DOI: 10.1515/cipms-2018-0026 Curr. Issues Pharm. Med. Sci., Vol. 31, No. 3, Pages 135-139

Current Issues in Pharmacy and Medical Sciences
Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

journal homepage: http://www.curipms.umlub.pl/

Potential risks related to anabolic steroids use on nervous, cardiovascular and reproductive systems disorders in men

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ARTICLE INFO

Received 15 January 2018
Accepted 01 March 2018

Keywords:
anabolic steroids,
testosterone,
strength athletes,
nervous system,
cardiovascular system,
reproductive system.

ABSTRACT

Anabolic steroids (AS) have been a subject of intensive research for the last several decades. Due to wide use of AS in pharmacological treatment and in professional and amateur sport, it is, hence, worthwhile to describe the biochemical mechanism of the effects of AS usage in humans and its potential health risks. In this work, the relationship between diet and its effect on the level of testosterone in blood is described. Testosterone affects the nervous system, however, there is need for further researches to examine the influence of AS therapy on emotional and cognitive functioning. AS therapy has known negative effects on the cardiovascular system: cardiac hypertrophy can occur, blood pressure can vastly increased, thrombotic complications can come about. These effects are observed not only in patients who are treated with AS, but also in athletes. The paper also describes the relationship between AS and reproductive system diseases. Decreased libido and erectile dysfunction are only some of the many side effects of an incorrect AS treatment.

INTRODUCTION

Several unique sex differences are observed in humans, for example, women tend to live longer than men [1]. One of the main hypothesis behind this is the differences in sex hormones, and the protective role of estrogen in women [1]. The last decades were fruitful in deriving pharmacological interventions which aim to modulate hormonal level in patients, for example, to increase testosterone action on muscle hypertrophy [2]. This is also the goal of off-label using of pharmacological agents, for example, in bodybuilding. Testosterone administration restores sex drive, sustains the male libido, increases muscle mass and aids in developing the ideal male physique. The popularity of illegal use of AS in professional sports has become a growing public health concern [3,4], as it has generated a copy-cat response in amateur sports [5].

In this work, articles in the EBSCO and the Google Scholar database have been analyzed using the keywords: anabolic steroids, testosterone, strength athletes, nervous system, cardiovascular system, reproductive system. The available literature was subjectively selected due to its usefulness in showing the potential risk of anabolic steroid consumption.

ANABOLIC STEROID BIOCHEMICAL MECHANISMS IN HUMANS

The majority of androgens in serum are connected with the plasma glycoprotein sex hormone-binding globulin (SHBG) and androgen-binding protein (ABP), while a minority are complexed with albumin [6]. The androgen synthesis begins from cholesterol as the precursor. The major circulating androgen: testosterone, is synthesized in the testis, while dehydroepiandrosterone and androstenedione are mainly produced in adrenal tissue [6]. Androgens are male sex steroid hormones that exert many physiological roles [6].

The mechanism of AS influence on humans seems to be complex. The anabolic steroids have their effect by binding to intracellular receptors. These receptors, through connection with their ligands, are transcription factors supporting the expression of genes controlled by steroid-response elements (SRE) [7]. However, gene expression modulation

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is not obligatory in the AS mechanism of action. This situation is called "nongenomic" [6].

Anabolic steroids are classified according to their biochemical mechanisms, specifically, their androgenic and anabolic effects. Tertiary sexual characteristics are one of these androgenic effects. These effects include increase of external genitalia, increase in body hair and mutation. Enhanced steroid concentration leads to growth of muscle mass, osteogenesis and increased protein synthesis. Some of these effects are employed in legal medical practice – and some off-label and illegal.

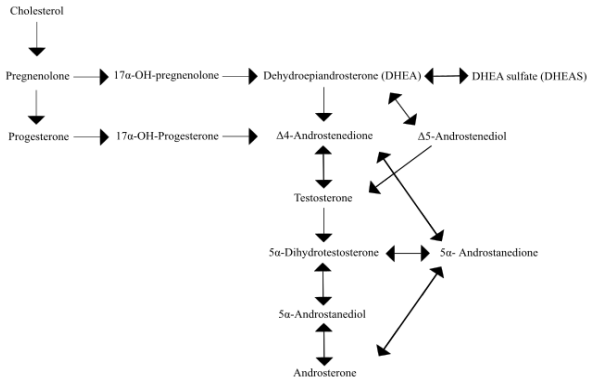

Figure 1. Biochemical pathway of steroids. Adapted from [8]

EFFECTS OF NONPHARMACOLOGICAL MODULATORS OF TESTOSTERONE LEVEL

Excessive amounts of adipose tissue contribute to changes in testosterone levels in the blood. Adipocytes, or adipose tissue, affect the production of enzymes that block the conversion of testosterone to estrogen, increasing the level of the hormone in the body [9]. Testosterone is a precursor of estrogens, but when the diet is poor in polyphenols, anthocyanins, ellagic acid, ursolic acid, triterpenoids, or fatty acids, the conversion rate of testosterone to estrogen is lowered. Among the products rich in polyphenols are grenadines, grapes, cabbage, celery, paprika, parsley, turmeric, as well as black and green coffee and tea [10]. Food ingredients such as phytosterols, tannins, flavonoids, saponins, or essential oils can also affect testosterone levels. They are inhibitors of testosterone metabolite products, resulting in increased concentration as testosterone is not metabolized to dihydrotestosterone (DHT). These nutrients can be found in such foods as chokeberry, currant, tomato, ginseng, aloe, legumes, coffee and tea [11,12].

An important vitamin in terms of testosterone level in B3. It is the only vitamin that can be produced from tryptophan – an exogenous amino acid. It participates in the transfer of NAD and NADP, or contributes to the formation of cholesterol, from Acetyl-CoA. AS therapy could potentially reduce High Density Lipoprotein (HDL) [13]. On the other hand, niacin supplementation significantly increased High Density Lipoprotein (HDL) level in patients under intensive statin therapy [14], therefore, it may be appropriate to supply patients who are undergoing AS therapy with niacin.

Vitamin D is also important with regard to testosterone level. Its receptors were largely found in Leydig cells located in the testis and in plasma 25-OH. Vitamin D correlates with testosterone level [15,16].

The synthesis of testosterone, moreover, depends on zinc, which in turn affects the synthesis of the remaining steroid hormones. It has been shown that testosterone levels are lowered in case of too low zinc intake from the diet, whereas in the case of supplementation with this element, serum testosterone levels increase [11]. The correct level of zinc intake ranges from 8 mg per day for women, to 11 mg for men [13,17]. In summary, there is an evidence that zinc depletion can lead to undesirable disturbances associated with low testosterone levels [18].

It should be underlined that diet induced alterations in serum testosterone relative changes concern differences in the order of a few nmol/litre. With regard to this, results of studies on the effects of a high-fat diet on serum total and free testosterone showed an increase of mean values for 0.8 and 0 nmol/litre, respectively [19]. In contrast, a low-fat diet lowered serum total and free testosterone levels by 1.8 and 0.01 nmol/litre, respectively.

Similarly, in the case of effects of diet supplements on serum testosterone level, a reduction noted after Trigonella foenum-graecum Extract consumption in mean level of testosterone level were in order of 0.5 nmol/litre (14.8 nmol/litre pre-intervention *vs* 14.3 nmol/liter post-intervention) [20]. Herein, an enhanced order of increased level could be obtained as acute effects of heavy-resistance training [21], but AS level elevations are rather transient. In contrast, exogenous use of 150 mg of testosterone enanthate increased mean value total testosterone and free- testosterone levels by circa 2-fold and 3-fold magnitude, in comparison to baseline in men with late-onset hypogonadism [22]. Therefore, it is worth ascertaining if any intervention based on diet or supplementation in healthy men could induce non-transient changes of testosterone level.

INFLUENCE OF ANABOLIC STEROIDS ON THE NERVOUS SYSTEM

Anabolic steroids play an important role in the functioning of the nervous system, herein, taking part in the organization of brain circuits (which are activated by gonadal steroids) [23]. They also play an important role in the neuroendocrine system, regulating the level of many hormones. High steroid levels decrease those of the gonadotropins, the gonadal steroids, free T3 and T4, as well as thyroid binding globulin. At the same time, researchers have noted enhanced Thyroid Stimulating Hormone (TSH) levels, without substantial changes in the pituitary-adrenal hormone levels.

Changes in some hormonal levels are known to affect behavior. Thus, anabolic steroids have been prescribed in the regulation of sexuality, aggression, cognition, emotion and personality [24]. It is believed that their use induces behavior typical of the male, therefore, different reactions to these substances should be emphasized, depending on the sex. It is also important to take adequate dosage of exogenous AS, because inappropriate dosage can act psychotoxically [23].

Behaviour is regulated by the neuroendocrine system, but GABAergic circuits in the forebrain seem to be their basis. These systems are steroid-sensitive and critical for the expression of behaviors altered with anabolic steroids use, therefore, they are serious candidates in explaining how

anabolic steroids affect the body in a molecular way. Accordingly, in men taking anabolic steroids, there is a change in the expression of the GABA(A) receptor, which leads to changes in the factors regulated by GABAergic transmission, such as puberty (and engendering adolescent body image disorder), as well as estrous cyclicity - leading to its deregulation and sexual receptivity, and increasing sexual desire [25].

Research on molecular changes while taking anabolic steroids have noted the importance of the serotonin receptor. Studies have shown that steroid use decreases levels of 5-HT-related messenger RNA in the prefrontal cortex and the amygdala of male mice. These results indicate that prefrontal cortex and amygdala are critical sites for steroids-induced effects and that serotonin receptors play a significant molecular role in psychical reactions after taking steroids [26]. Another neurotransmitter which is influenced by anabolic steroids is dopamine. This neurotransmitter takes part in processes of mobility, learning, emotions, appetite and positive reinforcing effects, but also plays a special role in the reward system. The last of these functions is particularly important, because it affects the pleasure of taking subsequent doses of steroids. This effect predisposes to dependence on the discussed substances. Other neurotransmitters regulated by anabolic steroids include norepinephrine, but the nature of its changes is still discussed, and the results of individual studies often differ significantly [27].

In people taking AS, it is especially dangerous to receive additional psychoactive substances. While the very taking of anabolic steroids alone do not have high addictive potential, this is increased significantly when additional psychoactive substances are taken [28]. In this situation, the level of aggression also increases, and many mental disorders such as hypomania and depression are more greatly expressed [29].

Knowledge of the effects of anabolic steroids on the functioning of the nervous system is still not sufficient, but development in behavioral assessment, autonomic reactivity, psychopharmacology and genetics has enhanced interest in this topic. It is possible that within a few years it will be necessary to change the perception of anabolic steroids as a purely negative substance. It has already been confirmed, for example, that some steroids increase performance [27]. This effect, with rational use, can bring many benefits to society. Unfortunately, there is still not enough research on the subject, and its quantity should be increased.

INFLUENCE OF AS ON CARDIOVASCULAR SYSTEM

Chronic AS therapy have a multitude negative effects on the cardiovascular system. Several AS-induced adverse cardiovascular consequences have been reported, such as increased blood pressure (BP) level, increased risk of pathological cardiac hypertrophy, impaired diastolic filling, arrhythmias, stroke and other thrombotic complications [30].

AS are potentially atherogenic through their influence on lipid metabolism [31,32]. Some studies also show a relationship between AS and levels of hepatic triglyceride lipase (HTGL), an enzyme that adjusts serum lipids and lipoproteins [30]. AS use increases HTGL activity, which in turn leads to increase of atherosclerotic plaques deposition by suppression of serum HDL level and the raising of Low Density Lipoprotein (LDL) level [32].

The effects on apolipoprotein A and B-1 are compatible with the effects on HDL and LDL, AS administration can induce an elevation of apolipoprotein A and a reduction of apolipoprotein B-1 [33]. Notwithstanding, the results in changes may vary considerably with regimen, types of AS used and route of administration [32]. The above changes in serum lipids and lipoprotein levels can lead to enhanced cardiovascular risk, although the influence of short-term disorders of the cardiovascular risk profile in healthy young athletes is unknown [32]. Still, data from studies and case reports show an association between AS use and fatal events, for example, acute coronary syndromes and ventricular arrhythmias [30].

Some athletes using AS have presented thromboembolic complications. Researchers have shown a connection between thrombosis and AS abuse [31]. Possible mechanisms for an increased risk of arterial thrombosis include increased platelet aggregation, enhanced levels of a few procoagulant factors, decreased fibrinolytic activity, declined synthesis of prostacyclin and increased endothelin release after vascular injury [31,34,35]. Notably, some researchers [36,37] have reported significantly raised levels of haematocrit and haemoglobin in athletes using AS. Such enhancements are associated with increased cardiovascular risk. Cases of sudden death due to right heart failure subsequent to venous thrombus formation are reported [38] among AS consumers.

The available literature is not unequivocal in relation to the effects of AS on BP level [32]. BP response to AS abuse normally shows a dose-response relation [25]. Elevated BP due to AS use has been observed in some cases [30,39-41]. The reduced elasticity and increased fibrous proteins in vascular tissue due to presence of androgen may be responsible for increased systolic and diastolic BP [31]. However, several studies analysing different AS regimens show no changes in BP in healthy strength athletes [42-44].

Athletes using AS often present Left Ventricular Hypertrophy (LVH) [31]. However, that aforementioned changes in heart structure may result from increased afterload from isometric exercise [41]. Researchers hold that the AS mechanism of action could induce changes in myocardium and systemic hypertension development, which, in turn, could explain the high risk of LVH occurrence in AS users. Indeed, several studies [45,46] have shown that AS can connect with androgen receptors and may directly cause hypertrophy. Moreover, AS may have influence due to regulation by the renin-angiotensin system [47].

RECREATIONAL USE OF ANABOLIC STEROIDS AND THE RISK OF REPRODUCTIVE DISEASES

The development of male reproductive organs is dependent on the significant role of androgens due to the androgen receptor which is stimulated both by testosterone and its metabolite DHT. The process of spermatogenesis depends on the level of testosterone secretion by Leydig cells. Moreover, male sexual function, puberty and male fertility depend on androgens [48].

Administration of anabolic androgens induces hypogonadotropic hypogonadism by way of negative feedback within the hypothalamic-pituary-gonadal axis, and, therefore, gonadotropin-releasing-hormone (GnRH) is inhibited. As a consequence, the concentration of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) decrease [49]. The average time of hypogonadism is influenced by various factors such as amounts, diversity and continuance of drug use [50].

In adult testis, the regulation of germ cell population is based on the significant role of apoptosis. Shokri *et al*., using an animal model, showed that nandrolone treatment can induce the intensive increase of spermatogenic cells apoptosis. Moreover, the downturn is intensified by physical exercise [48].

The level of endogenous testosterone is the lowest in the post-cycle period. This frequently the time when AS users complain the most of decreased libido and erectile dysfunction. From among all synthetic anabolic androgens, nandrolone when used alone is described as the cause of erectile dysfunction. Still, similar effects are reported after the use of other testosterone-enhancing drugs [50].

Research on animals have shown that anabolic steroids induce functional changes as well as morphological anomalies in the Leydig cells. Furthermore, the disappearance of advanced forms of spermatids has been reported as a consequence of spermatogenesis disability [48]. Through fluorescence *in situ* hybridization (FISH) sperm analysis amidst AS users, researchers have noticed XY and chromosomes 1 and 9 disomies, which suggest AS administration can cause genetic harm and abnormalities in the meiotic process [51]. However, differences can occur between individual users concerning the resulting kinetics of hypothalamic-pituitary-gonadal (HPG) axis. Younger AS users have a more "flexible" HPG axis and have better capacity to more rapidly recover GnRH pulsation and gonadotropin secretion than can older man [50].

The results of studies conducted by Gu *et al*. show the median period of the sperm production return, after interruption with 1,000 mg daily administration of testosterone and, additionally, a prescribed dose every month of 500 mg for 30 months was 182 days. However, for two of 729 patients, the recovery time was 15 months. This difference comes about because AS users often overdose and combine a large number of AS [52].

CONCLUSIONS

AS are a widely used substance for rapidly increasing muscle mass. Unfortunately, anabolic steroids interfere with the functioning of the body, disrupting the hormonal balance. Hormonal management is also disturbed in people who are overweight. The diet, hence, plays an important role in maintaining the proper conversion of testosterone to estrogens. It should be rich in polyphenols, vitamin B5 and D3 and zinc. Inappropriate dosage of exogenous AS negatively affects the nervous system, leading to changes in behaviour in terms of sexuality, emotions, personality and level of aggression. However, more researches on the effects of exogenous steroids on neural circuits are needed.

Steroids also negatively affect the cardiovascular system, increasing the risk of pathological cardiac hypertrophy, as well as enhancing blood pressure levels and inducing arrhythmia. The aforementioned effects may lead to acute coronary syndrome, stroke and thromboembolic complications.

In addition, taking exogenous anabolic steroids may lead to secondary hormonal failure of the testicles, and even to infertility. It could also affect negatively many organic systems, hence, bringing about a number of unwanted side effects. Therefore, more researches on the risk of exogenous anabolic steroids consumption is needed to examine the optimal form and dosage to be taken for performance enhancing activities.

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