International Journal of Physical Medicine & Rehabilitation

OPEN ACCESS Freely available online

Research Article

Adverse Events of Anabolic Agents in Doped Athletes: A Systematic Review of the Literature from 2010 to 2021

Abdulkarim Tutakhail[1], Julie Brionne[1]; David Balayssac[3], François Coudore[1,2]

[1]Department of Pharmacology, University Paris-Saclay, MOODS Team, INSERM UMR-1018, Gif-sur-Yvette, France; [2]Department of Biology, GH Paris Saint-Joseph, F-75014 Paris, France; [3]Université Clermont Auvergne, CHU Clermont-Ferrand, INSERM U1107 NEURO-DOL, Direction de la Recherche Clinique et de l'Innovation, F-63000 Clermont-Ferrand, France

ABSTRACT

This systematic review of the literature presents the important biological and clinical effects of Anabolic Agents (AA) used by athletes to dope themselves, identified in the scientific literature with keywords based on the name of both anabolic androgenic steroids identified by the World Anti-Doping Agency (WADA), in PubMed and Web of Sciences between 2010 and 2021. The selected publications recall the consequences on the cardiovascular and muscular systems, behavioral disorders but also at the hepatic, hematological and hormonal levels. It is useful to recall that the use of anabolic agents by athletes is prohibited and sanctioned by the WADA to preserve the fairness of competitions, but also because of the harmful effects of their use.

Keywords: Doping in sports; Anabolic agents; Adverse effects

INTRODUCTION

Sports doping is a problematic topic despite World Anti-Doping Agency (WADA) regulations. According WADA's 2019 Anti-Doping Rule Violations Report (ADRV), there were 2,701 adverse analytical findings (1%) out of 278,047 samples collected in doping controls, 57% of the adverse analytical findings were considered an anti-doping rule violation and resulted in a sanction [1]. However, doping prevalence rates in competitive sport had been estimated in a systematic review showing a higher prevalence ranged between 0% and 73%, but the most frequently under 5% in the publication assessed [2]. The most represented sports are bodybuilding (22%), athletics (18%), cycling (14%), weightlifting (13%) and powerlifting (9%) [1]. Among adverse analytical findings, the most represented substance groups were anabolic agents (47%), and thereafter, stimulants (15%) and diuretics and other masking agents (14%) [3].

Anabolic agents used as sports doping can be Androgenic Anabolic Steroids (AAS), which are synthetic derivatives of testosterone, a sex hormone that develops male sexual characteristics and incresases skeletal muscle growth through an anabolic action [4]. The most commonly AAS used by athletes are stanozolol, nandrolone and metandienone according to the National Institute on Drug Abuse [5], and stanozolol (14% of AAS identified in adverse analytical findings), dehydrochloromethyl-testosterone (13%), and drostanolone (10%) according to the WADA [3]. Other anabolic agents are also consumed such as beta-2 adrenergic agonists that have anabolic effects on muscles like clenbuterol [5]. Anabolic agents are used by professional and amateur athletes to improve performance and muscle mass [6]. AA represents a large part of sports doping, and WADA prohibits their use and updates a list of banned substances [7]. Today, it is known that the use of anabolic agents is responsible for adverse effects, especially because athletes have used very high doses compared to therapeutic ones [4].

Based on the importance of AA in sport doping, we performed a systematic review focused on the biological and clinical effects of these agents in sports doping presented in the scientific literature between 2010 and 2021.

METHODOLOGY

This systematic review of the scientific literature was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [8].

Eligibility criteria

Inclusion criteria were publications referring to AA according to

Correspondence to: François Coudore, Department of Pharmacology, University Paris-Saclay, MOODS Team, INSERM UMR-1018, Gif-sur-Yvette, France, E-mail: francois.coudore@universite-paris-saclay.fr

Received: 05-Oct-2022, Manuscript No. JPMR-22-19470; **Editor assigned:** 10-Oct-2022, PreQC No. JPMR-22-19470 (PQ); **Reviewed:** 28-Oct-2022, QC No. JPMR-22-19470; **Revised:** 04-Nov-2022, Manuscript No. JPMR-22-19470 (R); **Published:** 15-Nov-2022, DOI: 10.35248/2329-9096-22.11.654.

Citation: Tutakhail A, Brionne J, Balayssac D, Coudore F (2023) Adverse Events of Anabolic Agents in Doped Athletes: A Systematic Review of the Literature from 2010 to 2021. Int J Phys Med Rehabil.11:654.

the World Anti-Doping Code International Standard for the 2021 Prohibited List (1-androstenediol, 1-androstenedione, 1-androsterone, 1-epiandrosterone, 1-testosterone, 4-androstenediol, 4-hydroxytestosteron, 5-androstenedione, 7α-hydroxy-DHEA, 7β-hydroxy-DHEA, 7-keto-DHEA, 19-norandrostenediol, 19-norandrostenedione, androstanolone, androstenediol, androstenedione, bolasterone, boldenone, boldione, calusterone, clostebol, danazol, dehydrochlormethyltestosterone, desoxymethyltestosterone, drostanolone, epiandrosterone, epi-dihydrotestosterone, epitestosterone, ethylestrenol, fluoxymesterone, formebolone, furazabol, gestrinone, mestanolone, mesterolone, metandienone, metenolone, methandriol, methasterone, methyl-1-testosterone, methylclostebol, methyldienolone, methylnortestosterone, methyltestosterone, metribolone, mibolerone, nandrolone, norboletone, norclostebol, norethandrolone, oxabolone, oxandrolone, oxymesterone, oxymetholone, prasterone, prostanozol, quinbolone, stanozolol, stenbolone, testosterone, tetrahydrogestrinone, trenbolone, clenbuterol, andarine, LGD-4033, ligandrol, Enobosarm, ostarine, RAD140, tibolone, zeranol, zilpaterol) [9], abstract available, sport doping, human species, original article and in English language. Exclusion criteria were defined as follows languages different from English one, book, review, meta-analysis, letter to the editor, case report, animal studies, *in vitro* studies, analytical studies, epidemiological studies, studies assessing prevention strategies, agents different from anabolic ones (e.g. erythropoietin, plants...)

Information sources

The bibliographic search was performed in PubMed and Web of Sciences databases from January 1st 2010 and June 2nd 2021.

Search strategy

The search strategy in PubMed was done on June 2nd, 2021, with the following keywords sequence: "(1-androstenediol or 1-androstenedione or 1-androsterone or 1-epiandrosterone or 1-testosterone or 4-androstenediol or 4-hydroxytestosteron or 5-androstenedione or 7α-hydroxy-DHEA or 7β-hydroxy-DHEA or 7-keto-DHEA or 19-norandrostenediol or 19-norandrostenedione or androstanolone or androstenediol or androstenedione or bolasterone or boldenone or boldione or calusterone or clostebol or danazol or dehydrochlormethyltestosterone or desoxymethyltestosterone or drostanolone or epiandrosterone or epi-dihydrotestosterone or epitestosterone or ethylestrenol or fluoxymesterone or formebolone or furazabol or gestrinone or mestanolone or mesterolone or metandienone or metenolone or methandriol or methasterone or methyl-1-testosterone or methylclostebol or methyldienolone or methylnortestosterone or methyltestosterone or metribolone or mibolerone or nandrolone or norboletone or norclostebol or norethandrolone or oxabolone or oxandrolone or oxymesterone or oxymetholone or prasterone or prostanozol or quinbolone or stanozolol or stenbolone or testosterone or tetrahydrogestrinone or trenbolone or clenbuterol or andarine or LGD-4033 OR ligandrol or Enobosarm or ostarine or RAD140 OR tibolone or zeranol or zilpaterol and sport and doping and English language not review (Publication Type)), and between 2010-2021.

The search strategy in Web of Science was done on June 2nd, 2021, with the following associations of keywords sequences: 1. "Ts=sport and doping and language: English and document types: Article" (Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S,BKCI-SSH, ESCI Timespan=2010-2021). "Ts=1-androstenediol or 1-androstenedione or 1-androsterone or 1-epiandrosterone or 1-testosterone or 4-androstenediol or 4-hydroxytestosteron or 5-androstenedione or 7β-hydroxy 8DHEA or 7β-hydroxy-DHEA or 7-keto-DHEA or 19-norandrostenediol or 19-norandrostenedione or androstanolone or androstenediol or androstenedione or bolasterone or boldenone or boldione or calusterone or clostebol or danazol or dehydrochlormethyltestosterone or desoxymethyltestosterone or drostanolone or epiandrosterone or epi-dihydrotestosterone or epitestosterone or ethylestrenol or fluoxymesterone or formebolone or furazabol or gestrinone or mestanolone or mesterolone or metandienone or metenolone or methandriol or methasterone or methyl-1-testosterone or methylclostebol or methyldienolone or methylnortestosterone or methyltestosterone or metribolone or mibolerone or nandrolone or norboletone or norclostebol or norethandrolone or oxabolone or oxandrolone or oxymesterone or oxymetholone or prasterone or prostanozol or quinbolone or stanozolol or stenbolone or testosterone or tetrahydrogestrinone or trenbolone or clenbuterol or andarine or LGD-4033 or ligandrol or Enobosarm or ostarine or RAD140 or tibolone or zeranol or zilpaterol and language: English and document types: Article" (Indexes=SCIEXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=2010-2021).

Selection process

Two readers (JB and AT) performed a first selection of manuscripts according to inclusion and exclusion criteria based on title and abstract of each manuscript. In the event of disagreement between the two readers, a third reader (DB) took part in the decision with a reading of the full-text of the manuscript, until a consensus was reached. Full-text of each selected manuscript was finally obtained for analysis. Manuscripts could be excluded during analysis of full-texts.

Data collection process

Manuscript data from PubMed and Web of Sciences were collected and imported into Zotero software (Roy Rosenzweig Center for History and New Media at George Mason University). Thereafter, data from Zotero was exported to Excel (Microsoft) software format for data analysis. These two Excel files (PubMed and Web of Science data) were merged in a single Excel one, and keeping only the following information for analysis: publication years, authors, journal name, publication title, abstract, and the unique identifier number used in PubMed (PMID) or the Web of Science identifier.

Data items

From full-text manuscript, each publication was analyzed to retrieve the following information: Name of anabolic agents, doses, durations of use (if available), total number of subjects, number of doped and clean subjects, type of athletes, and biological and clinical effects.

RESULTS

Selection of publications

The bibliographic search identified 689 publications: 415 publications on PubMed and 274 publications on Web of Sciences.

One hundred and sixty-five duplicates between PubMed and Web of Sciences were removed from database. Finally, 17 publications met inclusion criteria and 507 publications were removed from analysis because of exclusion criteria (Figure 1) [10].

The analysis of the selected publications allowed identifying the following system and classes of adverse effects related to the use of anabolic agents in sport doping: Cardiovascular, anthropomorphic, muscular, behavioral, endocrine, biochemical, hematological and hepatic effects.

Cardiovascular effects

Six publications were identified and analyzed as related to cardiovascular effects [4,11-15], with a total of 323 subjects of which 155 were doped and 168 were clean subjects. The clean subjects are represented by 108 athletes and 60 sedentary subjects who do not use anabolic agents.

A significant blood pressure increase was observed in athletes consuming AA [4,12,13,15]. However, in one publication, there was no significant change in blood pressure after a clenbuterol consumption [14].

Heart rate of trained athletes was lower than that of sedentary persons (55.8 ± 7.8 *vs.* 75.3 ± 10.8, p<0.001) [13]. The use of anabolic agents increased heart rate in doped athletes [13,14], but two studies did not highlight this increase [4,12]. In addition, 4 cases of tachycardia were reported among 155 doped subjects (2%) across all publications [11,14].

Echocardiography results in doped and non-doped athletes highlighted a decrease in Left Ventricular Ejection Fraction (LVEF) in doped athletes [4], but two studies did not report any difference [12,13]. Regarding myocardial anatomy, left ventricular wall thickness was comparable between doped and non-doped individuals [4,12,13]. In doped athletes, a higher left ventricular mass was observed in doped athletes than in non-doped, this may reflect the higher risk of cardiac hypertrophy for these athletes [4]. About the left atrium of the myocardium, a significant alteration in the emptying fraction and lateral deformation of the left atrium in doped subjects was observed. A correlation between the decrease in left atrium deformation and the decrease in capacity during exercise was reflected by variation of peak VO2 (r=0.68; p<0.001) [12].

The QT interval is shorter in doped subjects compared to non-doped subjects, but no significant difference was demonstrated between doped and sedentary subjects. It is necessary to mention that the mean QT interval was normalized by corrective formulas and only two corrected QT (QTc) were significant with a variation of up to 59 milliseconds (350 ± 33.2 *vs.* 409 ± 47.8 milliseconds, so these QT interval data should be treated with caution [12]. The risk of atherosclerosis was also increased, as evidenced by the significant increase in coronary plaques in doped individuals. Furthermore, in the same study, 3% of long-term users had an history of heart attack, but none of the non-users [4]. This risk is also marked by decreased endothelial functions such as blood flow-dependent vasodilation [15]. Noteworthy, changes in blood pressure related to platelet concentration and HDL cholesterol are both markers of atherothrombosis risk [15] (Table 1).

Anthropomorphic effects

Four publications addressed anthropomorphic effects, with a total of 274 subjects, 122 doped and 130 non-doped [4,13,15,16]. The non-doped subjects were represented by a group of 110 non-doped athletes and 20 sedentary subjects not using anabolic agents.

One of the primary goals of consumers of anabolic agents is to increase their muscle mass leading to anthropomorphic changes. Among these modifications, there is a significant difference between body surface area and Body Mass Index (BMI) of doped and non-doped subjects. Indeed, these two parameters were increased in athletes using anabolic agents [4,13]. This would be related to the body mass of doped subjects higher than that of non-doped subjects, observed in the majority of studies [13,15].

In addition, one study showed a significant decrease in body fat, which can be compared with the increase in lean mass index in doped subjects. There was also an increase in the average lean mass and the average body cell mass in this same category of subjects [16] (Table 2)

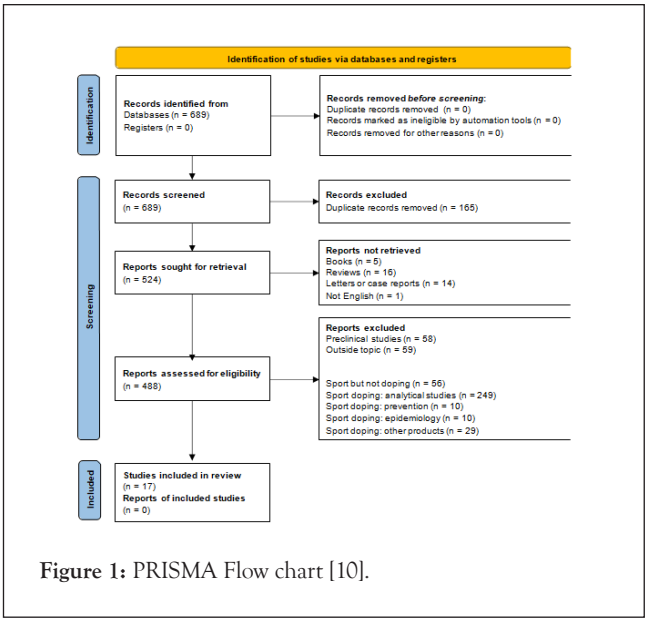

Figure 1: PRISMA Flow chart [10].

Table 1: Cardiovascular effects.

		Djordjević et al. [13]	Severo et al. [15]	Baggish et al. [4]	D'Andrea et al. [12]	Jessen et al. [14]	Börjesson et al. [11]
Number of subjects	Doped	10 strength athletes	10	86	35	6	8
	Non-Doped	12 endurance athletes	12	54	30	0	0
	Controls	AAS-free sedentary controls=20	0	0	Age and sex matched sedentary=40	0	0
Doping detection		Non users: All negative during and out of competition	NC	Test	LH and FSH levels	NC	Self-reported and confirmed by analysis
Dosage/ duration		combination of oral and injectable for at least 2 years (up to 5 years)	At least one year	Cumulative lifetime AAS dose (g): 366 (166-608)	Number of weeks per year: 31.3 ± 6.4. Weekly AAS dosage 525.4 ± 90.7 mg.	80 µg oral clenbuterol	7 weeks-2 years (mean: 58 weeks)
Blood pressure (mmHg) (mean ± SD)	Doped	Systolic: 133 ± 23 mmHg; P=0.085 Diastolic: 88 ± 14.2 mmHg P< 0.001	Systolic: 155 ± 27 mmHg; P=0.001 Diastolic: 93 ± 16 mmHg. P=0.005	Systolic: 118 ± 11 mmHg Diastolic: 76 ± 9 mmHg	Systolic: 138.8 ± 8.5 mmHg; p<0.01 (*vs.* controls) Diastolic: 85.3 ± 5.5 mmHg	Systolic : before ingestion: 115 ± 10; after 140min: 120 ± 9; p=0.068 Diastolic : before: 63 ± 5; after 140 min: 61 ± 8; p=0.472	
	Non-Doped	Systolic: 118 ± 12 mmHg Diastolic: 71 ± 8.4 mmHg	Systolic: 119 ± 12 mmHg Diastolic: 77 ± 10 mmHg	Systolic: 115 ± 10 mmHg Diastolic: 72 ± 9 mmHg	Systolic: 128.4 ± 7.3 mmHg Diastolic: 81.3 ± 4.7 mmHg		
	Contrôles	Systolic:124 ± 11 mmHg Diastolic: 74 ± 5.6 mmHg			Systolic: 124.8 ± 5.5 mmHg Diastolic: 84.5 ± 7.2 mmHg		
Heart rate (bpm)	Doped	77.5 ± 15.9; p<0.001		65 ± 5; p=0.008	68.4 ± 8.8; p<0.01: users versus controls	Systolic: before ingestion: 51 ± 9; after 140 min: 71 ± 17 Diastolic : before: 63 ± 5; after 140 min: 61 ± 8; p=0.472	
	Non-Doped	55.8 ± 7.8		62 ± 6	67.4 ± 7.7		
	Controls	75.3 ± 10.8			77.3 ± 4.4		
Tachycardia	Doped					2 cases	2 cases
QT interval	Doped	348 ± 42.3 ms; p<0.05					
	Non-Doped	400 ± 34.2 ms					
	Controls	358 ± 18.8 ms					
LV Ejection Fraction (%)	Doped	All subjects had preserved left ventricular systolic function (LV ejection fraction>0.55)		52 ± 11 p<0.001; 71% of users showed LVEFs falling	56.8 ± 5.4		
	Non-Doped			63 ± 8	61.6 ± 5.1		
	Controls				60.8 ± 4.1		

LV mass	Doped	217.4 ± 47.3 g; p<0.001		245 ± 62 g; p<0.001	
	Non-Doped	244.8 ± 58.9 g; p<0.001		192 ± 40 g	
	Controls	156.4 ± 19.6 g; p <0.001			
LV mass index	Doped	97.3 ± 20 g/m^2; p<0.001		111 ± 61 g/m^2; p<0.001	69.9 ± 8.4 g/m^2; p<0.001: users *vs.* controls
	Non-Doped	113.5 ± 28.2 g/m^2		89 ± 18 g/m^2	63.4 ± 8.9g/m^2 non-users *vs.* controls
	Controls	80.1 ± 11.9 g/m^2			48.4 ± 5.4g/m^2
LV stroke volume	Doped				41.5 ± 2.2 ml/m^2; p<0.001: users *vs.* controls
	Non-Doped				41.5 ± 2.7 ml/m^2
	Controls				35.2 ± 1.7 ml/m^2
Interventricular septum thickness	Doped	10.7 ± 2.1 mm; p=0.151		1.2 ± 0.2 cm; p<0.001	6.4 ± 1.7 mm/m^2 ; p<0.001: users *vs.* controls
	Non-Doped	10.7 ± 1.7 mm		1.1 ± 0.1 cm ; p<0.001	5.7 ± 1.2 mm/m^2; p<0.01: non-users vs. controls
	Controls	9.8 ± 0.7 mm			4.7 ± 0.7 mm/m^2
Posterior wall thickness	Doped	10.3 ± 2.1 mm; p=0.006		1.2 ± 0.2 cm ; p=0.003	5.9 ± 1.6 mm/m^2 ; <0.001: users *vs.* controls
	Non-Doped	9.9 ± 1.4 mm		1.1 ± 0.2 cm	5.15 ± 1.0 mm/m^2
	Controls	8.6 ± 1.1 mm			4.2 ± 1.2 mm/m^2
Flow-mediated dilatation	Doped		2.4 ± 1.5 %; p=0.032		
	Non-Doped		6.7 ± 1.5 %		
Endothelium-independant dilatation	Doped		11.9 ± 1.0 %; p=0.29		
	Non-Doped		9.2 ± 1.5 %		
Left Atrial (LA) diameter	Doped			3.6 ± 0.5 cm; p=0.42	35.9 ± 3.5mm ; p<0.01: users *vs.* controls and non-users
	Non-Doped			3.5 ± 0.5 cm	32.5 ± 3.4 mm
	Controls				31.4 ± 3.4 mm
LA Volume index	Doped				31.9 ± 5.3 ml/m^2; p<0.001: users *vs.* controls and non-users
	Non-Doped				27.3 ± 2.1 ml/m^2
	Controls				25.4 ± 1.8 ml/m^2
LA active empting fraction	Doped				37.9 ± 3.2 % ; p<0.01: users *vs.* controls and non-users
	Non-Doped				41.3 ± 3.7 %
	Controls				40.2 ± 4.2%

LA lateral strain	Doped	33.9 ± 6.4 %. p<0.001: users *vs.* controls and non-users
	Non-Doped	50.4 ± 4.9 %
	Controls	52.3 ± 5.8 %
Longitudinal 4-chamber strain	Doped	-16 ± 4; p <0.001
	Non-Doped	-20 ± 3
Coronary plaque volume	Doped	3 (0-174) mm^3; p =0.012
	Non-Doped	0 (0-69) mm^3
Degree of stenosis for most severe stenosis*	Doped	0.5 (0-1); p=0.052
	Non-Doped	0.5 (0-1)
Number of diseased coronary artery segments**	Doped	0.5 (0-2); p=0.059
	Non-Doped	1 (0-1)
Maximal HR during physical effort	Doped	172.9 ± 8.4 bpm
	Non-Doped	173.4 ± 9.8 bpm
	Controls	178.5 ± 10.4 bpm
Maximal Blood pressure during physical effort	Doped	180.4 ± 14.8 mmHg; p<0.01: users *vs.* controls and non-users
	Non-Doped	166.8 ± 10.8 mmHg
	Controls	165.8 ± 15.4 mmHg
Rate pressure product during physical effort	Doped	0.59 ± 0.6 bpm × mmHg × 10 ^ 3
	Non-Doped	0.54 ± 3.4 bpm × mmHg × 10 ^ 3
	Controls	0.53 ± 0.2 bpm × mmHg × 10 ^ 3
Maximal workload achieved	Doped	160.2 ± 24.7 Watts
	Non-Doped	200.7 ± 33.5 Watts; p<0.001: users *vs.* controls and non-users
	Controls	150.5 ± 32.4 Watts
Peak VO2 during physical effort	Doped	49.3 ± 8.7 ml/kg/min
	Non-Doped	55.9 ± 7.4 ml/kg/min
	Controls	44.9 ± 6.4 ml/kg/min

Note: *p<0.05; **significant difference between Pla and DHEA/(p<0.01, significant difference between Pla and DHEA)

Table 2: Anthropomorphic effects.

			Publications			
			Djordjević et al. [13]	**Severo et al. [15]**	**Baggish et al. [4]**	**Meinhardt et al. [16]**
Parameters (mean ± SD)	Number of subjects	Doped	10 strength athletes	10	86	16
		Non-doped	12 endurance athletes	12	54	32
		Controls	AAS-free sedentary controls=20	0	0	0
	Doping detection		Non-users: all negative during and out of competition	NC	Test	-
	Dose/duration		combination of oral and injectable for at least 2 years (up to 5 years)	At least one year	Cumulative lifetime AAS dose (g): 366 (166-608)	250 mg/wk for 5 weeks
	Height (cm)	Doped	181 ± 4.6; p<0.001	(175 ± 7); p= 0.26	180 (170-180); p=0.16	180 ± 8
		Non-doped	190 ± 10.8	178 ± 6	180 (170-180)	185 ± 5
		Controls	182 ± 9.1			
	Body weight (kg)	Doped	100.4 ± 18.6; p<0.001	93 ± 14; p=0.015		83.3 ± 18.5
		Non-doped	89.6 ± 14.9	77 ± 8		90.5 ± 12.2
		Controls	78.6 ± 8.3			
	Body surface area (m^2)	Doped	2.2 ± 0.23; p=0.001		2.2 (2.1-2.3); p=19	
		Non-doped	2.2 ± 0.24		2.2 (2.0-2.3)	
		Controls	1.9 ± 0.12			
	Body mass index (kg/m^2)	Doped			31 (29-33); p<0.001	25.4 ± 3.7
		Non-doped			29 (27-31)	26.1 ± 3.1
	Fat-free mass index	Doped			26 (24–28); p<0.001	
		Non-doped			23 (21-25)	
	Mean fat mass (kg)	Doped				16.2 ± 9.1
		Non-doped				18.8 ± 7.99
	Mean lean body mass (kg)	Doped				63.1 ± 10.2
		Non-doped				67.6 ± 7.1
	Mean body cell mass (kg)	Doped				41.8 ± 7.0
		Non-doped				44.4 ± 5.3

Muscular effects

Muscular effects were described in 3 publications [14,16], with 71 subjects including 32 doped subjects and 39 clean subjects. Muscle effects reported by doped subjects included muscle pain [16,17]. One study reported a case of muscle tremor in six clenbuterol-doped subjects [14].

According Yu, et al. ratios of protein muscle concentration levels in doped athletes, between 5 and 15 years of consumption, versus non-doped ones for CMTK2 (metabolism) and ACTAC1 (mobility and contractility) were increased, but decreased for HSPB1 (cell protection), PGM-1 (metabolism) and myoglobin (transport and storage), suggesting alteration of muscle metabolism and contractility injury. A study in 6 doped subjects using oral clenbuterol (80 µg) showed increases of phosphorylation of mTORSer 2448 (+121%, p=0.004), of PKA-dependent substrates (+35%, p=0.006) and of the resting energy expenditure (+21%, p<0.01) [14].

Endocrine effects

Ten publications addressed the effects of anabolic agents on blood concentrations of hormones [11,14-21]. These studies included a total of 535 subjects including 181 doped subjects, 287 non-doped subjects, 46 sedentary subjects and 21 subjects participating in a crossover study with a doped and a non-doped period.

The administration of testosterone and of synthetic derivatives of testosterone leaded to significant changes in the blood concentrations of sexual hormones. Among these changes, there was significant increases in the concentrations of testosterone, estradiol and estrone [15,18,19,22], but also luteinizing hormone, follicle stimulating hormone, and inhibin B [15,18,19,21]. The use of anabolic agents impacted the hypothalamic-pituitary-gonadal axis through changes in luteinizing hormone, follicle stimulating hormone, and inhibin B variations [19]. Libido alteration, gynecomastia, testicular atrophy [17,20], clitoral hypertrophy, voice changes and menstrual disorders [11] were described (Table 3).

Table 3: Endocrine effects.

		Publications									
		Meinhardt et al. [16]	**Severo et al. [15]**	**Razavi et al. [21]**	**Hengevoss et al. [20]**	**Börjesson et al. [11]**	**Bordin et al. [17]**	**Collomp et al. [18]**	**D'andrea et al. [19]**	**Jessen et al. [14]**	**Solheim et al. [22]**
Number of subjects	Doped	16	10	72	5	8	20	10 men+11 women	35	6	9
	Non-doped	32	12	178	5	0	20		30	0	10
	Controls	0	0	0	6	0	0	0	age and sex matched sedentary=0	0	0
Doping detection		-	NC	Self-declaration	NC	Self-reporting and confirmed by analysis	Self-declaration	-	LH and FSH levels	NC	-
Doses/Duration		250 mg/week for 5 weeks	At least one year	34.7%<six months, 16.7% to 12 months, 11.1% to 24 months and 37.5% to 12 yrs.	NC	7 weeks-2 yrs. (average: 58 weeks)	1g/week for one year	DHEA 100 mg/day	31.3 ± 6.4 wk per yr. 525.4 ± 90.7 mg per wk.	80 µg oral clenbuterol	Testosterone esters:250 mg
Testosterone	Doped	Change in testosterone group-change in placebo group (95% CI) : 397.69 (155.62 to 737.75) ng/dL; p<0.005	80%>54.69 pg/ml (median (interquartile range)); p=0.003		Increase		649.45 (340.9) ng/dl; p=0.25	Men: basal=6.61 ± 0.40 ng/ml, at mid-treatment : 7.48 ± 0.37 ng/ml*, at end of treatment=7.26 ± 0.29 ng/ml*/ Women: basal=0.38 ± 0.02 ng/ml ++, at mid-treatment=3.41 ± 0.51 ng/ml**++, at end of treatment=3.33 ± 0.46 ng/ml**++			Serum testosterone increased (p<0.001) from pre-administration (19.8 ± 7.6 nmol/L) to post-administration (81.4 ± 21.9 nmol/L) in the treated group and that the post- administration level was higher (p<0.001) in the treated group (81.4 ± 21.9 nmol/L) compared with in the control group (30.0 ± 5.4 nmol/L)
	Non-doped		0%>54.69 pg/ml		No change		545.2 (156.0) ng/dl	Men: basal=5.76 ± 0.17 ng/ml, at mid ttt=5.92 ± 0.29 ng/ml, at end ttt=6.04 ± 0.33 ng/ml/Women: basal=0.40 ± 0.02ng/ml ++, at mid ttt=0.42 ± 0.03 ng/ml ++, at end ttt= 0.40 ± 0.02 ng/ml ++			

Estradiol	Doped	70%>42.6 pg/ml (median (interquartile range)); p=0.04				Increase in the TE group (99.0 ± 54.2 pmol/L) compared with pre-administration (63.5 ± 24.2 pmol/L, p=0.04) and compared with the control group (58.0 ± 23.2 pmol/L, p=0.05)
	Non-doped	8.3%>42.6 pg/ml				
FSH	Doped	100%<0.7 mIU/ml (median (interquartile range)); p=0.0001			Decrease	No effect of time
	Non-doped	0%<0.7 mIU/ml			No change	
LH	Doped		Decrease		Decrease	Decrease (p=0.02) from pre-(3.8 ± 1.7 IU/L) to post-administration (1.6 ± 0.7 IU/L) in doped group, Decrease (p<0.001) after administration in doped group (1.6 ± 0.7 IU/L) compared to undoped group
	Non-doped		No change		No changes	
Estrone (pg/ml)	Doped			Men: basal=77.1 ± 7.1 ng/ml, mid=160.6 ± 20.8 ng/ml**, late =174.1 ± 9.3ng/ml**/Women: basal=45.7 ± 2.4 ng/ml, mid =197.9 ± 15.4 ng/ml**, late=253.3 ± 26.6ng/ml **+		

	Non-doped			Men: basal=62.6 ± 5.8 ng/ml, mid=66.7 ± 4.0 ng/ml, end=71.6 ± 5.8 ng/ml Women: basal=53.4 ± 2.8 ng/ml, mid =61.9 ± 8.8 ng/ml, end=62.8 ± 9.0 ng/ml	
Insulin	Doped				After ingestion: +105%; p=0.009
	Non-doped				
Inhibin B	Doped		Decrease		
	Non-doped		No changes		
Clitoral hypertrophy	Doped		6 cases		
Change of voice	Doped		5 cases		
Menstrual disorders	Doped		5 cases		
Impaired libido	Doped	9.70%	35%		
Gynecosmastia	Doped		15%		
Testicular atrophy	Doped		27.50%		

Note: *p<0.05; **significant difference between Pla and DHEA/(p<0.01, significant difference between Pla and DHEA); +p<0.05, significant difference between genders; ++p<0.01, significant difference.

One study also reported an increase in insulin (+105%; p=0.009) after administration of anabolic agents [14].

Biochemical effects

Six publications addressed the biochemical effects, with a total of 249 subjects including 122 doped subjects, 86 non-doped subjects and 41 subjects participating in a crossover study with a doped and a non-doped period [4,14,15,17,18,23].

A decrease in HDL-cholesterol concentration was observed in the doped subjects. In a study comparing 86 doped and 54 non-doped subjects with a consumption of about 366 g AA (166-608 g) during approximately 7.4 years (4.0-11.6 years), higher prevalence of dyslipidemia was reported in the groups using anabolic agents in comparison to non-users [4]. Finally, a significant correlation between decreased endothelial function, reflected by the flow-mediated dilation, and HDL-cholesterol concentration was found (r=0.49, p=0.03) [15].

Clenbuterol use by 6 subjects (80 µg per os) increased the blood concentrations of glucose by 25% (p<0.001), lactate by 87% (p=0.004) and fatty acids by 129% (p=0.001) [14].

The use of 100 mg DHEA during 28 days did not significantly alter the concentrations of adipokines (leptin, adiponectin and resistin) [23] or of cholesterol, glucose, and triglycerides [18,23].

Also, uric acid, urea and creatinine concentrations of a group of 20 subjects doped with 1 g per week for one year were significantly increased from the clean group. In addition, there was a correlation between the increase of these markers and the hematocrit concentrations [17]. Urea and creatinine retention could show renal dysfunction caused by the intake of these anabolic agents [24] (Table 4).

Table 4: Biochemical effects.

		Publications					
		Severo et al. [15]	Baggish et al. [4]	Bordin et al. [17]	Collomp et al. [18]	Gravisse et al. [24]	Jessen et al. [14]
Number of subjects	Doped	10	86	20	10 men+11 women	20	6
	Non-doped	12	54	20			0
	Controls	0	0	0	0	0	0
Doping detection		NC	test	Self-declaration	-	-	NC
Doses/ duration		At least one year	Cumulative lifetime AAS dose (g):366 (166-608)	1g/week for one year	DHEA 100 mg/day	100 mg DHEA for 28 days	80 µg oral clenbuterol
Total cholesterol	Doped	151 (35) mg/dl; p=0.78			Men: basal=1.54 ± 0.11 g/L; mid-treatment=1.43 ± 0.10; end of treatment=1.47 ± 0.10/Women: (p<0.05, significant difference between Men and Women) basal=1.70 ± 0.09; mid-treatment=1.79 ± 0.11; end of treatment=1.70 ± 0.08		
	Non-doped	154 (25) mg/dl			Men: basal=1.47 ± 0.1 g/L; mid-treatment=1.45 ± 0.13; end of treatment=1.46 ± 0.11/Women: basal=1.76 ± 0.13; mid-treatment=1.79 ± 0.11; end of treatment=1.74 ± 0.10		
Triglycerides	Doped	100 (62) mg/dl; p=0.83			Men: basal=0.65 ± 0.08 g/L; mid-treatment=0.77 ± 0.12; end of treatment=0.79 ± 0.14/Women: basal=0.78 ± 0.11; mid-treatment=0.66 ± 0.04; end of treatment=0.65 ± 0.11		
	Non-doped	96(37) mg/dl			Men: basal=0.59 ± 0.07 g/L; mid-treatment=0.76 ± 0.13; end of treatment=0.69 ± 0.10/Women: basal=0.89 ± 0.12; mid-treatment=0.83 ± 0.11; end of treatment=0.79 ± 0.10		

LDL Cholesterol	Doped	109(28) mg/dl; p=0.17			Men: basal=0.87 ± 0.09 g/L; mid-treatment=0.81 ± 0.08; end of treatment=0.82 ± 0.10/Women: basal=1.02 ± 0.10; mid-treatment=1.15 ± 0.12; end of treatment=1.05 ± 0.08	
	Non-doped	93 (24) mg/dl			Men: basal=0.85 ± 0.10 g/L; mid-treatment=0.84 ± 0.10; end of treatment=0.83 ± 0.09/Women: basal=1.06 ± 0.12; mid-treatment=1.11 ± 0.11; end of treatment=1.08 ± 0.09	
HDL Cholesterol	Doped	21 (6) mg/dl; p=0.0001			Men: basal=0.53 ± 0.03 g/L; mid-treatment=0.48 ± 0.03; end of treatment=0.49 ± 0.03/Women: basal=0.52 ± 0.02; mid-treatment=0.51 ± 0.02; end of treatment=0.50 ± 0.02	
	Non-doped	42 (37) mg/dl			Men: basal=0.50 ± 0.03 g/L; mid-treatment=0.46 ± 0.04; end of treatment=0.49 ± 0.03/Women: basal=0.52 ± 0.03; mid-treatment=0.52 ± 0.03; end of treatment=0.50 ± 0.02	
Dyslipidemia	Doped		Higher prevalence of dyslipidemia			
	Non-doped					
Glucose	Doped				Men: basal=0.83 ± 0.03 g/L; mid-treatment=0.86 ± 0.03; end of treatment=0.83 ± 0.03/Women: basal=0.81 ± 0.02; mid-treatment=0.76 ± 0.02; end of treatment=0.85 ± 0.02	After ingestion: +25%; p<0.001
	Non-doped				Men: basal=0.88 ± 0.03 g/L; mid-treatment=0.82 ± 0.03; end of treatment=0.82 ± 0.02/Women: basal=0.79 ± 0.03; mid-treatment=0.81 ± 0.03; end of treatment=0.82 ± 0.03	
Lactate	Doped					After ingestion: +87%; p=0.004
Fatty acids	Doped				After ingestion: +129%; P=0.001	
Adipokines	Doped					No changes
Uric acid	Doped		5.9 (0.8) mg/dl; p<0.007			
	Non-doped		5.1 (0.8) mg/dl; ref values: 4.5-8.1			
Urea	Doped		42.8 (6.4) mg/dl; p<0.0001			
	Non-doped		34.6 (4.7) mg/dl; ref values: 17-42			
Creatinine	Doped		1.7 (0.2) mg/dl; p<0.0001			
	Non-doped		1.1 (0.1) mg/dl; ref values: 0.7-1.3			

Hematological effects

Three publications described hematological effects, with a total of 61 subjects including 39 doped and 22 non-doped subjects [15,17,22].

A greater number of abnormal blood profiles in doped individuals was shown by Soldheim, et al. [22] with a significant increase in platelet count, but low variations in hematocrit, hemoglobin concentration and red cells indices (mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration) [15,17]. No significant alteration was demonstrated for white blood cell counts and fibrinogen concentrations [15,25,26].

Hepatic effects

Two publications addressed the effects of anabolic agents on hepatic functions [18,27]. These studies included a total of 166 subjects, including 145 doped subjects and 21 subjects participating in a crossover study with a doped and a non-doped period.

A study carried out with DHEA did not show any significant modification of transaminase (aspartate transaminase and alanine transaminase) concentrations following a 100 mg/day DHEA use [18]. A second study was conducted with doped subjects consuming cocaine. It only showed a significant increase in gamma-glutamyl transferase in cocaine users (39.4 ± 44.6 UI/L *vs.* 27.2 ± 13.5 UI/L, p=0.02) [27].

Behavioral effects

Three publications addressed cognitive and behavioral effects, with a total of 298 subjects including 100 doped, 198 non-doped [11,17,20]. One study (n=20 doped and n=20 non-doped) showed that 12.5% of subjects reports anxiety and 15% reports depression after one year of consumption of 1 gram anabolic agent per week [17]. Another study showed increase of depression cases in 6.9% of 72 doped subjects with consumption duration between less than 6 months to 12 years.

Anabolic agents act on the behavior of consumers and it was mainly observed an increase in the aggressiveness [11,20], as well as an increase in cases of depression [11,17]. Borjesson, et al. noted memory impairment (1/8 cases), mood changes (3/8 cases) and depression (4/8 cases) when using anabolic agents [11].

DISCUSSION

The strategy used in this bibliographic research allowed us to have an up-to-date vision of the different biological and clinical effects notified in the scientific literature, caused by the use of anabolic agents, which clearly shows that athletes expose themselves to several risks.

The effects of anabolic agents on the muscles are important to remember, effects that some athletes want for aesthetic purposes, but alter the muscle protein profile and can lead to muscle damage [28]. It should be remembered that training increase the effects of androgens on muscle, do not improve muscular endurance or the contractile quality of the muscle. The increase of muscle mass is associated with hypertrophy of muscle fibers. Endocrine effects, renal dysfunction, heart hypertrophy, increase of BMI, blood pressure increase and atherosclerosis are mainly reported. The endocrine adverse effects primarily relate to gonadal dysfunction and dose-dependent suppression of hypothalamic and pituitary gonadotropins [29]. Indeed, the consumers have more risks to have adverse effects as dystrophy of sexual organs, gynecomastia by peripheral aromatization of androgens to estradiol, but also to liver as hepatocellular adenoma. A hypothesis has been put forward concerning the risk of liver disorders following the consumption of anabolic agents, which introduces the role of the polymorphism of the gene coding for UGT2B17 linked to a deletion type mutation [30]. Indeed, UGT2B17 is an enzyme that catalyzes glucurono-conjugation, involved in the main pathway of elimination of anabolic agents, so individuals of UGT2B17 may increase the risk to develop renal disorders [30].

Furthermore, the use of anabolic agents has important consequences on the behavior of the consumers. It is mainly reported that it increases aggressiveness, but also behavioral disorders such as depression, anxiety or addiction. Maybe it is due to their easy crossing of the blood-brain barrier and binding to brain androgen receptors when using anabolic androgenic steroids [31].

Nevertheless, not all the known effects were found in this bibliographic search, because they were not all detailed in the selected publications. Indeed, it is reported in a review not listed here, that anabolic agents are also responsible for fertility problems with a significant decrease in the fertility index [32]. In addition, the concomitant use of substances such as alcohol, tobacco or illicit drugs may increase the effects of anabolic agents and may lead to changes in the blood lipid profiles of these users, although the mechanisms of action remain to be determined [27].

CONCLUSION

This study reminds us that non-therapeutic use of anabolic agents made by professional and amateur athletes is not without important risk. According to the different chapters detailed in this study, the use of anabolic agents involves many health risks for the athlete, despite the sanctions incurred in case of control by WADA. Indeed, their use leads to many pathophysiological changes, some of these changes are searched by the consumer, but it is also exposed to the appearance of adverse effects, including the effects on the cardiac system, behavior, or changes in biochemical and hematological profiles. The consumer may be subject to other dysfunctions such as liver and kidney dysfunctions. It is for these reasons that the WADA prohibits and controls the use of these substances, particularly through the athlete's biological passport.

It is therefore important to enhance the scientific literature on the effects of these anabolic agents to better adapt the prohibition list maintained by WADA, but also to implement prevention among athletes who are not all aware of the impacts of using sports doping agents such as anabolic agents.

REFERENCES

1. World Anti-Doping Agency. World Anti-Doping Program-2019 Anti-Doping Rule Violations (ADRVs) Report. 2021
2. Gleaves J, Petróczi A, Folkerts D, De Hon O, Macedo E, Saugy M, et al. Doping prevalence in competitive sport: evidence synthesis with "best practice" recommendations and reporting guidelines from the WADA Working Group on Doping Prevalence. Sports Med. 2021;51(9):1909-1934.

3. World Anti-Doping Agency. 2020 Anti-doping testing figures. 2021

4. Baggish AL, Weiner RB, Kanayama G, Hudson JI, Lu MT, Hoffmann U, et al. Cardiovascular toxicity of illicit anabolic-androgenic steroid use. Circulation. 2017;135(21):1991-2002.

5. Steroids NI. Other Appearance and Performance Enhancing Drugs (APEDs). National Institute on Drug Abuse (NIDA). 2018.

6. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. Sports Med. 2004;34(8):513-554.

7. World Anti‐Doping Agency. 2017 anti‐doping testing figures.

8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. J Clin Epidemiol. 2020;10(1):1-1.

9. World Anti-Doping Agency. World Anti-Doping Code–International Standard Prohibited List. 2021.

10. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Ann Intern Med. 2009;151(4):264-269.

11. Börjesson A, Gårevik N, Dahl ML, Rane A, Ekström L. Recruitment to doping and help-seeking behavior of eight female AAS users. Subst Abuse Treat Prev Policy. 2016;11(1):1-6.

12. D'Andrea A, Radmilovic J, Caselli S, Carbone A, Scarafile R, Sperlongano S, et al. Left atrial myocardial dysfunction after chronic abuse of anabolic androgenic steroids: A speckle tracking echocardiography analysis. Int J Cardiovasc Imaging. 2018;34(10):1549-1559.

13. ‌orlevi‌ V, Stankovi‌ I, Stipac VA, Putnikovi‌ B, Neškovi‌ AN. Short QT interval is unreliable marker of anabolic androgenic steroid abuse in competitive athletes. Srp Arh Celok Lek. 2012;140(11-12):711-716.

14. Jessen S, Solheim SA, Jacobson GA, Eibye K, Bangsbo J, Nordsborg NB, et al. Beta2‐adrenergic agonist clenbuterol increases energy expenditure and fat oxidation, and induces mTOR phosphorylation in skeletal muscle of young healthy men. Drug Test Anal. 2020;12(5):610-618.

15. Severo CB, Ribeiro JP, Umpierre D, Silveira AD, Padilha MC, De Aquino Neto FR, et al. Increased atherothrombotic markers and endothelial dysfunction in steroid users. Eur J prev Cardiol. 2013;20(2):195-201.

16. Meinhardt U, Nelson AE, Hansen JL, Birzniece V, Clifford D, Leung KC, et al. The effects of growth hormone on body composition and physical performance in recreational athletes: A randomized trial. Ann Intern Med. 2010;152(9):568-577.

17. Bordin DM, Bettim BB, Perdona GC, de Campos EG, Martinis BS. Understanding alterations on blood and biochemical parameters in athletes that use dietary supplements, steroids and illicit drugs. Toxicology. 2017;376:75-82.

18. Collomp K, Buisson C, Gravisse N, Belgherbi S, Labsy Z, Do MC, et al. Effects of short-term DHEA intake on hormonal responses in young recreationally trained athletes: Modulation by gender. Endocrine. 2018;59(3):538-46.

19. Hengevoss J, Piechotta M, Müller D, Hanft F, Parr MK, Schänzer W, et al. Combined effects of androgen anabolic steroids and physical activity on the hypothalamic–pituitary–gonadal axis. J steroid Biochem Mol Biol. 2015;150:86-96.

20. Razavi Z, Moeini B, Shafiei Y, Bazmamoun H. Prevalence of anabolic steroid use and associated factors among body-builders in Hamadan, Western Province of Iran. J Res Health Sci. 2014;14(2):163-166.

21. Solheim SA, Mørkeberg J, Juul A, Freiesleben SY, Upners EN, Dehnes Y, et al. An intramuscular injection of mixed testosterone esters does not acutely enhance strength and power in recreationally active young men. Front Physiol. 2020;11:563620.

22. Solheim SA, Mørkeberg J, Dehnes Y, Hullstein I, Juul A, Upners EN, et al. Changes in blood parameters after intramuscular testosterone ester injections–Implications for anti‐doping. Drug Test Anal. 2020;12(8):1019-1030.

23. Gravisse N, Vibarel-Rebot N, Buisson C, Le Tiec C, Castanier C, Gagey O, et al. Short-term DHEA administration in recreational athletes: Impact on food intake, segmental body composition and adipokines. J Sports Med Phys Fitness. 2018;59(5):808-816.

24. Tidmas V, Brazier J, Hawkins J, Forbes SC, Bottoms L, Farrington K. Nutritional and non-nutritional strategies in bodybuilding: impact on kidney function. Int J Environ Res Public Health. 2022;19(7):4288.

25. Yu JG, Isaksson A, Rova A, Tegner Y, Eriksson A, Malm C. Potential effects of long-term abuse of anabolic androgen steroids on human skeletal muscle. J Sports Med Phys Fitness. 2020;60(7):1040-1048.

26. Yoon MS. mTOR as a key regulator in maintaining skeletal muscle mass. Front physiol. 2017;8:788.

27. Schwingel PA, Zoppi CC, Cotrim HP. The influence of concomitant use of alcohol, tobacco, cocaine, and anabolic steroids on lipid profiles of Brazilian recreational bodybuilders. Subst Use Misuse. 2014;49(9):1115-1125.

28. Mullen C, Whalley BJ, Schifano F, Baker JS. Anabolic androgenic steroid abuse in the United Kingdom: An update. Br J Pharmacol. 2020;177(10):2180-2198.

29. McBride JA, Coward RM. Recovery of spermatogenesis following testosterone replacement therapy or anabolic-androgenic steroid use. Asian J Androl. 2016;18(3):373.

30. Deshmukh N, Petróczi A, Barker J, Székely AD, Hussain I, Naughton DP. Potentially harmful advantage to athletes: a putative connection between UGT2B17 gene deletion polymorphism and renal disorders with prolonged use of anabolic androgenic steroids. Subst Abuse Treat Prev Policy. 2010;5(1):1-7.

31. Westberg L, Eriksson E. Sex steroid–related candidate genes in psychiatric disorders. J Psychiatry Neurosci. 2008;33(4):319-330.

32. Bonetti A, Tirelli F, Catapano A, Dazzi D, Dei Cas A, Solito F, et al. Side effects of anabolic androgenic steroids abuse. Int J sports med. 2008;29(08):679-687.