, especially on the face), masculinization of the voice and the body, alopecia (hair loss), atrophy of the breasts and uterus, hypertrophy of the clitoris, menstrual irregularities, amenorrhea (lack of menstruation), and oligomenorrhea (light menstruation) |
| **Effects common to males and females** |
| severe acne<br>musculoskeletal injuries: ruptured tendons, torn muscles<br>liver problems: development of bloody cysts in the liver, jaundice, liver cancer<br>cardiovascular problems: increased risks of arteriosclerosis, thromboembolisms, myocardial infarctions, strokes, edema, hypertension<br>mental problems: anxiety, irritability, aggressiveness, loss of perception of certain realities and values, insomnia, nightmares, depression, suicidal thoughts, mental confusion, hallucinations, delusions of grandeur, paranoid personality disorder, schizophrenia, and other psychoses<br>physical and psychological dependence |

*Cardiovascular effects*. They have been conducted many studies on cardiovascular system alterations (25), on changes in blood pressure and plasmatic lipoprotein concentrations induced by AS use. In particular, the use of oral 17-alkylated androgens decreases rapidly, both in man and in women, cholesterol levels related to high density lipoprotein (HDL) while increasing cholesterol levels related to low density lipoprotein (LDL ) as well as total cholesterol levels (26), by reducing the HDL/LDL ratio. It may appear that AS stimulates liver triglyceride lipase (HTL), an enzyme responsible for the clearance of HDL (27). Some studies showed a mean HDL of 26 mg / dl in weight lifters who had used steroids, compared with values of 50 mg / dl found in weight lifters who had not used such substances. More recent studies have shown that HDL levels remains low even with an at least 8 weeks break between consecutive steroid cycles (16). The abuse of these drugs may also increase platelet aggregation (16). This may lead to the onset of stroke or acute myocardial infarction (28). Regarding AS effects on blood pressure, there is no unanimity. The answer is probably dose-dependent, because some data suggest that high doses of AS caused an increase in diastolic blood pressure (29). In addition, echocardiograph examinations on bodybuilders, who used AS, showed a left ventricular hypertrophy with reduced diastolic relaxation (30).

*Psychiatric effects and addiction induced by anabolic steroids*. A high dosage administration of AS is related to the occurrence of a series of disorders that can be classified as: a) positive mood changes (euphoria, increased energy, aggression, enhance libido); b) negative behavioural changes (irritability, emotional lability, hostility, anxiety, decreased libido); c) cognitive disorders (confusion, memory loss, distractibility); d) psychiatric manifestations (hypomania, mania, dysphoria, depression, suicidal tendencies, paranoia, psychosis, hallucinations and delusions) (3*1,* 32). A study conducted on 160 athletes including 88 AS users and 68 control athletes, showed that the prime difference between the two groups concerned the incidence of psychiatric effects; in fact, 23% of users manifested maniacal symptoms, hypomania and depression (33). As for the addiction symptoms induced by AS abuse, literature data show that these symptoms meet the criteria of the "Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (32). The DSM-IV defines the AS "substances which sometimes produce an initial sense of well-being (or even euphoria), which is replaced, after repeated use, by lack of energy, irritability and other forms of dysphoria." A study (32) conducted in 49 weight lifters found that the most common symptom of AS addiction is abstinence characterized by fatigue, depressed mood, restlessness, anorexia, insomnia and decreased libido. Other withdrawal symptoms commonly reported are desire to assume greater amounts of AS, dissatisfaction with physical appearance, headache, suicide. Many studies also suggest, that the use of AS can lead to criminal acts of violence (33). These effects appear to be dose-dependent, so these effects are more frequent in individuals who use the equivalent of 1000 mg of testosterone per week (33), occasional for intermediate doses and rare at doses that do not exceed 300 mg per week (32). It 'also interesting to note that the start of AS use has similar characteristics to those of drugs such as cocaine, opiates and alcohol. In fact, as for drugs abuse, the initial use is strongly related to other peoples influence. In particular, among adolescents, the use of AS can be promoted by the need to improve their physical image. Even the so-called stacking, i.e. the simultaneous intake of more than one anabolic steroid at a time, is analogous habit of those who abuse of more “classic” drugs. The effects of testosterone and androgen on CNS dependent on different mechanisms, which seem to involve a number of testosterone receptors in the brain, which interacts with several central neurotransmitter systems, such as serotonin (34), dopamine (35), the 'gamma-amino butyric acid (GABA) (36). The results of a study conducted in rats treated with four different AS and to which were measured neuronal serotonin and dopamine levels in various brain areas after treatment, indicated that high doses of AS markedly increase cerebral metabolism of dopamine and serotonin, probably by virtue of an increased turnover of these neurotransmitters (34). The action in the central nervous system is predominantly dopaminergic, with characteristics similar to the amphetamine action; the doping drug initially acts on intellect by stimulating the production of dopamine. The result is a euphoric sense, the subject, at least initially, warns a state of wellness, happiness, does not feel bored during workouts and doesn’t feel fatigue (34). Over time, the euphoria turns into aggression, and can spill over into antisocial behaviour. However, as the euphoric effect is not always occur, a direct

correlation between euphoria and addiction is not yet demonstrated. Another theory, on the other hand, (35) suggests that the AS addiction is develops in response to social reinforcement and the pleasure resulting from having a well shaped and muscular body. Other studies (32) however, indicate that AS users express dissatisfaction with their bodies rather than appreciation and satisfaction. Addiction, according to these authors, leads to negative reinforcement (try to avoid an uncomfortable feeling of inadequacy of proper body), rather than to a positive reinforcement (pleasurable effects of psycho-physical result of providing).

*Other side effects.* AS are extremely toxic for liver, the liver is, in fact, the place where androgens are metabolized and thus their continued use may cause the occurrence of harmful effects. One of the most grave consequence is certainly peliosis hepatis (36), a disease characterized by the formation of hemorrhagic cysts (sometimes at splenic level), which can break and cause intra-abdominal haemorrhage, and death of the patient. Regarding the effects on glucose metabolism, AS reduce glucose tolerance and increase insulin resistance (37). Such drugs also affect thyroid function; in fact, AS administration, reduces TSH, T3, T4 and TBG synthesis. However, these effects are reversible a few weeks after AS suspension (38). In addition, AS abuse cause immune system suppression (39). Many studies have shown that immunoglobulin levels (IgG, IgM and IgA) were significantly lower steroid users compared to control groups (40,41). These studies suggest that high doses of anabolic steroids alter the immune mechanism and that the suppression of the immune system for a long period could lead to higher risks of infection or certain malignant cancers. Furthermore, it has been demonstrated that in patients treated with androgens has been reported an increase in T-suppressor lymphocytes (42). Actually, the athletes using steroids, said they felt stronger and thought to be more resistant against diseases; generally, however, after the desertion of these drugs they are more susceptible both to bacterial and viral infections (43-44).

Last but not least, studies conducted on animals and humans suggest that AS use, associated with an intense training period, may cause severe damage on connective tissue, which reduce the mechanical and elastic properties of tendon (tendon rupture) (45).

## Conclusion

In conclusion, AS use for doping purposes is a dangerous practice, that exposes who uses them to considerable risks (23, 43-47). This practice must be discouraged not only for social and moral reasons but also for toxicological reasons, both in short and long term. On the whole, doping substances must be banned from sports, making a work of vigilance and authority accountability of sports nucleus and authorities in this field.

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