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Cardiovascular Effects of Anabolic-Androgenic Steroids in Dietary Supplements

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ABSTRACT

Dietary supplements are regularly consumed by more than 70 % of the US population, as well as by competitive and non-competitive athletes. Anabolic-androgenic steroids (AAS) are frequently found in dietary supplements, and have the potential for multi-organ toxicity, including significant effects on the cardiovascular system. Cardiovascular toxicities of AAS include coronary artery effects, e.g. spasm, thrombosis and plaque rupture, leading to acute coronary syndromes and myocardial infarctions, as well as direct myocardial toxicity, causing left ventricular hypertrophy, fibrosis and dysfunction. Coronary and myocardial effects converge towards a common final pathway, causing heart failure, life-threatening arrhythmias and sudden cardiac death. The unregulated nature of AAS in dietary supplements has many ramifications. Both coaches and athletes should be aware that testing positive for a prohibited substance (including AAS) constitutes a potential doping violation. We advocate for improved education of the public at large regarding the potential for AAS to be included in dietary supplements, as well as its regulation by the appropriate authorities.

Keywords: cardiovascular, anabolic steroids, dietary supplements, myocardial infarct, stroke, sudden cardiac death

Conflict of interests: the authors declare no conflict of interest.

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Sports Medicine: research and practice

Сердечно-сосудистые эффекты анаболических андрогенных стероидов в пищевых добавках

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АННОТАЦИЯ

Пищевые добавки регулярно потребляются более чем 70 % населения США, а также участвующими в соревнованиях и не участвующими в соревнованиях спортсменами. Анаболические и андрогенные стероиды (ААС) часто встречаются в пищевых добавках и обладают потенциальной полиорганной токсичностью, в том числе значительным воздействием на сердечно-сосудистую систему. Сердечно-сосудистая токсичность ААС влияет на коронарные артерии, вызывая спазм, тромбоз и разрыв бляшки, приводящие к острым коронарным синдромам и инфарктам миокарда, а также прямую миокардиальную токсичность, вызывающую гипертрофию, фиброз и дисфункцию левого желудочка. Коронарные и миокардиальные эффекты в итоге вызывают сердечную недостаточность, опасные для жизни аритмии и внезапную сердечную смерть. Нерегулируемость ААС в пищевых добавках имеет множество последствий. И тренеры, и спортсмены должны знать, что положительный результат теста на запрещенное вещество (включая ААС) представляет собой потенциальное нарушение антидопинговых правил. Мы выступаем за улучшение информирования широкой общественности о возможности включения ААС в пищевые добавки, а также за его регулирование соответствующими органами.

Ключевые слова: сердечно-сосудистая система, анаболические стероиды, пищевые добавки, инфаркт миокарда, инсульт, внезапная сердечная смерть

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1. Introduction

Dietary supplements in various forms are consumed daily by more than 70 % of the US population, including competitive and non-competitive athletes [1, 2]. This has led to an ever-expanding, multi-billion dollar global industry. This phenomenon is underpinned by aggressive marketing techniques in which scientifically unsubstantiated claims are frequently made. Anabolic-androgenic steroids (AAS), which have the potential for serious adverse effects relating to the cardiovascular system, are frequently found in dietary supplements. In this review, we provide an overview of the regulatory aspects of dietary supplements, and subsequently, a summary of the cardiovascular effects of AAS.

2. Regulatory aspects of dietary supplements

The explosive growth of the dietary supplement industry has been facilitated in many countries by acts similar to the US Dietary Supplement Health and Education Act (DSHEA) of 1994 [3]. According to this and similar acts, a dietary supplement is defined as any product intended to supplement the human diet, and is not subject to a strict definition or regulatory scrutiny before market approval. This may include a plethora of compounds, e.g. but not limited to: vitamins, minerals, herbs or other botanical products, amino acids and substances such as enzymes, organ tissue extracts, glandulars, and metabolites [3, 4]. Dietary supplements may be formulated as tablets, capsules, soft gels, gelcaps, liquids or powders. These supplements may also take the form of foodstuffs, e.g. snack bars, in which case labelling can be misleading.

The DSHEA categorizes dietary supplements as "foods", not drugs, and requires that every supplement added to a dietary food supplement, be labelled separately as such.[5] Foods items that are fortified with nutrients e.g. vitamins and minerals to raise nutrient levels, are not considered dietary supplements. The term "nutraceutical" is not defined by US law, but is generally understood to be a purified product derived from a human food source, which is purported to provide extra health benefits beyond the basic nutritional value found in foods. The Food and Drug Administration (FDA) regulates dietary supplements in a very different way than pharmaceuticals. A manufacturer of a pharmaceutical compound is required to document and submit its safety and efficacy data, which regulatory authorities then scrutinize before allowing marketing approval. Manufacturers of dietary supplements are not allowed to claim that the supplement can be used to diagnose, cure, mitigate, treat or prevent any particular disease. However, in the US, statements pertaining to general well-being, bodily function and health are allowed, provided a disclaimer is added to the product label with the following text: "This statement has not been evaluated by the FDA. This product is not intended to diagnose,

treat, cure, or prevent any disease". The burden rests on regulatory authorities to demonstrate that a particular product is harmful before steps can be taken to remove it from the market. In this respect, the FDA logged 776 dietary supplements from 2007 to 2016 as being adulterated with pharmaceutical compounds [6]. These lax dietary supplement regulations have facilitated the bringing to market of potentially harmful substances, to which not only to the general population but also athletes, are exposed [2]. Estimated use in the latter group of individuals varies between 44 % and 100 % [2]. Large quantities of nutrients, commonly found in normal human diets, are consumed without there being much knowledge of possible health risks and the maximum daily safe doses involved [7].

While concentrations of these non-approved substances may be too low to achieve any health or performance-enhancing effects, they may be high enough for athletes to fail a doping test.

Abuse of an ever-expanding armamentarium of chemical entities to boost, even by small margins, their strength and performance is prevalent among professional as well as amateur athletes [8]. In addition to providing an unfair advantage to athletes, significant potential health risks are associated with the abuse of performance-enhancing agents. While a multitude of potential adverse effects exist, those pertaining to the cardiovascular system are the most life-threatening [9]. Substances primarily responsible for adverse cardiovascular effects can be grouped into three major classes i.e. 1) AAS, 2) stimulants and 3) narcotics. "Classic AAS", however, are the most commonly abused, and therefore the proximate cause of the majority of adverse effects in cases of doping.

3. "Classic" AAS

The vast majority of drug doping cases in athletes involve anabolic-androgenic agents. [10]. Studies from 2001 and 2002, based on nutritional supplements purchased in 13 different countries, including the US, suggested that approximately 15 % of nutritional supplements contained undeclared AAS [11]. The steroid category of compounds includes the "classic" AAS, e.g. metandienone, stanozolol, boldenone, oxandrolone and dehydrochloromethyl-testosterone, which have been found in high amounts (> 1mg/g) in certain over-the-counter dietary supplements and vitamin preparations [12]. These AAS were either listed on package labels under alternative names or not disclosed at all. Amounts of steroids identified in supplements were often of such orders that even within the limits of recommended supplement intake, potentially harmful doses of AAS would be ingested [12]. Many athletes and non-athletes, including women, adolescents and children, regularly consume dietary supplements in excess of the recommended, safe daily doses, exposing them to the potential harmful effects of e.g. AAS [12]. Athletes are prone to use supraphysiologic doses of AAS, e.g. testosterone. While the replacement of testosterone in individuals with hypotestosteronaemia is unlikely to have any adverse effects, even physiologic doses may be harmful in those without a deficiency

AAS upregulate and increase the number of androgen receptors, leading to an acceleration of the transcription of deoxyribonucleic acid (DNA) in skeletal muscle [14]. These agents are consumed to increase skeletal muscle mass and strength, while at the same time they reduce adipose tissue [15, 16]. AAS are not selective in their action, and exert effects on multiple organ systems in humans that are in possession of androgen receptors [17]. In men acne, hepatic injury, testicular atrophy, prostatomegaly, decreased spermatogenesis, subfertility, erectile dysfunction and changes in libido may occur [18]. Furthermore, gynecomastia can also develop in some male abusers of steroids. In women using AAS, acne, potentially irreversible masculinization, clitoromegaly, menstrual irregularities and changes in libido may result. Psychiatric effects may be induced in both males and females, e.g. aggression (so-called "roid" rage), psychoses, mood disorders and anxiety disorders. Long-term steroid abuse has also been associated with dependency and a withdrawal syndrome associated with suicidal ideation, an increased incidence of tumors and premature mortality. In adolescents and children, virilization and premature closure of the epiphyseal growth plates, which may result in stunted growth, have been described.

Of particular concern are the effects of AAS on the cardiovascular system, including cholesterol and lipid metabolism, arterial hypertension and procoagulant effects, leading to acute coronary syndromes, myocardial infarctions and strokes. The preponderance of data on the cardiovascular toxicity of AAS originate from case reports, and are not consistent with regard to all adverse effects [14, 17]. This may be a reflection of the lack of systematic data, the heterogeneity of individuals sampled and the fact that many different substances or steroids are often abused in conjunction. A systematic autopsy series of 34 patients, however, confirmed coronary artery disease, left ventricular hypertrophy and myocardial fibrosis to be the most common abnormalities (Figure 1) [17, 19]. Abuse of these agents may lead to increases in arterial blood pressure at rest and during exercise, elevation of low-density lipoprotein (LDL) and lowering of high-density lipoprotein (HDL) levels, causing atherosclerosis [14, 20, 21]. Male recreational weight lifters in the age group 34 – 54, abusing AAS, have been compared to a steroid-free control group, demonstrating increased levels of coronary artery plaque, compared to those in the control group [22]. Plaque rupture, intracoronary thrombus formation and spasm lead to acute coronary syndromes, with or without myocardial infarction [18]. Spasm may be caused by inhibition of the extraneuronal uptake of neuroamines, leading to augmentation of the arterial response to norepinephrine [17]. Coronary artery spasm may also be mediated by a deficiency of nitric oxide (a vasodilator) [14]. A procoagulant state may be induced by AAS, causing or contributing to coronary artery thrombus formation [14]. Thrombin levels are increased, in conjunction with thrombocyte activation, increased levels of factors VIII and IX and enhanced erythropoiesis [14, 23, 24]. AAS increase the platelet production of thromboxane A2, as well

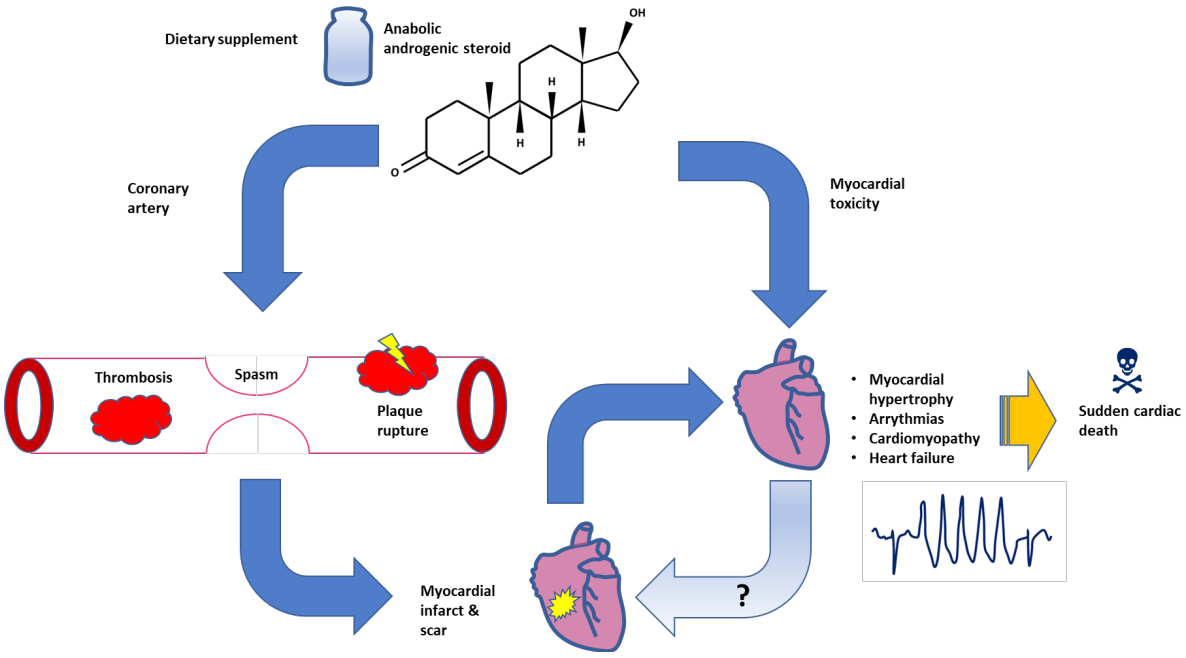

Fig. 1. Cardiovascular effects of anabolic-androgenic steroids (AAS). AAS cause cardiovascular toxicity by means of coronary artery-mediated mechanisms and direct myocardial effects. Direct myocardial toxicity leads to left ventricular hypertrophy, arrhythmias and heart failure, which are associated with an increased risk of sudden cardiac death

Рис. 1. Сердечно-сосудистые эффекты анаболико-андрогенных стероидов (ААС). ААС вызывают сердечно-сосудистую токсичность посредством механизмов, опосредованных коронарными артериями, и прямого воздействия на миокард. Прямая токсичность для миокарда приводит к гипертрофии левого желудочка, аритмиям и сердечной недостаточности, которые связаны с повышенным риском внезапной сердечной смерти

an increase in the density (but not affinity) of thromboxane A2 receptors [25, 26].

A second mechanism of cardiovascular toxicity comprises direct myocardial effects, which include left ventricular dilatation and hypertrophy, as well as myocardial fibrosis (Figure 2) [14, 17, 18, 27]. Myocardial fibrosis is postulated to be a response to cardiomyocyte necrosis, similar to what is seen in catecholamine toxicity, and is accompanied by intimal hyperplasia of the intramural coronary arteries [17, 18]. Diastolic dysfunction of the left ventricle has been reported, as well as effects on right ventricular function [14, 28]. Both coronary and direct myocardial toxicity have the potential to cause heart failure, lethal arrhythmias and sudden cardiac death (Figure 1) [28]. Preclinical models have furnished evidence of autonomic dysregulation with chronic exposure to AAS, which constitutes a further risk factor for lethal arrythmias and sudden cardiac death [29]. Life-threatening arrythmias require a trigger (e.g. myocardial ischemia caused by coronary artery spasm) imposed on an arrhythmic substrate (e.g. myocardial scar tissue) [30]. The arrhythmogenic process can be further facilitated by modulating factors, e.g. autonomic nervous system dysregulation. The triad of a trigger, substrate and modulator, is sometimes known as Coumel's triangle of arrhythmogenesis [30]. Direct arrhythmogenic effects of AAS may include prolonged activation of repolarizing potassium channels, and electrocardiographic risk markers for ventricular arrhythmias, e.g. prolonged QTc intervals and QT dispersion, have been recognized in the presence of AAS abuse [31]. Since AAS are most often abused by athletes, the distinction between so-called "athlete's heart" (structural and functional changes in response to a high frequency and/or high intensity of training, e.g. myocardial hypertrophy), hypertrophic cardiomyopathy and AAS-induced cardiomyopathy, is not always straightforward [14, 17, 18, 32]. Echocardiographically-derived left ventricular myocardial work is a potential imaging biomarker with which to distinguish these entities.[32] Subtle signs of cardiac dysfunction have been documented in AAS abusers, e.g. impaired left ventricular and left atrial speckle tracking strain [28, 33]. Interestingly, echocardiographic evidence for impaired left atrial electromechanical function has been demonstrated in persons who abuse AAS [34]. This is often a precursor to atrial fibrillation, which may be a complication of AAS abuse [34, 35].

4. "Designer" AAS

These steroid molecules were first synthesized some five decades ago and evaluated in pre-clinical studies for their anabolic and androgenic effects. While they are not approved for clinical use, they are classified as prohibited substances by the World Anti-Doping Agency (WADA) and are manufactured exclusively for the dietary supplement "black" market. Examples of such designer agents are prostanozol, methasterone, andostatrienedione, 1-testosterone (dihydroboldenone), trenbolone enanthate, desoxymethyltestosterone, tetrahydrogestrinone and methylstenboloneprostanozol, but

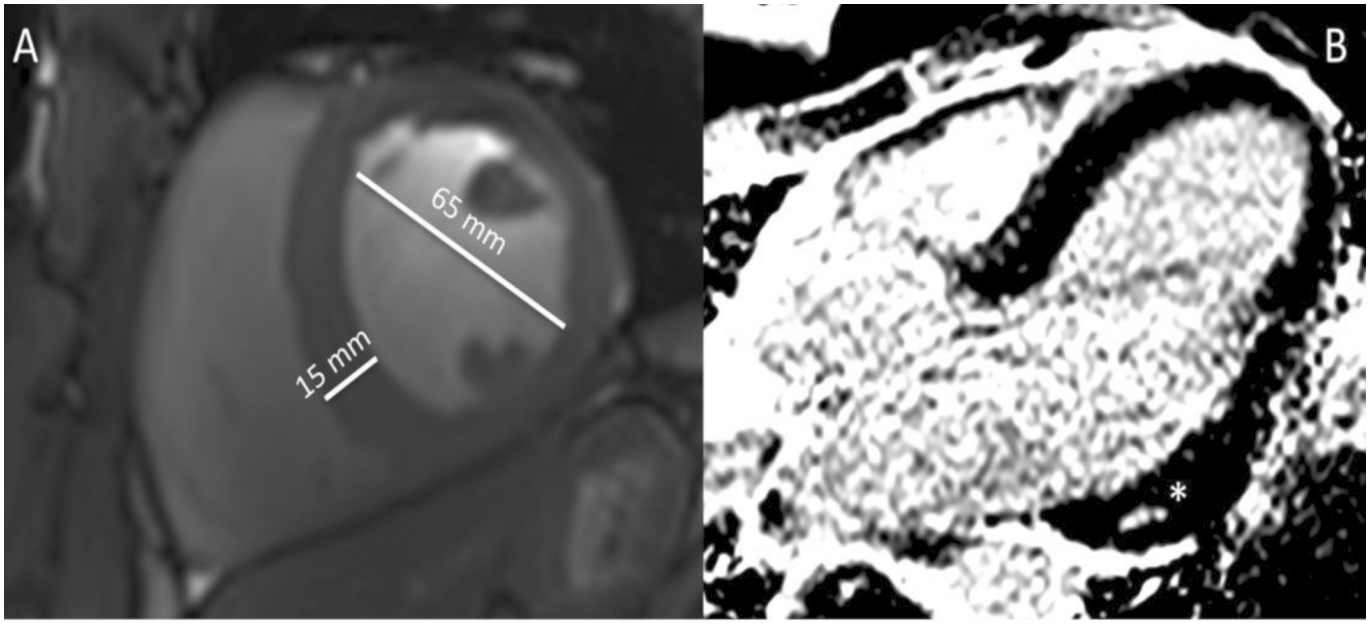

Fig. 2. Cardiac magnetic resonance. Steady-state free precession, short-axis image, demonstrating a dilated (65 mm) and hypertrophied (15 mm) left ventricle in a patient who had been abusing anabolic-androgenic steroids (panel A). Late gadolinium enhancement in the inferolateral wall (asterisk *) of the left ventricle in the same patient (panel B). Reproduced from Sivalokanathan et al. [14]
Рис. 2. Магнитно-резонансная томография сердца. Стационарная свободная прецессия, изображение по короткой оси, демонстрирующее расширенный (65 мм) и гипертрофированный (15 мм) левый желудочек у пациента, злоупотреблявшего анаболическими-андрогенными стероидами (панель А). Позднее увеличение содержания гадолиния в нижнелатеральной стенке (звездочка *) левого желудочка у того же пациента (панель В). Воспроизведено по материалам Sivalokanathan et al. [14]

to date a multitude of such "designer" steroid molecules have been detected in laboratories analyzing dietary supplements [36]. Because these agents are not registered for therapeutic use, little is known regarding their pharmacological actions and safety profiles in humans. Should metabolites of these "designer" steroids, however, be detected in an athlete's urine, doping infringement charges will more than likely ensue. The potential cardiotoxic effects of these agents are assumed to be similar to "classic" AAS.

5. AAS boosters

So-called "testosterone boosters" are products advertised to 'naturally' increase testosterone levels. These supplements typically contain numerous compounds, and include tongkat ali extract, horny goat weed, saw palmetto extract, boron and nettle extract, amongst others [37]. In addition, some testosterone boosters have been found to contain AAS [37]. Testosterone-boosters have not been adequately studied with respect to their constituents, nor their effects in humans [37]. While some may increase testosterone levels, their safety and efficacy have not been documented [38].

6. Data collection on AAS abuse

Attempting to study the cardiovascular toxicity of AAS is limited by the fact that ethical and legal constraints prohibit their administration in athletes, even for research purposes. Accordingly, AAS preparations, dosage and duration of abuse are based on athlete self-reporting. Additionally, the majority of studies comprised cohorts of limited size and the majority of athletes consume combinations of different substances (sometimes referred to as "stacking"), prohibited or not, such that the registered effects cannot be attributed to AAS with certainty [39]. Despite these limitations, the results of 49 studies over the last 10 years in 1467 athletes abusing AAS, clearly demonstrate an increased frequency of coronary artery disease, arterial hypertension, myocardial infarction, heart failure, arrhythmias and sudden cardiac death [40].

7. Conclusions and future perspectives

Dietary supplement use among athletes to enhance performance is proliferating rapidly as more individuals strive to obtain a competitive edge. As a result, the concomitant use of dietary supplements containing AAS of those falling in the categories outlined in the current review, can also be expected to rise. A large variety of "classic AAS", most of them on the prohibited drug list of the WADA, are being produced on commercial scales in illicit factories worldwide, audacious marketing strategies are being employed by companies and these supplements can be easily ordered via e.g. the internet ("dark web"). It is also reasonable to expect that there will be an increased availability in future of supplements containing "designer" AAS.

On the counter side, ever-increasing sophisticated analytical methodologies are being used and developed to assay dietary supplement and urine samples in doping laboratories. Chromatographic techniques, combined with mass spectrometry, leading to identification of molecular fragments

and product ions, will assist in accurately identifying these substances. In order to do so, large data banks of these chemical entities will have to be compiled. To prevent accidental doping, clear information regarding dietary supplements must be provided to athletes, coaches and physicians at all levels of competition. The risks of accidental doping via dietary supplement ingestion can be minimized by using "safe" products listed on databases, e.g. such as those available in the Netherlands, Germany and the US [41, 42]. Finally, it must be brought to the attention of athletes and coaches that if the former test positive for prohibited substances not disclosed on the package label of supplements, it may constitute a doping violation. We advocate for improved education of the public at large regarding the potential for AAS to be included in dietary supplements, as well as its regulation by the appropriate authorities.

Author contributions:

Pieter van der Bijl — concept and publication design, writing the first draft of manuscript, collection and analysis of literature;

Pieter van der Bijl (Jr) — editing of the text, collection and analysis of literature.

Вклад авторов:

Питер ван дер Бийл — концепция и дизайн публикации, написание первой версии текста, сбор и анализ литературных данных;

Питер ван дер Бийл (мл.) — написание и редактирование текста, сбор и анализ литературных данных.

References

1. **Ronis M.J.J., Pedersen K.B., Watt J.** Adverse Effects of Nutraceuticals and Dietary Supplements. Annu. Rev. Pharmacol. Toxicol. 2018;58:583–601. https://doi.org/10.1146/annurev-pharmtox-010617-052844

2. **van der Bijl P., Tutelyan V.A.** Dietary supplements containing prohibited substances. Vopr Pitan. 2013;82(6):6–13.

3. **Mueller C.** The regulatory status of medical foods and dietary supplements in the United States. Nutrition. 1999;15(3):249–251. https://doi.org/10.1016/s0899-9007(98)00186-5

4. National Institutes of Health. Office of Dietary Supplements. Background Information: Dietary Supplements [internet]. Available at: https://ods.od.nih.gov/factsheets/dietarysupplements-Consumer/.

5. Food and Drug Administration. Dietary Supplements [internet]. Available at: https://www.fda.gov/food/dietary-supplements

6. **Tucker J., Fischer T., Upjohn L., Mazzera D., Kumar M.** Unapproved Pharmaceutical Ingredients Included in Dietary Supplements Associated With US Food and Drug Administration Warnings. JAMA Netw. Open. 2018;1(6):e183337. https://doi.org/10.1001/jamanetworkopen.2018.3337

7. **Delimaris I.** Adverse Effects Associated with Protein Intake above the Recommended Dietary Allowance for Adults. ISRN Nutr. 2013;2013:126929. https://doi.org/10.5402/2013/126929

8. **Mazzeo F.** Drug abuse in elite athletes: doping in sports. Sport Science. 2016;9(2):33–41.

9. **Tlili R., Zayed S., Saoudi W., Azaiez F., Hentati R., Ben Ameur Y.** Adverse cardiovascular effects of doping in athletes. Tunis Med. 2019;97(11):1211–1218.

10. La **Gerche A., Brosnan M.J.** Cardiovascular Effects of Performance-Enhancing Drugs. Circulation. 2017;135(1):89–99. https://doi.org/10.1161/CIRCULATIONAHA.116.022535

11. **Bhasin S., Storer T.W., Berman N., Callegari C., Clevenger B., Phillips J., et al.** The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N. Engl. J. Med. 1996;335(1):1–7. https://doi.org/10.1056/NEJM199607043350101

12. **Geyer H., Parr M.K., Koehler K., Mareck U., Schanzer W., Thevis M.** Nutritional supplements cross-contaminated and faked with doping substances. J. Mass Spectrom. 2008;43(7):892–902. https://doi.org/10.1002/jms.1452

13. **Lincoff A.M., Bhasin S., Flevaris P., Mitchell L.M., Basaria S., Boden W.E., Cunningham G.R., Granger C.B., Khera M., Thompson I.M.,** Jr. et al. Cardiovascular Safety of Testosterone-Replacement Therapy. N Engl J Med. 2023;389:107–117. doi.org/10.1056/NEJMoa2215025

14. **Sivalokanathan S., Malek L.A., Malhotra A.** The Cardiac Effects of Performance-Enhancing Medications: Caffeine vs. Anabolic Androgenic Steroids. Diagnostics (Basel). 2021;11(2):324. https://doi.org/10.3390/diagnostics11020324

15. **Forbes G.B., Porta C.R., Herr B.E., Griggs R.C.** Sequence of changes in body composition induced by testosterone and reversal of changes after drug is stopped. JAMA. 1992;267(3):397–399.

16. **Golestani R., Slart R.H., Dullaart R.P., Glaudemans A.W., Zeebregts C.J., Boersma H.H., et al.** Adverse cardiovascular effects of anabolic steroids: pathophysiology imaging. Eur. J. Clin. Invest. 2012;42(7):795–803. https://doi.org/10.1111/j.1365-2362.2011.02642.x

17. **Montisci M., El Mazloum R., Cecchetto G., Terranova C., Ferrara S.D., Thiene G., Basso C.** Anabolic androgenic steroids abuse and cardiac death in athletes: morphological and toxicological findings in four fatal cases. Forensic Sci. Int. 2012;217(1-3):e13–18. https://doi.org/10.1016/j.forsciint.2011.10.032

18. **Fineschi V., Riezzo I., Centini F., Silingardi E., Licata M., Beduschi G., Karch S.B.** Sudden cardiac death during anabolic steroid abuse: morphologic and toxicologic findings in two fatal cases of bodybuilders. Int. J. Legal Med. 2007;121(1):48–53. https://doi.org/10.1007/s00414-005-0055-9

19. **Thiblin I., Lindquist O., Rajs J.** Cause and manner of death among users of anabolic androgenic steroids. J. Forensic Sci. 2000;45(1):16–23.

20. **Hartgens F., Rietjens G., Keizer H.A., Kuipers H., Wolffenbuttel B.H.** Effects of androgenic-anabolic steroids on apolipoproteins and lipoprotein (a). Br. J. Sports Med. 2004;38(3):253–259. https://doi.org/10.1136/bjsm.2003.000199

21. **Riebe D., Fernhall B., Thompson P.D.** The blood pressure response to exercise in anabolic steroid users. Med. Sci. Sports Exerc. 1992;24(6):633–637.

22. **Baggish A.L., Weiner R.B., Kanayama G., Hudson J.I., Lu M.T., Hoffmann U., Pope H.G.,** Jr. Cardiovascular Toxicity of Illicit Anabolic-Androgenic Steroid Use. Circulation. 2017;135(21):1991–2002. https://doi.org/10.1161/CIRCULATIONAHA.116.026945

23. **Gralnick H.R., Rick M.E.** Danazol increases factor VIII and factor IX in classic hemophilia and Christmas disease. N Engl J Med. 1983;308:1393–1395. https://doi.org/ 10.1056/NEJM198306093082305

24. **Kluft C., Bertina R.M., Preston F.E., Malia R.G., Blamey S.L., Lowe G.D., Forbes C.D.** Protein C, an anticoagulant protein, is increased in healthy volunteers and surgical patients after treatment with stanozolol. Thromb Res. 1984;33:297–304. https://doi.org/ 10.1016/0049-3848(84)90165-8

25. **Gonzales R.J., Ghaffari A.A., Duckles S.P., Krause D.N.** Testosterone treatment increases thromboxane function in rat cerebral arteries. Am J Physiol Heart Circ Physiol. 2005;289:H578–585. https://doi.org/ 10.1152/ajpheart.00958.2004

26. **Ajayi A.A., Mathur R., Halushka P.V.** Testosterone increases human platelet thromboxane A2 receptor density and aggregation responses. Circulation. 1995;91:2742–2747. https://doi.org/ 10.1161/01.cir.91.11.2742

27. **Sachtleben T.R., Berg K.E., Elias B.A., Cheatham J.P., Felix G.L., Hofschire P.J.** The effects of anabolic steroids on myocardial structure and cardiovascular fitness. Med. Sci. Sports Exerc. 1993;25(11):1240–1245.

28. **Baggish A.L., Weiner R.B., Kanayama G., Hudson J.I., Picard M.H., Hutter A.M.,** Jr., **Pope H.G.,** Jr. Long-term anabolic-androgenic steroid use is associated with left ventricular dysfunction. Circ. Heart Fail. 2010;3(4):472–476. https://doi.org/10.1161/CIRCHEARTFAILURE.109.931063

29. **Pereira-Junior P.P., Chaves E.A., Costa E.S.**R.H., **Masuda M.O.,** de **Carvalho A.C., Nascimento J.H.** Cardiac autonomic dysfunction in rats chronically treated with anabolic steroid. Eur. J. Appl. Physiol. 2006;96(5):487–494. https://doi.org/10.1007/s00421-005-0111-7

30. **van der Bijl P., Bax J.J.** Imaging for risk stratification of sudden cardiac death. Herzschrittmacherther Elektrophysiol. 2022;33(3):261–267. https://doi.org/10.1007/s00399-022-00884-6

31. **Maior A.S., Menezes P., Pedrosa R.C., Carvalho D.P., Soares P.P., Nascimento J.H.** Abnormal cardiac repolarization in anabolic androgenic steroid users carrying out submaximal exercise testing. Clin. Exp. Pharmacol. Physiol. 2010;37(12):1129–1133. https://doi.org/10.1111/j.1440-1681.2010.05452.x

32. **Grandperrin A., Schnell F., Donal E., Galli E., Hedon C., Cazorla O., Nottin S.** Specific alterations of regional myocardial work in strength-trained athletes using anabolic steroids compared to athletes with genetic hypertrophic cardiomyopathy. J. Sport Health. Sci. 2023;12(4):477–485. https://doi.org/10.1016/j.jshs.2022.07.004

33. **D'Andrea A., Radmilovic J., Caselli S., Carbone A., Scarafile R., Sperlongano S., Tocci G., 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. https://doi.org/10.1007/s10554-018-1370-9

34. **Akcakoyun M., Alizade E., Gundogdu R., Bulut M., Tabakci M.M., Acar G., et al**. Long-term anabolic androgenic steroid use is associated with increased atrial electromechanical delay in male bodybuilders. Biomed. Res. Int. 2014;2014:451520. https://doi.org/10.1155/2014/451520

35. **Sullivan M.L., Martinez C.M., Gallagher E.J.** Atrial fibrillation and anabolic steroids. J. Emerg. Med. 1999;17(5):851–857. https://doi.org/10.1016/s0736-4679(99)00095-5

36. **Geyer H., Braun H., Burke L.M., Stear S.J., Castell L.M.** A-Z of nutritional supplements: dietary supplements, sports nutrition foods and ergogenic aids for health and performance -- Part 22. Br. J. Sports Med. 2011;45(9):752–754. https://doi.org/10.1136/bjsports-2011-090180

37. **Balasubramanian A., Thirumavalavan N., Srivatsav A., Yu J., Lipshultz L.I., Pastuszak A.W.** Testosterone Imposters: An Analysis of Popular Online Testosterone Boosting Supplements. J Sex Med. 2019;16:203–212. https://doi.org/ 10.1016/j.jsxm.2018.12.008

38. **Morgado A., Tsampoukas G., Sokolakis I., Schoentgen N., Urkmez A., Sarikaya S.** Do "testosterone boosters" really increase serum total testosterone? A systematic review. Int J Impot Res. 2023. https:// doi.org/ 10.1038/s41443-023-00763-9

39. **Deligiannis A.P., Kouidi E.I.** Cardiovascular adverse effects of doping in sports. **Hellenic J.** Cardiol. 2012;53(6):447–457.

40. **Perry J.C., Schuetz T.M., Memon M.D., Faiz S., Cancarevic I.** Anabolic Steroids and Cardiovascular Outcomes: The Controversy. Cureus. 2020;12(7):e9333. https://doi.org/10.7759/cureus.9333

41. **Geyer H., Parr M.K., Mareck U., Reinhart U., Schrader Y., Schanzer W.** Analysis of non-hormonal nutritional supplements for anabolic-androgenic steroids - results of an international study. Int. J. Sports Med. 2004;25(2):124–129. https://doi.org/10.1055/s-2004-819955

42. **Bailey R.L.** Current regulatory guidelines and resources to support research of dietary supplements in the United States. Crit. Rev. Food Sci. Nutr. 2020;60(2):298–309. https://doi.org/10.1080/10408398.2018.1524364

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