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Abuse of androgenic-anabolic steroids and adverse effects in athletes

By Fumihiro Yamasawa

ABSTRACT

Androgenic-anabolic steroids (AASs) have been a major element in doping in sports for 50 years and they are the most abused substances in athletics. While it is true that AASs can contribute to improved performance in several sports, there are numerous reports of negative side effects, especially in the cardiovascular, hepatobiliary, reproductive and psychiatric systems. This article includes overviews of the abuse of AASs in sport and the techniques used in the practice as well as a detailed explanation of how AASs work on users. Its main focus, however, is on a long list of reported negative side effects, some of which can be fatal. The author concludes by stressing the importance of the fight against doping and the need to educate athletes and those around them, stressing the dangers involved AAS abuse.

AUTHOR

Fumihiro Yamasawa MD, DMSc is the Director of the Maubeni Clinic in Tokyo, Japan. He serves as the Director the Medical Committee of the Japan Amateur Athletic Federation and a member of the IAAF Medical and Anti-Doping Commission.

Introduction

Androgenic-anabolic steroids (AASs) are variants of the endogenous androgen testosterone, many of which have been synthesised since the 1950's. While AASs have been prescribed ethically for delayed puberty, hematological disorders, catabolic diseases and some kinds of cancer, athletes have, unfortunately, misused them to try to improve their performances. In fact, AASs have been a major element of doping in sports for about 50 years. The history of AAS abuse is practically the history of doping, and sports or competitions where AAS abuse seems prevalent are sometimes referred to as 'Chemical Games'.

According to the annual reports of the IOC Medical Commission, AASs have been the substances most abused by athletes. Over the past 20 years, the IAAF has conducted more than 33,000 doping tests and 37% of the approximately 1,200 positive cases were for AASs. Perhaps the most notorious recent scandal in sports involved many top performers in athletics and several other sports in the United States who illegally used tetrahydrogestrinone (THG), an AAS distributed by the BALCO company that was designed to avoid detection in ordinary doping control tests.

The World Anti-Doping Code and its associated international standards, including the 'Prohibited List' and the 'Therapeutic Use Exemption,' have been in effect since 1 January 2004. Together, these will harmonise and promote the worldwide fight against doping. The

2004 Olympic Games in Athens were the first held under the code and many measures were taken before and during the Games both inside and outside of the competition areas. Unfortunately, Athens has been called 'the Doping Olympics' because the number of positive cases was the highest in the history of the Games. Twenty-four athletes, including seven medallists, tested positive for prohibited substances. AASs were detected in several, including one gold medallist.

Abuse of AASs is not limited to top athletes. They are well known across a range of sports. It has been reported that many weightlifters have used 20 to 100 times the amount of a normal therapeutic prescription of AAS. AAS use is also known to be a common practice of many amateur and even young sportsmen and sportswomen. Moreover, many of the people who use one or more of the commercially available dietary supplements may unwittingly be taking AASs or precursors of testosterone as some of these products have been intentionally or unintentionally contaminated.

It is well known that sportsmen and sportswomen abusing AASs indicate disturbances of their mental and physical status[1,2,3,4,5,6]. As an extreme example, an increased incidence of premature mortality among powerlifters has been shown[7]. However, the adverse effects cannot be determined scientifically for all cases because many are only described in individual case reports[4,5,6]. Moreover, the critical dose of any AAS that causes health troubles has yet to be identified and it may depend on the individual taking the drug.

Though randomised, double blind, placebo-controlled studies are scientifically preferable for the investigation of the effects of any drug, there are ethical considerations when working with sportsmen and sportswomen. It is hardly acceptable to expose healthy young athletes to potentially hazardous drugs in supra-physiological dosages to determine whether these drugs improve performance or to confirm the adverse effects that may occur. Accepting these limitations in investigations, this article will, after introductory explanations of how AASs are used in doping practice and the nature and mechanism of action of naturally occurring testosterone and synthetic AASs, focus on the adverse effects on the health of AAS abuser-athletes.

The author fully supports current anti-doping regulations. It is the hoped that the provision of the information contained in this article will help athletes, coaches and medical personnel to make morally and ethically sound decisions and that it will contribute to the greater efforts ensure that sport on all levels is both fair and safe.

Techniques of AAS abuse

Athletes abusing AASs often use more than one type at a time, combining oral and pareteral preparations, a practice known as 'stacking'[1].

In another, very common practice, called 'cycling', periods (6 to 16 weeks in length) of high-dose use of AASs are alternated with periods of low-dose use or no drug at all. These intermittent discontinuations are believed by AAS abusers to allow the endogenous testosterone levels, sperm count and hypothalamic-pituitary-gonadal axis to return to normal. Abusers also believe that cycling prevents detection and insures peak performance during competition[2].

Some AAS abusers slowly escalate their steroid use (numbers, dose and frequency), reach a peak amount at mid-cycle and gradually taper the dose toward the end of the cycle. This practice is called 'pyramiding'.

Athletes may take AASs for a limited period in order to achieve a particular goal while others, such as bodybuilders and bodyguards, may take them for extended periods.

AASs stay in the body for anywhere from a couple of days to more than 12 months, depending on the characteristics of the particular AAS[2].

Testosterone and AASs

The testicular hormone testosterone was isolated in crystalline form in 1935. Its chemical structure was soon elucidated and the hormone was synthesised in the same year[8]. After that, many laboratory investigations were conducted to study the effects of testosterone. There are four other endogenous androgenic steroids. Except for dihydrotestosterone (DHT), which is a strong intracellular androgen, they are weak androgens that are transformed into testosterone in peripheral tissue and are thought to be precursors of testosterone.

Testosterone promotes masculine characteristics and virilisation, including acne, body hair, low voice, growth of the penis, alopecia (baldness) and an oily face. Its anabolic action results in hypertrophy and strengthening of muscles, enhancement of tissue repair and erythropoiesis[8]. The most prevalent reason for athletes to initiate AAS abuse is to enhance muscle mass and strength. Recent studies have shown that gains in muscle mass are greater when testosterone is administered in combination with a strength training programme[9].

Endogenous testosterone is mainly synthesised in the Leydig cells of the testes in males and in the ovaries in females[8]. The production and secretion of endogenous testosterone is stimulated and regulated by the luteinising hormone (LH). LH is also called interstitial cell stimulating hormone (ICSH) and the Leydig cell is an interstitial cell. LH is secreted from the anterior lobe of the pituitary gland under the control of the hypothalamus. When the serum concentration of androgen is high, the release of LH is suppressed by a feedback mechanism. A normal adult male produces testosterone at a rate of 2.5 to 11mg/day and a normal adult female produces only 0.25mg/day[8]. Serum testosterone concentration depends on sex and age; approximately 20ng/dl in pre-adolescent boys, 30 to 50ng/dl in normal adult females and 500 to 700ng/dl in normal adult males. The great difference in serum testosterone concentrations in adult males and females is reflected in the muscular body contours and aggressiveness in males. Serum testosterone concentration shows an elevated value during pre-ovulation and luteinising phases because there are LH surges during the menstrual cycle.

Anabolic steroids are synthetically produced variants of testosterone. They have androgenic effects (promoting masculine characteristics) and anabolic effects (tissue building). The androgenic effect cannot be separated from the anabolic effect. Therefore, the most appropriate name for this class of medicine is androgenic-anabolic steroids. Many AASs have been designed to strengthen their anabolic actions. It may be possible to create an AAS with 100% anabolic action in vitro, but in practice, the androgenic effect cannot be separated from the anabolic effect. No pure anabolic steroid without androgenic effect has ever been described and any kind of AAS has both anabolic and androgenic action. Most health problems come from the androgenic action of an AAS. The virilisation of a female AAS abuser is caused by the androgenic action of an AAS and low LH release. The low LH release accompanies low oestrogen release, and then the androgen/oestrogen balance becomes disturbed in the peripheral tissues.

Approximately 98% of testosterone in plasma is bound to the sex hormone binding globulin (SHBG), albumin and other proteins in serum and only 2% exists in the free form[8]. The anabolic action of an AAS depends on the concentration of plasma free form because AASs enter the target cells by a diffusion mechanism. While an AAS decreases the rate of hepatic synthesis of sex hormone binding globulin, oestrogens inversely increase the hepatic synthesis of the globulin. So, the concentration of the globulin in women is usually twice as high as that in men. The globulin concentration will be reduced if female athletes begin to abuse AASs and the free concentration of the AAS will be increased. It can, therefore, be said that females are more susceptible to AASs than males.

After diffusion into the target cells, testosterone binds directly or after conversion to the more active compound DHT, to specific receptors for androgens. The DHT-specific receptor protein complex has a 10 time higher affinity

to the DNA binding site than the testosterone-specific receptor protein complex. Binding to the receptor is followed by dissociation of heat shock proteins in the cytoplasm, accompanied simultaneously by a conformational change of the receptor protein, resulting in a transformation and a translation to the nucleus. Upon binding in the nucleus to specific DNA-sequences, the receptor dimerises with a second molecule and the homodimer entity recruits additional proteins (e.g. co-activators, general transcription factors, RNA-polymerase II) resulting in specific activation of transcription at discrete sites on the chromatin[10]. The conversion of testosterone to DHT is catalysed by the microsomal enzyme 5-alpha reductase and is NADPH dependent and irreversible. The enzyme 5-alpha reductase is the key enzyme that converts testosterone into DHT. The most important organ systems with high 5-alpha reductase activity are the male accessory sex glands, the skin, the prostate, the lungs, the brain, fat cells, and bone[4]. Therefore, these organs possess a high affinity to androgenic rather than anabolic compounds. Conversely, heart and skeletal muscles have a low 5-alpha reductase activity and exert a stronger response to anabolic substances.

As with testosterone, an AAS will bind to intracellular androgen receptor proteins and make AAS-androgen receptor protein complexes in the cytoplasm. The affinity between an AAS and intracellular androgen binding receptor protein depends on the type of steroid, the individual, sex and age[11,12]. With respect to binding with high affinity androgen receptors, 19-nortestosterone and metenolone are recognised as strong androgens. It is also recognised that stanozolol and fluoxymesterone are weak androgens because they have low affinity to androgen receptors[11,12].

The anabolic action in muscle cells is dependent on the concentration of intracellular androgen receptor proteins. Androgen receptor proteins exist more in the upper trunk muscles (chest wall, neck, shoulder girdle and upper extremities) than in the lower trunk muscles[13]. Therefore, AASs are more effective for muscular hypertrophy in the upper trunk. This is apparent in normal males but not in females who do not use AASs. As there is a limitation of available intracellular receptor proteins, when a supra-physiological level of an AAS is administered, intracellular receptor proteins will be fully saturated with testosterone and androgen. When many an AAS abusers use a lot of AAS, as in the practice of 'stacking', the AAS cannot combine with the receptor proteins any further and may not stimulate additional protein synthesis due to the regional differences in the body[14]. This phenomenon is dependent on each individual. With large dosages of an AAS, the possibility of side effects increase in other AAS target organs.

Testosterone (but not DHT) is also converted to the female sex hormones such as oestradiol and oestrone inside the cell[8,15]. This conversion is carried out under the aromatase activity. Female sex hormones bind to the oestrogen receptor protein and form an oestrogen-receptor protein complex. Fat tissue, Leydig cells and Sertoli cells are the main target cells of the female sex hormone. This mechanism will be activated when the androgen receptor system is saturated by testosterone and an AAS. When supra-physiological doses of AAS are given, the androgen receptor protein will be saturated, which will lead to conversion of an AAS to female sex hormone. Activated protein synthesis occurs in fat tissue and the breasts and induces fat deposition and breast development, or gynecomastia[1,2,3,15].

Three therapeutic preparations of AAS are clinically useful[8]. The first preparation is the parenteral injection type. Esterification of the 17 beta-hydroxyl group decreases the polarity of molecule and makes it more soluble in the lipid vehicles used for injection. AASs with esterification are effective when given at one or two-week intervals. The second type is administered orally. Alkylation at the 17-alpha position allows androgens to be effective orally. Oral types of AAS should be taken several times a day to obtain satisfactory effects. They are catabolised by the liver, but the alkyl group is not removed metabolically. Hence, the alkylated derivatives converted by 5-alpha reductase mediate the action of the hormone with-

in cells. Alkylation of androgens at the 17-alpha position markedly retards their hepatic metabolism and can cause hepatotixicity. The third type is a transdermal application, which avoids the destructive first pass action in the liver. Forms of gels and creams of native testosterone are also clinically available[8].

AAS related health troubles

There are many reports covering both the adverse effects found in athletes taking physiological dosages for longer periods and athletes taking supra-physiological dosages for relatively short courses[1,2,3]. However, the sources of some case reports are not reliable. Thus, the disputes over the adverse effects of AAS abuse in athletes are complicated. The adverse effects of AAS abuse depend on the age and sex of the individual, the duration and total dose of exposure, and the type of steroid used. Prolonged AAS use can be accompanied by minor or serious internal and external side effects. External side effects are relatively mild, but the internal side effects of prolonged AAS use are often much more substantial and serious.

The most thorough investigation of the devastating effects of AAS abuse was the report by German researchers, one a former German Democratic Republic (GDR) athlete who had been doped for several years[16]. The report disclosed the circumstances of intentional administrations of AASs to thousands of GDR athletes over 30 years. It revealed that minors of both sexes were given AASs to enhance their performances. The AAS administrations obviously caused many side effects, including serious liver dysfunction, gynecomastia, polycystic ovarian syndrome, failure of growth in adolescence, infertility, birth defects, and premature deaths. Three cases of AAS-related deaths are covered in the report, including one were the person died of liver dysfunction and intra-hepatic cholestasis.

In the following sections current knowledge of the health risks associated with AAS abuse are summarised:

1. Cardiovascular disorders

The occurrence of serious cardiovascular events in healthy young athletes is associated with the abuse of AASs. These events include coronary artery disease, acute myocardial infarction, atrial fibrillation, QT dispersion, development of cardiomyopathy, cerebro-vascular accident, systemic thrombosis and cardiac sudden death[6,17,18,19]. However, it is quite difficult to prove the relation between AAS abuse and these events.

It is certain that AASs strongly affect the risk factors of cardiovascular diseases. Serum cholesterol metabolism is affected by AAS use[20]. High-density lipoprotein (HDL)-cholesterol is an independent risk factor for the occurrence of cardiovascular disease. There is strong evidence that HDL-cholesterol level is suppressed remarkably by AAS use. This suppression is more than 50% dependent on the steroids used and dosage. The reduction can be observed within a few days of AAS administration. On the other hand, low-density lipoprotein (LDL)-cholesterol levels generally increase with AAS administration. LDL-cholesterol is an independent risk factor for generalised arteriosclerosis, which is characterised by the thickening of arterial walls and narrowing of arterial internal diameters. Most AASs cause water and electrolytes storage in the muscles. Several studies have shown an elevation of systolic or diastolic pressure results from high doses of AAS[21]. High blood pressure is related to water and sodium retention in the body. Edema may occur when large doses of AASs are used. Elevated blood pressure normalises within six to eight weeks of abstinence from AAS.

Use of AAS may lead to structural changes in the heart. Some echocardiography studies report mild hypertrophy of the left ventricle and thickening of the left ventricular posterior wall and interventricular septum in AAS-abusing bodybuilders[22]. However, the reports of structural changes relating to AAS abuse are still controversial, and are based upon the results of published prospective studies[23].

In summary, AAS abusers who take large

doses for longer periods will have serious disturbances of lipoprotein metabolism and high blood pressure, which are strong risk factors for generalised arteriosclerosis. These can lead to coronary artery diseases, cerebro-vascular disease and peripheral arterial occlusions in AAS abusers. Hence, AAS can present significant cardiovascular risks to the users.

2. Hepatic side effects

Hepatic side effects due to AAS abuse are hazardous and have been a great concern for athletes. As the 17-alpha alkylated AASs are taken orally, they are absorbed in the small intestine and catabolised by the liver. Alkylation of androgens at the 17-alpha position markedly retards their hepatic metabolism and can cause hepatotixicity. Hepatic side effects include intra-hepatic cholestasis, peliosis hepatis and hepatocellular carcinoma[24]. Fluoxymesterone, methyltestosterone, methandrostenolone, oxandrolone, stanozolol and oxymetholone are substances of the 17-alpha alkylated AAS group. Parenterally administered AASs seem to have less serious side effects on the liver.

Cholestatic hepatitis has been reported developing after two to five months of 17-alpha AAS use. The initial symptoms are prominent jaundice and itch. Increases in plasma activity of liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT) are often associated with hyperbilirubinemia. Peliosis hepatis is a hemorrhagic cystic degeneration of the liver, which may lead to fibrosis and portal hypertension[25]. Intra-abdominal hemorrhage and rupture of the cyst may lead to fatal bleeding. Recent studies suggest that individuals with abnormal liver functions before AAS use appear to be at risk for liver diseases. Persons who have used large amounts of a 17-alpha alkylated AAS for prolonged periods may develop hepatocellular carcinoma[26], but AAS associated liver cancers have been reported in only a few athletes.

3. Adverse effects on female reproductive system and female athletes

Daily production and plasma concentration of testosterone is less than 10% in females compared males[8]. Therefore, intra-cellular androgen receptors are not saturated with testosterone in females and exogenous AASs can have strong effects both anabolic and androgenic when used in females. Female AAS abusers may show male muscularity and masculine facial characteristics[1,2,3,4,5,6].

AASs affect the hypothalamic-pituitary-gonadal axis. An increase of plasma androgens will inhibit the production and release of LH and follicular stimulating hormone (FSH) from the anterior pituitary lobe, a process that is known as the endogenous negative feed back mechanism. This results in a decline in serum levels of oestrogen and progesterone. These changes of female hormones inhibit follicle formation and ovulation and thus lead to irregularities of the menstrual cycle. However, there exists an inter-individual difference in response to AASs.

Other side effects of AAS abuse in female athletes are acne, coarsening of the skin, hair loss, recession of the frontal hairline, deepening of the voice, increased facial hair growth, increased sexual desire, breast atrophy and hypertrophy of the clitoris. The breast atrophy, lowering of the voice and hypertrophy of the clitoris are generally irreversible. The severity of the side effects, which occur in female AAS abusers, is related to the type of AAS, dosage and duration of use.

4. Feminising side effects and other adverse effects on male athletes

AAS administered to healthy males work as 'relatively weak' androgens because plasma concentrations of testosterone are already at a naturally high level. As the androgen-receptor proteins are almost saturated with testosterone and DHT, exogenous AAS cannot have as strong an effect on peripheral cells. So, AASs can work as relatively weak androgens and large anabolic effects may not be obtained in muscle cells even if the athletes use doses of AASs that are 20-100 times larger than the

therapeutic dose. In fact, the administration of supra-physiological doses of AASs may not result in any more growth of muscle than is afforded by the normal concentrations of testosterone. Further, much of the AAS will be converted to estrogens in peripheral tissues (aromatisation) and so the administration of testosterone esters causes an increase in plasma concentration of oestrogen[8,27]. The androgen/oestrogen imbalance will result in gynecomastia, fat deposit, water retention and erectile dysfunction. There is a great deal of difference in what percentage of each AAS will be aromatised to oestrogen. For example, it is reported that 20% of methandrostenolone and 40% of oxymetholone will be aromatised.

LH and FSH are responsible for regulating spermatogenesis and steroidogenesis in the testis[8,27,28]. When AAS is administered to male athletes, the production and secretion of LH and FSH will be reduced within 24 hours in the same manner as in the female athletes, and then testosterone secretion will be decreased. The decline of plasma concentration of LH, FSH and testosterone will result in oligospermia, azoospermia and shrinkage of the testicles. The practice of 'stacking' will strongly suppress the male gonadal function for a long period. The recovery of the male gonadal function will take from several months to one year after interruption of AAS abuse.

One of the most well known side effects of AAS abuse is gynecomastia in male athletes[15]. Gynecomastia is the abnormal enlargement of one or both breasts, an effect sometimes referred to as 'bitch tits'. It is a great concern for some athletes because of the cosmetic problem. They may experience swelling of the breasts and painful nodular tissues. Gynecomastia in males is caused by increased levels of plasma oestrogens, which are formed by aromatisation and conversion of large amounts of AAS in peripheral tissues. Gynecomastia is generally irreversible and some athletes have to have surgical procedures to remove the soft tissues[29].

Some AAS abusing athletes use human chorionic gonadotropin (HCG), anti-oestrogens (clomiphen citrate, tamoxifen) and aromatase inhibitors (testolactone) at the same time to stimulate steroidogenesis in the testis and overcome increased oestrogen activities. These processes are thought to be effective in preventing the formation of gynecomastia. This seems to be theoretically true, but the response is different in each individual. In fact, some cases have shown a worsening of the gynecomastia with these preventive processes. The best treatment for gynecomastia is to quit AAS use completely.

Additionally, long-term AAS use may result in prostate cancer in males[6].

5. Psychological effects

AAS abuse (generally with high doses) can cause adverse psychological effects. These include irritability, hostility, aggression, euphoria, increased anxiety, and increased sexual desire[30,31]. With prolonged high dosage, abusers come to have a dependency on AASs and develop extremely aggressive behaviour. This mental state results in inability to control behaviour, loss of friendship and depression, sometimes with suicide. Other side effects are schizophrenic and manic-depressive disturbances, pathological anxiety, sleep disturbances and acute neurosis, such as hallucinations and paranoia. The occurrence and seriousness of AAS associated mood disturbances are thought to be dose dependent.

6. Infectious complications

As AASs are often obtained on the black market, contamination can be a serious problem, especially in cases where they are administered parenterally. Skin infections and dermal abscesses at injection sites have been reported. Abusers can also develop infective endocarditis. Human immunodeficiency virus (HIV) and hepatitis B and C virus infections have also been reported among people who shared contaminated needles to inject AASs[3].

7. Adverse effects in musculo-skeletal system

Idiopathic ruptures of the tendons are strongly related to AAS abuse. Though AASs may cause hypertrophy of muscles, they will not strength-

en the tendons and may even cause tendon degeneration. Tendons, therefore, may be damaged by the contraction of hypertrophied muscles and the risk of tendon rupture will be increased. It may be reasonable to assume that tendon injuries are mostly associated with high-doses of AAS abuse over a long period.

8. Adverse effects in pre-pubertal boys

When androgens and AASs are given in pre-pubertal boys, the effect will be precocious sexual development; penis enlargement and increased frequency of penile erections. AASs will cause the premature closure of the growth plates in the long bones and result in a decrease in the total height achieved[32].

Conclusion

AASs have been a major element of doping in sports for about 50 years and they remain the most abused doping substances. Abuse of AASs is not limited to top athletes, as it is also known to be a common practice of many amateur and even young athletes.

It is true that AASs contribute (unfairly) to sports performance and that their negative effects on the health abusers have not been scientifically proven yet, however there are numerous reports that AASs are associated with very serious and even fatal side effects. These dangers have been best shown in relation to the cardiovascular system, hepatobiliary system, reproductive system and psychiatric system but other problems have also been noted

It is vitally important that all athletes as well as their support personnel, families, coaches, medical and paramedical staffs understand more thoroughly how serious the health risks of AAS abuse are. Success in the fight against doping will only be achieved if this information is communicated effectively throughout the whole of the sporting community.

Please sent all correspondence to:

Fumihiro YAMASAWA, MD, DMSc
Email: Yamasawa-F@marubeni.com

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