



## Sports supplements: a health risk?

Suplementos deportivos: ¿riesgo a la salud?

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### ABSTRACT

Sports supplements are a category of dietary supplements that in recent years has not only increased in quantity and availability, but also in the number of new products. Athletes of all levels are interested in the consumption of supplements that are useful to increase muscle mass gain, thus making the consumption of these products a frequent practice. Unfortunately, there are some products that are doping substances which are offered as sports supplements; on the other hand, certain sports supplements may contain active pharmaceutical ingredients, or their analogues, not declared in their ingredients to effectively enhance the benefits that these products ensure, exposing consumers to a significant potential health risk, especially those unfamiliar with sports supplements. It is important that health professionals are aware of the possible implications of consuming certain products offered in the sports nutrition market when evaluating their patients for a variety of pathologies.

**Keywords:** dietary supplements, sports supplements, ergogenic aids, doping substances, adulteration, contamination

### RESUMEN

Los suplementos deportivos son una categoría de los suplementos alimenticios que en los últimos años no solo ha incrementado en cantidad y disponibilidad, sino también en el número de nuevos productos. Deportistas de todos los niveles se interesan en el consumo de suplementos que son útiles para incrementar la ganancia de masa muscular convirtiendo así el consumo de estos productos en una práctica común. Desafortunadamente existen algunos productos que en realidad son sustancias dopantes que son ofertadas como suplementos deportivos, por otra parte ciertos suplementos deportivos pueden contener sustancias con actividad farmacológica o sus análogos no declarados en sus ingredientes probablemente para potenciar de manera efectiva los beneficios que estos productos aseguran, exponiendo a los consumidores a un riesgo potencial significativo a la salud, sobre todo a aquellos que no están familiarizados con los suplementos deportivos. Es importante que los profesionales de la salud tengan el conocimiento de las posibles implicaciones por el consumo de ciertos productos ofertados en el mercado de la nutrición deportiva al momento de evaluar a sus pacientes para una variedad de patologías.

**Palabras clave:** suplementos alimenticios, suplementos deportivos, ayudas ergogénicas, sustancias dopantes, adulteración, contaminación

### INTRODUCTION

An adequate nutrition is a key component to optimize sports performance, since individual nutritional needs differ widely depending on the type of sports discipline, sports training period, training days and rest, among other factors. The nutritional strategies implemented include adjustments in energy balance, proportion and nutrient timing, as well as supplementation (Bytomski, 2018). Dietary supplements, also known as nutritional or food supplements, are a category of food products that include over-the-counter formulations consumed in addition to the usual diet, with the aim of providing additional nutrients (Augustin and Sanguansri, 2012).

The companies that market these products, associates their properties to the wide variety of ingredients in the different formulations, such as improvement in the general state of health, enhancement of the physical and mental performance, increased energy, weight loss, decreased pain and other favorable effects (Knapik *et al.*, 2016b), although the need and efficacy of certain ingredients remains under considerable debate (Kerksick *et al.*, 2018) 2082 articles were published under the key words 'sport nutrition'. Consequently, staying current with the relevant literature is often difficult. Methods: This paper is an ongoing update of the sports nutrition review article originally published as the lead paper to launch the Journal of the International Society of Sports Nutrition in 2004 and updated in 2010. It presents a well-referenced overview of the current state of the science related to optimization of training and performance enhancement through exercise training and nutrition. Notably, due to the accelerated pace and size at which the literature base in this research area grows, the topics discussed will focus on muscle hypertrophy and performance enhancement. As such, this paper provides an overview of: 1.. Dietary supplements should not contain active pharmaceutical ingredients in their formulation, since these are used to diagnose, prevent, or cure a disease. These products are not drugs and should not make any of the above claims (Edenfield, 2020).

For most countries and regions worldwide, dietary

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supplements are regulated as a food category. When attempting to bring a product to the market, a notification or registration-based system is required for its approval, the acceptance and safety of the product depends in great part on the ingredients used in the formulation, which are ruled by the requirements in food additives considered by local regulations such as the Federal Commission for the Protection against Sanitary Risks (COFEPRIS) in the case of Mexico and the Food and Drug Administration (FDA) in the United States of America. This approach contrasts with the premarket approval approach required for drugs in most countries, and appropriately fits the category of foods, as these inherently pose low safety risks relative to drugs (Shao, 2017)nutraceuticals, and functional foods vary from country to country, but most include a form of premarket registration or notification, and several have no specific requirements for entry. However, in recent years countries that embraced the concept of appropriately balancing consumer access with consumer protection have begun to develop market entry requirements. From a global perspective, there has been some convergence from key markets toward the use of a notification-based market entry system for finished products. Although it is too early to know how these shifts have benefited stakeholders, the expectation is that this has reduced the cost and barriers to market entry (for both industry and government).

In sports sciences, dietary supplements are considered nutritional ergogenic aids (Lopez-Samanes *et al*, 2015) since some of these products have an impact in the improvement of physical-athletic performance, which is the reason of why they are also known as sports supplements (Jovanov *et al*, 2019).

A wide variety of these products are available in the market ensuring that they improve the physical performance, but only a few have scientific evidence of their benefits, in addition to the fact that the performance improvements are a function of the type of sports practice, competition level and timing at which they are consumed, which can vary widely between individuals due to several factors, including age, sex, genetics, intestinal microbiota, regular diet, among others (Maughan *et al*, 2018).

The sports supplement industry is constantly growing and over the last decades its consumption has increased considerably, estimating that the global sports nutrition market will reach approximately 34.5 billion dollars by 2028, mainly due to the increase in product demand by bodybuilders and other athletes (Grand View Research, 2020). However, the constant innovation in these products by manufacturers to catch and keep consumers' attention, as well as trends of interest, may carry a risk in pleasing consumers in terms of what they firmly believe they need to improve their physical performance (Garthe, 2019).

## SPORTS SUPPLEMENTS

Sports supplements are products formulated with food-source ingredients, as well as nutrients that are ingested

in addition to the regular diet in an adequate effective dose, that can be used in certain specific training phases with the purpose of increasing physical performance by improving adaptations to exercise, skills, recovery capacity and correction or prevention of nutritional deficiencies, as well as aiding in the body composition improvement, helping individuals to train and compete more effectively (Muñoz Maldonado *et al*, 2021). These products can be classified according to their level of scientific evidence (Garthe and Maughan, 2018), although probably the most widely known classification by its consumers is the bodybuilding supplement classification (Navarro *et al*, 2014). Previous research has documented that the most popular supplements consumed by bodybuilders include protein and peptide-based supplements, branched chain amino acids (BCAAs), individual amino acids, polyunsaturated fatty acids (PUFAs), complex, oligomeric, or simple carbohydrates-based supplements, individual or complex vitamins and minerals, creatine, "pre-workout" supplements, "fat burners", supplements for "joint health", "testosterone boosters", among other supplements rarely used to be classified (Chappell *et al*, 2019; 2018). The consumption and type of these products vary widely between practitioners and sports disciplines, especially in those where strength and power predominate, where the use of supplements can be considered a rule (Maughan *et al*, 2004),

## Prevalence of sports supplements consumption

Sports nutrition market primarily targets three diverse types of consumers:

- Bodybuilders and other professional athletes who seek to increase muscle mass through the combination of high calorie intake and resistance training (also known as weight training).
- Recreational athletes, since most of them do physical exercise as a hobby or are "fitness" enthusiasts, even though they do not achieve the same levels of physical effort as professional athletes.
- Consumers with healthy lifestyles, who do not necessarily use these products for improving their physical performance since they incorporate these supplements into their lifestyle to improve their health, replace food with beverages, nutritional bars, among others.

To attract consumers, sports nutrition companies continue to innovate their marketing and product strategies to offer products with high expectations (Agriculture and Agri-Food Canada, 2019). Unfortunately, it is difficult to obtain a complete description of the consumption prevalence of these products since different data collection methods have been used in the many studies related to this topic. When supplement use is pooled by sport discipline, sport populations, as well as the various supplement classifications, there is high variability between studies. In general, the use of supplements among men and women who are professional athletes is 69% and 71% respectively, whereas for recreational athletes is 48% and 42%, thus being similar

the consumption of these products among people from both groups. Furthermore, some athletes tend to consume supplements in up to 100% of individuals depending on the type of sport and the level of competition (Knapik *et al.*, 2016a). On the other hand, among recreational teen athletes, around 60% have mentioned the use of sports supplements, 42% of which, state using more than one type of supplement with high frequency of consumption, and up to 86% do not verify the nutritional label of the chosen supplement (Tsarouhas *et al.*, 2018).

In the case of bodybuilders, up to 87% of these athletes at the amateur level are consumers of sports supplements (Montuori *et al.*, 2021), while of professional bodybuilders, 100% use these products (Sánchez-Oliver *et al.*, 2019). Recently, other sports disciplines at a professional level have exhibited a high prevalence of consumption such as cycling (86%), watersports (77%), and weightlifting (75%). In turn, in team sports such as American football and soccer, similar frequencies of up to 57% and 75% have been observed, respectively (Baltazar-Martins *et al.*, 2019). Interestingly, in athletics, long and medium distance athletes are the largest consumers of sports supplements with frequencies of 76% and 72%, respectively, followed by sprinting and obstacle course with up to 58% in both disciplines (Tabata *et al.*, 2020).

A large part of the studies related to the consumption prevalence of these products concludes a marked trend towards greater use of sports and herbal supplements. In general, athletes have conventionally been the largest consumers of sports supplements, representing more than a third of the overall market. However, the growing population of recreational athletes and individuals with a "fitness" lifestyle creates a new dimension of potential consumers for the manufacturers and sellers of these products, with an increasing trend of multi-ingredient supplements and varied content of biologically active compounds (Garthe, 2019). Another aspect to be considered is the commonness of the situation in which consumers exceed the recommended doses and timing of supplement consumption, which may be due to the belief that "more is better" (Maughan *et al.*, 2004). Moreover, it is a fact that supplementation is a frequently self-prescribed practice and without adequate medical or nutritional assessment, since the relevant information and recommendations usually come from other athletes, personal trainers, friends, or even relatives (Tsarouhas *et al.*, 2018). Likewise other media such as bodybuilding magazines (Iraki *et al.*, 2019), as well as online resources such as forums and social networks, are important sources of information and influence, although unfortunately the information presented in these media does not always have scientific support (Waller *et al.*, 2019).

Although estimates of the general use of dietary supplements are available in national surveys, these studies have used different categorizations, and most lacking specific data for these products (Geller *et al.*, 2015). It is important to note that during 2008, Mexico was the second largest international market for sports supplements with 192 million

dollars in sales to retailers alone. If we consider that sports supplements sales have increased significantly, it would not be surprising that currently our country continues to maintain or has even surpassed this position (Muñoz Maldonado *et al.*, 2021).

## PERFORMANCE-ENHANCING DRUGS OFFERED AS SPORTS SUPPLEMENTS

Currently, a wide range of possible performance-enhancing substances is available, mostly offered through the internet as sports supplements (Joseph and Parr, 2014), as "safe" and "legal" alternatives to performance-enhancing drugs (Abbate *et al.*, 2015). This, present a high prevalence of consumption by, but not limited to, bodybuilders (Sánchez-Oliver *et al.*, 2019), and between sports where strength and power predominate (Jokipalo and Khudayarov, 2021).

As such, these products from the black market often contain active pharmaceutical ingredients without prior authorization by the corresponding national regulatory entities, no clinical approval and/or even without authorization for human use, and therefore without a known complete toxicological profile. Additionally, the lack of quality control and the incorrect labeling of these products implies potential health risks, although unfortunately, this situation does not limit the use and abuse by the consumers. Although until the early 2000s these products were almost exclusively steroid prohormones and designer steroids, nowadays the selective androgen receptor modulators (SARMs) are also available, which are synthesized from several pharmacophores (Geldof *et al.*, 2017).

### Designer steroids

Taking advantage of the ease and convenience for obtaining food supplements, certain manufacturers carry out chemical modifications to existing anabolic androgenic steroids (AAS), in order to avoid legal controls regarding the manufacture and supply of current medicines; the synthesized compounds are called "designer steroids" and are marketed as sports supplements (Voelker *et al.*, 2019). The term "designer drug" was originally introduced to describe new substances that are synthesized from known substances of abuse, preserving, or enhancing pharmacological effects while remaining outside of legal control; currently this term is broadened to include substances that are derived from industrial or academic research, but never receive medical approval. Some designer drugs may be approved in some countries, and in a strict sense, they should not be considered as such as they do not conform to the classical definition (Luethi and Liechti, 2020). Designer steroids are offered as supplements or ingredients in some of these products for muscle mass gain, commonly referred to misleading and incorrect terms such as "testosterone boosters", "natural steroids" and "prohormones" (Rahnema *et al.*, 2015). The term prohormone refers to the precursors, in this case, of the steroid hormone testosterone such as dehydroepiandrosterone (DHEA), an-

drostenedione, androstenediol or other similar compounds. They have also been sold as "andro-supplements", stating that these active ingredients are converted into testosterone or its analogues, to improve adaptations to resistance training. Even though it has been shown that the use of steroid prohormones does not provide any ergogenic benefit, their use is widely extended, despite their consumption is prohibited by the World Anti-Doping Agency (WADA) and different sports governing organizations (Brown *et al.*, 2006).

Designer steroids are typically manufactured and sold by smaller scale companies that often dissolve or change their name when they meet resistance from regulatory agencies (Rahnema *et al.*, 2015). In the United States, the Designer Anabolic Steroid Control Act of 2014 expanded the list of anabolic steroids regulated by the Drug Enforcement Administration (DEA), thus decreasing their sale and acquisition. However, the continued synthesis of new designer steroids by manufacturers means that these compounds are not on the current banned substance lists (Brown, 2017).

Just like testosterone, designer steroids share common mechanisms of action by interacting at the androgen receptor, as well as aromatization and 5- $\alpha$  reduction for some of these compounds. Like all androgens, the parameters by which they are characterized differ among the different compounds as they exhibit varying proportions of anabolic and androgenic activity. Most designer steroids are formulated to be consumed orally with varying degrees of bioavailability through 17- $\alpha$  alkylation, however this modification increases the compound toxicity. On the other hand, it seems that the benefits from the use of these products are minimal and even non-existent, compared to the considerable number of adverse health effects. Like exogenous androgens, designer steroids have the potential to cause reversible adverse effects such as hypertension, secondary hypogonadism, infertility, as well as polycythemia and adverse changes in lipoprotein subfractions. There is evidence that some designer steroids can cause more permanent adverse effects, such as hepatotoxicity, cardiotoxicity, and ischemic stroke (Rahnema *et al.*, 2015). It is noteworthy to mention that evaluations of their side effects or metabolism in humans is scarce, making the continuous synthesis of new compounds even more difficult to determine. In addition to the above mentioned effects, designer steroids may also show side effects related to the activation of other steroid receptors, such as the glucocorticoid receptor (Joseph and Parr, 2014). Since designer steroids are derived from anabolic androgenic steroids, their use has been banned by sports' governing organizations since athletes who consume these products may result in a positive doping test for anabolic steroids (Kazlauskas, 2010).

A study published in the UK (Abbate *et al.*, 2015) accurate mass liquid chromatography-mass spectrometry (LC-MS) investigated the presence and estimate of specific active substances amounts present in a total of 24 "prohormone supplements" selected according to information available on the internet from sellers, bodybuilding forums discussing these products, as well as consumers familiar with

these products. The samples were purchased from different distributors such as gym equipment stores and online stores that claimed on the product label the different designer steroids content. Of the samples analyzed, one of them did not contain any steroids and about 70% were substituted products containing classic steroids (such as DHEA, methyl-1-testosterone, 4-androstenedione, desoxymethyltestosterone, methasterone, androst-4-en-3, 11,17-trione and furazabol) other than those indicated on the label. In addition, the spelling of some of the chemical names for the active compounds was incorrect, probably in order to hide the true ingredients from both consumers and regulatory agencies. All identified compounds were controlled or potentially controlled substances in the UK under the Misuse of Drugs Act 1971. Furthermore, the estimated amounts for 17-alkylated steroids equaled or exceeded the established therapeutic doses for this type of drugs.

### Selective androgen receptor modulators

In an attempt to mitigate the risks associated with the administration of testosterone and other AAS in pathologies that result in the loss of muscle mass and function, as well as in hormone replacement therapies, SARMs were developed, which have a targeted therapeutic effect through binding to the androgen receptor in muscle and bone tissues (Thevis and Schänzer, 2018). The pharmacophores present in SARMs have an unprecedented potential for chemical modifications, these include steroid substances such as testosterone itself and non-steroids such as aniline, aryl-propionamides, benzimidazole, bicyclic hydantoins, bridged tricyclics, diarylaniline, indole, quinolones, tetrahydroquinolones, tricyclics and pyrazoline derivatives (Machek *et al.*, 2020).

In various clinical trials, certain SARMs have shown improvements in fat-free mass in healthy men, sarcopenic and postmenopausal women, as well as the cancer population, although the effects on the muscular strength and physical performance increase remain inconsistent, and with unknown effects of its long-term use. Just like androgens, SARMs have adverse effects, although to a lesser degree compared to the use of testosterone. In clinical trials, a decrease in high-density lipoproteins (HDL), hepatotoxicity with an increase in liver transaminases and alterations in plasma levels of anabolic hormones involved in the hypothalamic-pituitary-gonadal axis have been reported. To date, and despite their clinical potential, none of the existing SARMs are approved for human use in any country, even though some have progressed to phase II and III trials (Fonseca *et al.*, 2020) undesirable side effects have raised concerns about prostatic hypertrophy in men as well as virilization in women. Selective androgen receptor modulators (SARMs). Unfortunately, SARMs have attracted the attention of athletes as novel compounds due to their anabolic effects and few side effects, and because of this, the WADA has placed SARMs on the list of banned substances since 2008 due to the potential high risk of abuse (Temerdashev and Dmitrieva, 2020).

There are two recent studies (references) conducted to contrast the precision of the labeling with respect to composition and concentration, considering the claims of various products offered as SARMs. It is worth mentioning that in the samples from both investigations up to 20 – 55% of the products mentioned the liability exemptions of "not suitable for human consumption" and/or "for research purposes only", nevertheless, some of them detailed the information of the suggested portion. Also, between 45 – 85% of the products were sold as sports supplements and some of the products were stacks containing different multiple SARMs.

A study carried out in the United States of America (Van Wagoner *et al.*, 2017) reported that 44 products purchased from 21 online distributors in the same country were analyzed. Some manufacturers and distributors used the term SARM on the product label and advertising, although they were not selective modulators of androgen receptor. These included the agonist compounds of the peroxisome proliferator-activated receptor gamma (PPAR $\delta$ ) GW501516, growth hormone secretagogue ibutamoren, nuclear receptor agonist Rev-ErbA- $\alpha$  SR9009, and the anabolic compound 5 $\alpha$ - hydroxy-laxogenin, all of them included in the WADA list of prohibited substances and without scientific evidence of the efficacy or safety of these substances. Chemical analysis determined that, of the 44 products, 73% matched the active substance indicated on the label, however, only 18 products contained the declared amount, three products contained additional prohibited substances, and 11 products differed with a lower amount. Furthermore, in eight products, the active substances were not found, but were replaced by other prohibited substances in lower amounts, and in four products, no active substances were found.

Similar findings were found in the UK (Leaney *et al.*, 2021), derived from an analysis of 20 products available in the UK market purchased from 12 manufacturers online. Of the total of the products evaluated, only 30% were consistent with the label content, while 35% had at least one active substance absent in the content. In addition, two products substituted with different prohibited active substances, one product did not contain the presence of any active substance, and nine products with amounts less than those indicated.

## HEALTH CONCERN RELATED TO THE CONSUMPTION OF SOME SPORTS SUPPLEMENTS

It is important to know that certain sports supplements may contain substances prohibited by WADA, which are performance-enhancing drugs not labeled in the ingredients of the product (Martínez-Sanz *et al.*, 2017; Rocha *et al.*, 2016) year after year. Related to the high rates of use, unintentional doping occurs. Unintentional doping refers to positive anti-doping tests due to the use of any supplement containing unlisted substances banned by anti-doping regulations and organizations, such as the World Anti-Doping Agency (WADA, and they can even contain plant compounds

that have no history of human usage and are often used as ingredients to mask banned substances (Jędrzejko *et al.*, 2021).

When the content of active ingredients in a supplement is variable, it is due to inadequate quality control during the manufacturing process. However, there is also evidence that some products do not contain the indicated amount of the highest value ingredients declared on the label and, in some cases, the active ingredient is completely absent and the product contains only low-cost materials, even relatively inexpensive ingredients may be absent or present in trivial amounts (Maughan *et al.*, 2011). Poor manufacturing practices can likely lead to cross-contamination of supplements on the same production line (Geyer *et al.*, 2008), but in most cases it is deliberately by the manufacturers themselves in order to obtain more noticeable effects claimed by their product (Odoardi *et al.*, 2015). Supplements that are intentionally added with illegal substances or with pharmacological activity not declared on the nutritional label are called adulterated supplements (Ronis *et al.*, 2018). These products could be problematic as they expose professional athletes to inadvertent doping, as well as potential health risks for consumers in general, due to the inadvertent intake of substances with pharmacological activity. These risks go beyond the inherent effects of consuming these substances in high amounts, polypharmacy, and the fact that some of these are often not tested in humans and the effects when combined with exercise are unknown (Mathews, 2018).

The health consequences caused by adulterated and/or contaminated sports supplements are unclear, due to the lack of precise reports on adverse events. Also, some side effects are not acute events, but could appear as delayed and chronic health problems (Eichner and Tygart, 2016). The presented data in the case reports of adverse events associated with the use of adulterated sports supplements are difficult to collect, due to incomplete information such as the lack of the product name or manufacturer, and confounding variables such as drug addiction of the individual, concomitant medication, and other pre-existing risks. The main factors that influence the reliability of these reports are the product identity and quality, unfortunately most of the supplements are not properly identified, analyzed or characterized in the reports, which makes it difficult to assign or determine the product (Gardiner *et al.*, 2008). Also, most patients do not report on supplement use, causing physician to be unable to identify associated adverse events as frequently as they do with pharmaceuticals, in addition to possible limited knowledge of drug-supplement interactions (Geller *et al.*, 2015).

It is well known that the acquisition of sports supplements is well known that the acquisition of sports supplements is due to their easy accessibility and availability through websites, supplement stores and gyms without the need for any type of prescription or clinical approval. Additionally, the number of supplements from the informal market has increased dramatically in recent decades due

to high demand from consumers (Odoardi *et al.*, 2015). An example of sports supplements that may present a greater risk of adulteration and/or contamination are supplements for muscle mass gain (Kulkarni *et al.*, 2017; Pomeranz *et al.*, 2015).

### Sports supplements for muscle mass gain

These products have the objective of increasing the anabolic response in the muscle induced by resistance training, these include a wide variety of supplements with nutritional ingredients (Yager and McLean, 2020). Some products included in the supplement category for muscle mass gain are:

- a) Protein and multi-ingredient protein-based supplements

Most of these products are milk, egg, and plant-based protein and peptide powders that are reconstituted with the addition of water, juice, or milk (De Ceglie *et al.*, 2015) as ingredients, amino acids and proteins with important nutritional values as milk, soy and egg proteins. An EU Food Supplements Directive (2002). They are also found in combination with other safe and authorized nutritional ingredients, such as mixtures with different proteins and/or peptides, carbohydrates, amino acids (individual or combined), creatine,  $\beta$ -hydroxy- $\beta$ -methylbutyrate (HMB), PUFAs, vitamins, minerals (O'Bryan *et al.*, 2020), and some plant compounds (Directo *et al.*, 2019), to mention just a few examples.

- b) Mass gainers, weight gainers or muscle gainers

These hypercaloric supplements are designed for those individuals who find it difficult to gain muscle mass. Most of these products contain a high amount of carbohydrates and proteins making them a good replacement for some meals (Wójcicki, 2020).

- c) Testosterone boosters (T-boosters)

They are supplements with different herbal ingredients in combination with minerals and vitamins, in complexes or individually, being the plant material *Tribulus terrestris* the most widely known (Balasubramanian *et al.*, 2019; Santos *et al.*, 2019). T-boosters claim to improve muscle strength and endurance while increasing blood testosterone levels, as well as inhibiting its conversion to estrogen, thus stimulating muscle hypertrophy, statements from the internet or other means that try to encourage the use of T-boosters. The supposed beneficial effects is attractive for bodybuilders and professional athletes, however, the effectiveness and safety of these supplements is questionable (Herriman *et al.*, 2017; Pokrywka *et al.*, 2014). Various other ingredients and their combinations, to date, have not been shown to be conclusively effective in supporting the claims these products make (Clemesha *et al.*, 2020).

Different international research groups have analyzed the undeclared presence of AAS, steroid prohormonal compounds and designer steroids in sports supplements for muscle mass gain, since 1999 through chromatographic methods, due to the relationship between positive doping cases and sports supplements. Studies carried out in the early

2000s provided the first evidence that some non-hormonal supplements based on proteins, creatine and even vitamins and minerals had the presence of prohibited substances in around 15% of a sample of 634 supplements purchased from 13 countries, including 215 different distributors (Geyer *et al.*, 2008). The presence of AAS as adulterants was reported with five steroid hormones in up to 18% of products, from a sample of 28 protein and amino acid supplements combining other permitted ingredients (Martello *et al.*, 2007).

This situation seems to be highly prevalent in sports supplements for muscle mass gain, since currently, in the Netherlands, Duiven *et al.* (2021) evaluated a total of 66 products that claimed to modulate hormonal regulation, stimulate muscle mass gain, increase fat loss and/or increase energy, selected from 21 different brands and purchased from 17 online stores. A total of 21 products (32%) contained the presence of at least five different AAS, 1,4-androstenediene-3,17-dione (boldione) being mostly detected in 11 products, followed by 5-androstene-3 $\beta$ ,17 $\alpha$ -diol, in addition to DHEA, testosterone, and 5-androstanedione. On the other hand, in Iran (Alaedini *et al.*, 2021) was determined that up to 37% of a sample of 30 non-hormonal sports supplements selected from 12 different brands, purchased in pharmacies and the formal market, contained at least one of the AAS. The greatest relevance in the list of substances banned from WADA found, included 4-androstanedione and methyl-1-testosterone. Also, stanozolol and 5 $\alpha$ -hydroxy-laxogenin have been found in protein and amino acid supplements in South Korea (Lee *et al.*, 2020) and in Italy, in up to 10% of products identified as amino acids. These, are also consumed by professional athletes, and are adulterated with DHEA, while the same percentage for herbal products have come to contain dehydroepiandrosterone acetate (DHEA-acetate), methylandrostenediol, clasterone, testosterone propionate, 5 $\alpha$ -androstane-3 $\alpha$ ,17 $\beta$ -diol y progesterone (Micalizzi *et al.*, 2021).

Designer steroids have also been found with increasing regularity, in products offered as all natural herbal supplements marketed for muscle mass and strength gain, as is the recently reported androsta-3,5-diene-7,17-dione, an aromatase inhibitor, which is included in the WADA banned list. Although little is currently known about the pharmacological effects and/or toxicity of this compound, its structure is similar to that of AAS which are known to cause significant health risks (Lorenz *et al.*, 2019).

Supplements adulterated with these substances, should be considered for having significant pharmacological activity when consumed chronically. Health consequences of inadvertent use of steroid prohormones and designer steroids (in addition to the adverse effects mentioned above), could include cholestasis, kidney failure, gynecomastia, acne, psychological dependence, among others. Ingestion by women could cause absence of menstruation, virilization, alopecia and clitoromegaly (Mathews, 2018). In adolescents, the risk is greater since consumption, even in insignificant amounts, can suppress testosterone production for months,

as well as cardiovascular risks and mood alterations. Similarly, it can cause premature epiphyseal closure, brain remodeling and an increased risk of maladaptive behaviors and neurological disorders (Eichner and Tygart, 2016).

On the other hand, the SARM ostarine has been detected as an undeclared ingredient in several supplements, which opens the possibility that other SARMs are present as adulterants in sports supplements for muscle mass gain, leading to cases of inadvertent doping (Walpurgis *et al.*, 2020).

#### **Inadvertent doping prevention programs as tools for advice and recommendations when selecting sports supplements**

According to current scientific evidence, the risk that any sports and dietary supplement, in general containing a variety of substances with undeclared pharmacological activity, is close to 15% of the total of these products (Outram and Stewart, 2015). Not only AAS have been found as adulterants, but also has a variety of substances such as phosphodiesterase-5 inhibitors and antihistamines, found in supplements to improve sexual performance and blood pressure respectively (Kim *et al.*, 2017). Also found, are glucocorticoids and non-steroidal anti-inflammatory analgesics in herbal supplements for pain management (Garza-Ocañas *et al.*, 2013), as well as sympathomimetic agents, anorectics, and pancreatic lipase inhibitors in weight loss supplements (Ronis *et al.*, 2018). All of these substances are also prohibited by WADA since their consumption through these products has incurred in cases of positive doping, such is the case of Mexican professional athletes (Proceso, 2011).

Some programs try to protect athletes who consume sports supplements from inadvertent doping, the best known being the Sports Supplements Regulatory Framework of the Australian Institute of Sport (2021). This is designed for the specific needs of Australian sports organizations, to promote their use based on scientific evidence and other practical considerations that determine whether the product is safe, permissible and effective in enhancing athletic performance.

In recent years, laboratory tests for the detection of prohibited substances in sports supplements have been available to anyone interested, such as athletes, sports organizations, national anti-doping agencies and manufacturers of these products (Garthe and Ramsbottom, 2020) without the need for any further or additional supplementation. Nevertheless, the perception, from times of antiquity to the present day, is that taking additional food nutrients will enhance performance. A common rationale for use of supplements by athletes is to gain a 'competitive edge'. Current data suggests that the prevalence of supplement use among athletes is in the 40–70 % range, depending on the sport and definition or categorization of supplement. Athletes (youth/adult). Various third-party companies offer supplement analysis services for quality, purity, and composition. These must be free of conflicts of interest, have external accreditation, perform audits for good manufacturing practices, and have validated and accredited methods to analyze prohibited substances. When

approved, the supplement brand will receive the corresponding approval seal to be displayed on the product label; some of these companies are Consumer Labs (consumerlab.com), National Sanitation Foundation (NSF.org), Banned Substances Control Group (bscg.org) and Informed-Choice/Informed-Sport (informed-sport.com). These companies offer a variety of services that include certification of facilities and raw materials, compliance with good manufacturing practices, label verification and testing of the final product. The cost of these services can be an issue for small companies and larger companies may not see any market advantage in certification and will not consider this additional scrutiny. However, it is impossible to affirm that a product is free of all prohibited substances because it is not possible to analyze all of them due to the continuous synthesis of new adulterants. In summary, supplement certification cannot completely eliminate the risk of a product being contaminated, but it does have strong evidence of reduced risk (Mathews, 2018).

In Mexico, the National Association of Food Supplements Industry (ANISA) integrated of accredited dietary supplement companies (including sports supplements), determine those products that meet the regulatory requirements indicated by authorities in our country such as the Secretariat of Health, COFEPRIS and the Office of the Federal Prosecutor for the Consumer (PROFECO). These, have the purpose of protecting the consumer from the increasing bombardment of advertising and sale of products that potentially endanger the population's health, like the programs above. The accredited products have a certification seal, in addition to outreach program of technical and scientific information, to promote regulatory improvement through the generation of proposals aligned with global trends (Asociación Nacional de la Industria de los Suplementos Alimenticios, 2021).

#### **CONCLUSIONS**

The consumption of active pharmaceutical ingredients, steroid prohormones and designer steroids, offered as sports supplements for muscle mass gain, in addition to other ergogenic effects, as well as the inadvertent consumption of the same substances in sports supplements, is a potentially risk situation difficult to estimate, not only for professional sports but also for the consumers' health. This, due to the acute or chronic exposure of a wide range of substances with pharmacological activity in unknown quantities that have a variety of adverse effects that are not even fully determined yet. It is important to note that, although the percentage of supplement adulteration and/or contamination in general may seem minimal (around 15% of the total), there are minimal studies that have analyzed significant amounts of the great diversity of these products from the national market. Thus, there is no precise data on the approximation to this figure in Mexico, which is one of the main consumers of these products internationally.

When elaborating a routine medical history, it usually includes a patient questioning about drug use and drug addiction. However, due to the disclosure of sports supple-

ments or products, they probably will not be considered due to the belief that these do not cause damage to health. The latter, under the argument that they are not drugs or because are offered with statements such as being of natural origin and without adverse effects, or being safe and legal alternatives for other types of substances. Therefore, the authors encourage doctors and other health professionals who consider asking about the use of these products when relevant to perform a differential diagnosis. Similarly, it is necessary to standardize studies related to the consumption prevalence of these products with appropriate definitions and contextualization, since these play a key role in the assessment and quantification of risks to public and individual health.

It is not the intention of the authors to suggest that all sports supplements are likely to cause harm to the consumer's health, or lead to cases of positive doping in professional sports. There are ingredients and products whose scientific evidence has shown their effectiveness and safety when properly consumed and for their purpose. Instead, we highlight the importance of health professionals' involvement to mitigate the potential risks that the consumption of certain sports supplements entails, that could be adulterated and/or contaminated. In addition, this will produce additional elements to consider when assessing the causes of some pathologies, as well as issue the pertinent recommendations for the differentiation and consumption of these products.

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