ERGOGENIC AIDS AND SUPPLEMENTS

Running title: ergogenic supplements

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Abstract

Great interest is currently shown for the contribution of nutrition to optimize training and athletic performance, and a considerable debate exists about the potential ergogenic value of several dietary supplements. However, most of the products used by athletes do not provide sufficient scientific evidence regarding their efficacy in enhancing physical performance as well as their specificity of action and safety. For this reason, sport nutrition professionals need skills in evaluating the scientific value of papers and advertisements on ergogenic aids and supplements in order to support athletes in their choice.

In the present chapter, the efficacy of some of the most popular supplements used by athletes and sport practitioners will be discussed. A particular attention will be devoted to amino acids and derivates, caffeine and caffeine-energy drink, and some antioxidants.

An ergogenic aid is any training method, mechanical device, nutritional practice, pharmacological approach, or psychological technique that can improve exercise performance capacity and/or enhance training adaptations. This include aids that may help prepare an individual to exercise, improve the efficiency of exercise, and/or enhance recovery from exercise [1].

Nowadays, great interest is shown for the contribution of nutrition to optimize training and athletic performance and a considerable debate exists about the ergogenic value of various dietary supplements.

The use of dietary supplements is widespread, however individuals engaged in sport and physical activity represent a substantial portion of the population purchasing these products [2-4]. Dietary supplements can play an important role in helping athletes to consume the proper amount of calories and nutrients. However, they should not be considered as replacement for a good diet.
Today, the supplement industry is an international market worth billions of dollars. According to the estimates of the Nutrition Business Journal report, the global supplements market stood at US$104 billion in 2013 [5]. Strongly outpacing other major consumer health categories, sports supplements broke the US$10 billion retail value sales mark in 2014 [6]. North America holds the largest market share for sports supplements, followed by Europe and Asia Pacific [6].

Most data reported in literature show that nearly half of all athletes use supplements, with wide variation between different sports and between athletes of differing performance levels, ages and cultural backgrounds. For example, a high percentage of Canadian Olympic athletes were found to consume dietary supplements at the Atlanta (69%) and Sydney (74%) Olympic Games [7]. In some sports, such as strength and power sports, supplement intake is so common it is perceived as the norm.

Also individuals engaged in recreational sports or other fitness pursuits are much interested in the advantages of taking supplements.

A recent Italian survey from UISP (Unione Italiana Sport Per Tutti) with a grant from Istituto Superiore di Sanità (ISS) (2012), investigated the consumption of ergogenic substances and food supplements in a group of adolescents and adults attending gyms and fitness centers (n = 451) [8]. Results (**Table 1**) pointed out that vitamins were the most used supplements in both males and females (53.4% of individuals declared to have consumed them in the last year). Protein and amino acid derivates (mainly creatine) have been used by 12.4% of the individuals, with men consuming more than double the amount of women, probably due to the fact that males are more interested in enlarging muscle mass [8].

Interestingly, 77% of individuals interviewed met the costs for substances listed in **Table 1**. Percentage of minors who paid for these products was higher than thought, and comparable to the other class ages. The difference among class ages consisted in the volume of expenditure per year, that increased with age (46.7 Euro for young people aged 14 to 18, and 174 Euro for those aged 26 or over). About 10% of the sample declared to spend more than 250 Euro per year [8].

The regulation of supplements and sport foods is a contentious area. There is no universal system of regulation, and countries differ in their approach and practice. According to the European Commission (2002/46/EC) a food supplement is a concentrated source of nutrients or other substances with a nutritional or physiological effect whose purpose is to supplement the normal diet

[9]. They are marketed in dose form i.e. as pills, tablets, capsules, powders, liquids in measured small unit. The regulation clearly states that supplements may be used to correct nutritional deficiencies or maintain an adequate intake of certain nutrients. However, in many cases their sale and use are not completely in line with the spirit of the regulation.

Athletes should always consider the issue of efficacy, safety and legality associated with supplements before using them. However, the number of products is enormous while the correct information is limited. In many cases, "evidence" is related to insufficient data or low quality studies. Furthermore, studies are often not relevant to real-life sport events; for example, laboratory studies of cycle ergometer performance, treadmill running, and isometric strength may have little relevance to competitive athletes. Similarly, results could not apply to all different subpopulation groups. As a consequence, decision to use a supplement is frequently extrapolated from inappropriate data rather than clear-cut evidence. Maughan et al. [10] categorized some supplements according to athletes' belief of target function (**Table 2**).

SPORT SUPPLEMENT EFFICACY

Sport nutrition professionals need to know how to evaluate the scientific value of articles and advertisements on nutritional practices and supplements in order to recognize scientific evidences from marketing hype.

When assessing the ergogenic value of a dietary supplement the theoretical rationale behind the supplement and the scientific evidence supporting its ergogenic value must be carefully examined.

According to The International Society of Sports Nutrition (ISSN) [11] there are three main questions to ask when evaluating the potential ergogenic value of a supplement:
1) Does the theory make sense?
2) Is there any scientific evidence supporting the ergogenic value?
3) Is the supplement safe and legal?
As regards the second question, some important factors to consider when assessing research papers on sport supplements are summarized in **Table 3**. Among the most critical aspects, the measurement of the performance-enhancing effect is still open to debate, as many variables concur to make difficult to find the measurable outcome strictly correlated to the performance outcome. This aspect is even more complicated for sports where performance is not necessarily determined by physiological outcomes (e.g. basket and tennis).

According to Kreider et al. [11], four categories of supplements can be identified based on the actual level of scientific evidence:
1) Apparently effective (most research finds them to be effective and safe);
2) Possibly effective (supplements of which initial research has supported the theoretical rationale in consumption, yet further studies are required);
3) Too early to tell (supplements with insufficient scientific evidence to support their efficacy);
4) Apparently ineffective (supplements for which the rationale behind their consumption is low and research identifies them as ineffective).
Similarly, The APRID framework [12], devised by Stear and Currel, divided supplements into five categories based on a risk-benefit analysis from scientific research and clinical dietetic practice:
A – Acceptable (scientific research has shown a clear performance or health benefit);

B – Physiological (there is a physiological rationale but the performance or health outcome is unclear);
R – Research (there is practitioner based evidence);
I – Ineffective (there is no clear performance or health benefit);
D – Disallowed (products banned or at high risk).
On the basis of these proposals, a categorization of common supplements used for sports and physical activity is reported in **Table 4**.

It is also important to consider that, generally speaking, supporting evidence-based claims has become more challenging as regulators seek science behind claim specifications. The review of dossiers promoting health claims carried out by the European Food Safety Agency (EFSA) have reduced the marketing of health claim benefits of dietary supplements in Europe. The intention was not to obstruct supplements market rather to enforce scientific substantiation and regulatory standards. EFSA scientific opinion on some approved claims for sport supplements are summarized in **Table 5.** It is essential to highlight that the positive opinions were substantiated by taking into account the totality of the available pertinent scientific data and by weighing up the evidence. In particular, the evidence should demonstrate the extent to which:
- the effect is relevant for human health;
- a cause-and-effect relationship is established between the consumption of the nutrient/substance/food/or food category and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship);
- the effect is shown on a study group which is representative of the target population;
- the quantity of the food and pattern of consumption required to obtain the claimed effect could reasonably be achieved as part of a balanced diet.

SPORT SUPPLEMENT SPECIFICITY

As already mentioned, specificity of action is an important factor to consider when deciding to take a supplement. First of all the use of a supplement should be planned on the basis of the kind of sport and the performance level of the athletes. For example, although sodium bicarbonate may improve performance in middle-distance running (400-5.000 m) [18], there is no reason to think that there will be any benefit to jumpers or throwers. Furthermore, data from well trained athletes cannot be applied to sport practitioners without knowing their physical conditions and food habits before and during competitions.
For some supplements the nutritional status can affect the individual response. In fact, it is increasingly recognized that individual athletes will respond differently to vitamin or mineral supplements: the athlete who suffers from a deficiency is likely to show a benefit in response to a period of supplementation, but the well-nourished athlete is unlikely to see an improvement in health or performance when taking the same supplement [10].
Differences could be present also according to age, gender as well as structural, hormonal and metabolic characteristics. Regarding age, many young boys and girls eager to improve their performance are attracted by supplements. In a recent study performed by the National Health Interview Survey (NHIS) [19] emerged that more than 1.2 million American adolescents (1.6% of adolescents with an average age of 10.8) were taking supplements for sport performance. A longitudinal Australian study, including more than 900 young (12-17 years old) athletes competing

at an elite junior level, showed that about 4% of them took performance-enhancing drugs and supplements [20]. Supplement use tends to differ across genders for prevalence, types of supplements, as well as reasons for use. In this regard, males tend to put more emphasis on the athletic performance-enhancing effects whereas females tend to be more concerned with the health benefits. In a study by Zeigler et al. [21] on young elite figure skaters emerged that females consumed multivitamin/mineral supplements most frequently (83%), followed by herbal supplements (48%), and multivitamin-only supplements (42%). These products could be categorized as health-related supplements, where males also used multivitamin/mineral (61%) and herbal supplements (44%), but consumed protein bars (38%), protein powders (15%), amino acid powders (8%) and creatine (3%) more frequently than their female counterparts, confirming that males tend to use supplements claiming a more ergogenic effect. The only exception to this is that females (35%) consumed energy drinks and bars slightly more frequently than males (33%) [21].
Finally, athletes should also avoid to use supplements in an inappropriate way, taking them in the wrong time or at too high or too low doses.

ERGOGENIC AIDS: THE PROOF OF CONCEPT

In the present section the efficacy of some of the most popular supplements used to enhance physical performance will be discussed. A particular attention will be focused on: amino acids and derivates (e.g. creatine, beta-hydroxy-beta-methylbutyrate), caffeine and caffeine-energy drink and antioxidants (e.g. vitamins, glutathione).

Role of creatine on sport performance

Creatine is one of the most popular natural supplements formed by arginine and glycine. Creatine is produced endogenously in the liver, kidneys and pancreas (up to 1 g/day), or obtained through the diet (at about 1 g/day) [22]. In humans, the majority of creatine is in two forms: phosphorylated (up to 60% of the stores) or free (up to 40% of the stores). A total of 95% of the creatine is stored in skeletal muscle, and in particular in fast twitch type II fibers [22]. Cells use phosphocreatine as donor of phosphate to produce adenosine triphosphate useful as energy substrate for the contraction of skeletal muscle [22]. A 2013 NCAA survey study reported a 14% rate of use among student athletes, especially wrestlers [23]. A 2003 meta-analysis of 22 studies showed that although creatine supplementation was more effective on predominantly anaerobic intermittent exercise, there was some evidence of its positive effects also on endurance activities [24]. However, the ergogenic potential on aerobic endurance exercise diminished as the duration of the activity increased over 150 seconds, maybe due to a change in substrate utilization. A more recent meta-analysis of 60 randomized controlled trials on the effects of creatine on lower limb strength performance showed that a supplementation is effective in lower limb strength performance for exercise with a duration of less than 3 min, independent of population characteristic, training protocols, and supplementary doses and duration [25]. Creatine ingestion increases the total creatine content in human muscle by approximately 15-20 %; such increase can be achieved by ingestion of 20 g per day for 4-5 days, but also by ingestion of 3 g per day over a period of one month [15]. Long-term creatine supplementation (e.g. 4-12 weeks) in combination with training, appears to increase muscle mass and strength as a result of an improved ability to perform high-intensity exercise via increased creatine phosphate availability [15;26]. Collectively, in spite of a few controversial results [27-29], creatine supplementation combined with resistance training seems able to amplify performance enhancement on maximum and endurance strength as well muscle hypertrophy. On the base of these data, the INSS in a position statement of the 2007, declared that the use of creatine as a nutritional supplement within established guidelines is safe, effective to improve anaerobic capacity, strength, and lean body mass in conjunction with training [26].

Similarly, EFSA in weighing the evidence from short and long-term creatine supplementation studies adopted a favorable opinion about the role of creatine in increasing physical performance during short-term, high intensity, repeated exercise bouts. In order to obtain the claimed effect, 3 g of creatine should be consumed daily by adults performing high-intensity exercise. On the contrary, EFSA rejected the claims about the endurance capacity and endurance performance since a cause and effect relationship has not been yet established [15].

Creatine supplementation has been also shown to improve recovery from injury, muscle damage and oxidative stress induced by exercise. Bassit et al. [30] observed a decrease in several markers of muscle damage in a pilot study performed in a group of 4 athletes supplemented with 20 g/day plus 50 g maltodextrin during a 5-day period prior to an iron man competition. Cooke et al. [31] observed a positive effect of a prior (0.3 g/day/ kg body weight) loading and a post maintenance protocol (0.1 g/day/ kg body weight) to attenuate the loss of strength and muscle damage after an acute supramaximal eccentric resistance training session in young males. Rahimi [32] documented a significant increase in athletic performance, and a significant reduction in oxidative stress, induced by a single bout of resistance exercise, following 7-day supplementation of creatine monohydrate (20 g/day) in a group of male athletes. The above investigations indicate that creatine supplementation can attenuate muscle damage induced by a prolonged endurance training session and act as antioxidant agent. However, further studies should be performed in order to come to any conclusions.

Role of caffeine and caffeine-energy drink on physical performance

Caffeine is a fat-soluble molecule naturally present in many foods and drinks (i.e. coffee, tea, chocolate) and added to many energy drinks and sports food. The content varies widely in relation to the quality and variety of foods (from 5-10 mg for 60 g of chocolate, up to 200 mg for a cup of Expresso coffee) [33]. Typically, caffeine-containing energy drinks contain from 25 to 250 mg of caffeine in various forms, from alkaloid caffeine to caffeine-containing plant extracts [33]. Caffeine is the most used psychoactive substance in the world; it is estimated that the daily intake is around 200 mg. Caffeine intake from foods such as soft drinks, chocolate, gum and candy, in child and adolescents may reach up to 16 mg/day for children aged 7-8 years old, 24 mg/day for those 9-10 years old, and up to 37.4 mg/day for adolescents/young adults (18 years old) [34]. Most caffeine intake among young comes from soda. Once absorbed, caffeine is metabolized at hepatic level to paraxanthine (84%), theobromine (12%) and theophylline (4%); these substances maintain in part the biological activities of caffeine [33]. Recognized as a stimulant, caffeine is used mainly to improve cognitive function and physical performance. For this reason, it has long been considered a doping substance and banned from sports competition until 2004 [33]. Actually, caffeine is commonly used by athletes because of its reported ergogenic effects. Three seem the mechanisms by which caffeine may improve physical performance: 1) by increasing the mobilization of intracellular calcium; 2) by increasing free fatty acid oxidation; 3) by serving as an adenosine receptor antagonist in the central nervous system. This latter, seems the more plausible mechanism involved in the ergogenic effect as recently documented [35-36]. The link of caffeine to A1 receptor generates an increase in intracellular levels of cyclic AMP, with subsequent increase of the concentration of cytoplasmic calcium and activation of the pump Na^+ / K^+. Through this mechanism, caffeine may modulate central fatigue and influence ratings of perceived exertion, perceived pain and levels of vigor, all of which may lead to performance improvements [33;35-36]. Most of the ergogenic effects have been observed following the administration of low caffeine doses (3 mg/ kg body weight, about 200 mg for a 70 kg individual). Acute doses higher than 9 mg/kg did not show any performance gain, and in many cases, the administration of high doses induced several adverse effects such as palpitations, headache, weakness, shivers, anxiety [33;37].

In a recent review, the analysis of 24 studies showed that the administration of 2-5 mg/kg caffeine, prior to performance-based exercise, enhanced sport performances by increasing exercise duration and by improving completion time at about 3.6% [38]. The results are in accordance with the findings reviewed by Ganio et al. [37] that documented an improvement (about 3.2%) of athletic performance following the administration of similar doses of caffeine. Conversely, in a sedentary state, caffeine has shown to impair insulin action and, thus, glycemic regulation. A position stand from the ISSN summarized the effects of caffeine on exercise performance [37]. Briefly, caffeine is effective for enhancing sport performance in trained athletes when consumed in low-to-moderate dosages (about 3-6 mg/kg body weight), while no effect has been observed for high dosages (≥ 9 mg/kg body weight). Caffeine is ergogenic for sustained maximal endurance exercise, especially for time-trial performance and for enhancing vigilance during bouts of extended exhaustive exercise. Moreover, a supplementation with caffeine is beneficial for high-intensity exercise especially for those that are categorized by intermittent activity within a period of prolonged duration. Instead, it remains unclear the effects of caffeine on diuresis during exercise and on strength-power performance [37].

The most way of consuming caffeine among athletes is through energy drinks. It is important to consider that these products are extremely popular not only in adults but also in adolescents. The analysis of the recent literature reveals that frequent or excessive intake of caloric sport drinks and caffeine-energy drinks can induce tachycardia, cardiac dysrhythmias, hypertension and heart failure and substantially increase the risk of overweight or obesity in children and adolescents [39]. Regarding the potential ergogenic effects of caffeine-containing energy drinks, the analysis of the 7 studies reported in literature reviewed by Ganio et al. [37] confirmed the enhance performance. However, the results were highly variables depending on the beverages consumed, the range of caffeine doses administered, the timing of ingestion as well as the type, intensity and duration of physical activity performed. It is documented that the intake of a sugar-free caffeine-containing energy drink (3 mg/kg) is able to enhance sport performances in soccer, rugby, basketball and badminton players. The improvements were related to jump height, power output, distance covered, running speed, and the number of sprints performed within a game [40-45]. In a recent position statement, the ISNN concluded that the consumption of energy drinks (containing approximately 2 mg/kg body weight of caffeine) 45 to 60 minutes prior to anaerobic/resistance exercise may improve upper- and lower- body total lifting volume. However, no effect on repeated high intensity sprint exercise or on agility performance was observed [46]. On the contrary, the same energy drinks consumed 10 to 40 minutes prior to aerobic exercise improved cycling and running performance in both trained cyclists and recreationally active participants [46].

Similarly, EFSA in weighing the evidence from short and long-term caffeine supplementation adopted a favorable opinion about the role of caffeine to increase endurance performance and endurance capacity. The Panel considers that in order to obtain the claimed effect, caffeine should be consumed at doses of 3 mg/kg body weight one hour prior to exercise from adults performing endurance exercise. Moreover, the Panel concluded that a cause and effect relationship has been also established between the consumption of caffeine and a reduction in the rated perceived exertion/effort during exercise. In order to obtain this effect, caffeine should be consumed at doses of 4 mg/kg body weight one hour prior to exercise [17]. On the contrary, EFSA rejected the claim related to an increase in physical performance during short-term high-intensity exercise since a cause and effect relationship has not been yet established [17].

It is important to highlight that the potential ergogenic effects of caffeine and other stimulant substances contained in energy drinks on children and adolescents have not been deeply investigated. Few and recent studies reported an improvement of physical performance in junior tennis players [47] and adolescent basketball players [42]. Although the US Food and Drug Administration limits caffeine content in soft drinks, which are categorized as food, there is no such regulation for energy drinks, which are classified as dietary supplements. For most children, adolescents, and young adults, safe levels of caffeine consumption have not been established.

Role of beta-hydroxy-beta-methylbutyrate on sport performance

Beta-hydroxy-beta-methylbutyrate (HMB) is a metabolite of the branched-chain amino acid leucine and its keto acid alpha-ketoisocaproate (KIC). A 2013 National Collegiate Athletic Association (NCAA) survey study reported a 0.2% rate of use among student athletes [23]. HMB is believed to attenuate protein breakdown after workouts and it is extensively used by athletes and bodybuilders in order to increase strength, muscle mass and exercise performance. Three of the possible advocated mechanisms involved in the improvement of sport performance are: 1) enhancement of sarcolemmal integrity via cytosolic cholesterol, 2) inhibition of protein degradation via proteasomes, and 3) increased protein synthesis via the mammalian target of rapamycin (mTOR) pathway [48]. Recent studies suggested additional possible mechanisms for its physiological effects. These include decreased cell apoptosis and enhanced cell survival, increased proliferation, differentiation and fusion via the mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) and PI3K/Akt pathways, and enhanced IGF-I transcription [49].

The effect of HMB supplementation on sport performance has been studied in a variety of anaerobic and aerobic training conditions [50]. However, it is difficult to compare results due to different dosing schedules and amount of HMB, training levels of participants and performance outcomes. Several studies supported the efficacy of HMB supplementation to improve sport performance by enhancing recovery [51-52], lean body mass [51;53], strength [54], power [55], and aerobic performance [56] in athletes. However, other studies documented a more evident improvement in untrained subjects with respect to athletes [57-60]. For example, Palisin and Stacy [60] reported that HMB supplementation determined gains in strength and lean body mass in patients with wasting syndromes. Rowlands and Thomson [59] analyzed the effectiveness of HMB supplementation (range 1.5-6.0 g/day) on strength, body composition, and muscle damage in trained and untrained young men. The results documented a trivial effect of HMB supplementation on all muscle strength outcomes in trained men, while reported benefits on lower-body and average legs strength in untrained men [59]. In a recent systematic review, Molfino and coworkers concluded that the usual dose of 3 g/day of HBM may be routinely recommended to maintain or improve muscle mass and function in young and elderly untrained subjects and in those affected by chronic diseases [57].

It is against this background, therefore, that official statements and positions from scientific organizations and institutions is still controversial. A position stand from the INSS provided recommendations on the optimization of the effects of HBM on body composition, strength, power, and aerobic performance across varying levels of age, sex, and training status [48]. Briefly, the ISSN stated that HMB can be used to enhance recovery by attenuating exercise induced skeletal muscle damage in trained and untrained populations, and that a supplementation appears to be most effective when performed for 2 weeks prior to an exercise bout. Moreover, a daily supplementation (38 mg/kg of body mass) should enhance skeletal muscle hypertrophy, strength, and power in both untrained and trained subjects when the appropriate exercise prescription is utilized. Lastly, HMB has been demonstrated to increase lean body mass and functionality in elderly, sedentary populations and, in conjunction with a structured exercise program, may result in greater declines in fat mass [48].

On the other hand, EFSA ruled negatively about the capacity of HMB, alone or in combination with KIC, to reduce muscle tissue damage during exercise, to increase lean body mass, muscle strength, endurance performance, skeletal muscle tissue repair and faster recovery from muscle fatigue after exercise, since a cause and effect relationship has not been established [61]. In fact, data provided are still limited, inconsistent, and no evidence for a mechanism by which HMB could exert the claimed effect was provided.

For all these reasons, HMB is included in the list of "apparently effective" substances reported in **Table 4**.

Role of dietary antioxidants on sport performance

During physical activity, metabolism, muscle activity and oxygen utilization tend to increase bringing to the generation of reactive oxygen and nitrogen species that can alter cell structure and function, and contribute to muscle damage, immune dysfunction, tiredness and fatigue. Antioxidant supplements may benefit directly or indirectly exercise performance [62]. Direct effects could involve the reduction of muscle fatigue at the level of contractile function, while indirect effects could include enhancement of training, reduction of physiological stressor, or improvement in the ability to recover from training. However, there are many doubts regarding the advantages and disadvantages of using antioxidants to improve physical performance. The effects of a wide range of dietary antioxidants on sport performance will be summarized.

*Vitamin C -*Vitamin C is a water-soluble vitamin that plays an important role in the collagen and cortisol synthesis and in the scavenger of free radicals. Therefore, a supplementation with vitamin C could enhance athletic performance counteracting ROS production, reducing muscle damage and delaying-onset muscle soreness. The role of a vitamin C supplementation on sport performance has been investigated in many trials [63-65]. The majority of studies have attempted to examine the longer term effects of vitamin C supplementation instead of an acute effect. While the earliest studies appeared promising, recent and more rigorous trials do not seem to support the ergogenic role of vitamin C [66-68]. A recent review by Braakhuis [64] showed that high doses of vitamin C (>1 g/day) seem to impair sport performance by reducing training-induced adaptations in athletes, while physiological doses (at about 200 mg/day) have shown to be sufficient to induce a reduction of oxidative stress and provide beneficial effects on athletes without impairing training adaptations. The most important beneficial effects observed in exercise training are the attenuation of exercise-induced bronchoconstriction and asthma, the decrease in muscle damage as well as the maintenance of the normal functions of immune system during and after extreme physical exercise. This latter function was also recognized by EFSA that authorized the claim *"Contributes to maintain the normal function of the immune system during and after intense physical exercise"* for concentrations of vitamin C of 200 mg/day in addition to the usual diet [16].

In conclusion, considering current data, administration of non-physiological doses of vitamin C in healthy athletes seems not to be suggested because of the possibility to impair adaptation to regular exercise.

Vitamin E- Vitamin E is a well recognized fat-soluble vitamin with antioxidant activity capable to protect cell from oxidative damage thus, it should be able to defeat an oxidative stress condition by improving physical performance. However, data from human intervention studies are quite controversial. A recent review summarized the main results deriving from acute and chronic vitamin E supplementation in different sport performances [69]. Only one out of 12 studies was an acute study [70]. The intake of a single dose of carbohydrate-protein beverage fortified with vitamin E (20 mg during exercise, and 133 mg post exercise) seemed to confer performance benefits and attenuate post-exercise muscle damage in athletes [70]. On the contrary, studies on chronic intake of vitamin E (100-300 mg/day for 1-6 months) showed an impairment of physical performance rather than an ergogenic effect [69]. No effect was observed on performance during standard exercise tests and cardiac respiratory fitness tests, while it was documented a feeble effect in the modulation of muscle contraction and attenuation of muscle damage. Altitude showed to increase oxidative stress and reduce red blood cell deformability in climbers [71-72]. A supplementation with 300 mg/day vitamin E for 4 weeks at altitude of 5000 m. showed to offset the impairment by maintaining red blood cells deformability in climbers [71-72]. However, this evidence was observed only in two old studies performed in subjects exposed to extreme conditions and merits further investigations.

In conclusion, the evidence available suggests that the daily intake of doses of vitamin E higher than RDA levels (15 mg/day) should be avoided by athletes. More studies in humans are need to clarify the effects of a vitamin E supplementation on sport performance in athletes.

Glutathione and N-acetyl cysteine - Glutathione (GSH) is a tripeptide synthesized from cysteine, glycine and glutamate. It is an endogenous antioxidant that acts as scavenger against ROS and as cofactor of phase II antioxidant enzymes such as glutathione peroxidase and glutathione S-transferase. Moreover, GSH plays a crucial role in recycling several antioxidants, including vitamin C and vitamin E radicals [62;69]. The biosynthesis of GHS, by way of the gamma-glutamyl cycle, is important for maintaining its homeostasis and normal redox status. N-acetyl cysteine (NAC), a water soluble precursor of GSH, is one of the antioxidant supplements commonly used in exercise training by several athletes. The effects of NAC supplementation against oxidative stress in athletes and its capability to improve sport performance has been investigated in some small acute and chronic studies [69].

In an acute study, intravenous infusion of NAC (125 mg/kg/h for 15 min and then at 25 mg/kg/h for 20 min before and throughout exercise) was performed to evaluate the effect on fatigue during prolonged, submaximal exercise in endurance athletes. The results showed that NAC administration improved performance in well-trained individuals, with enhanced muscle cysteine and GSH availability a likely mechanism [73]. In another acute study on eight well-trained subjects the authors showed, using the same experimental conditions (intravenous NAC infusion of 125 mg/kg/h for 15 min and then at 25 mg/kg/h for 20 min before and throughout exercise), an attenuation in muscle fatigue and reduction of oxidative stress [74]. A significant reduction in the respiratory muscle fatigue was also observed following an acute oral dose of NAC (1.800 mg, 45 min prior to a 30 min discontinuous exercise) in a group of eight subjects during a heavy exercise [74].

Regarding the impact of NAC chronic supplementation, the results are controversial. Seven-day administration of 2400 mg of NAC decreased muscle fatigue in a group of 9 untrained healthy men following a maximal exercise [75]. In a more recent study, a 9-day oral NAC supplementation (1200 mg/day) improved cycling performance via an improved redox balance and promoted adaptive processes in a group of 10 well-trained athletes undergoing strenuous physical training [76]. On the contrary, a 7-day oral NAC supplementation (100 mg/kg body weight) in nine well-trained male cyclists showed to alter substrate metabolism and muscle fibre type recruitment during high-intensity interval exercise with detrimental effect on time-trial performance [76].

In conclusion, the ergogenic role of NAC is inconsistent and quite controversial. Most of the positive observations were showed in very small groups of subjects (max 10 athletes) and should be corroborated on a large scale. Moreover, recent findings on cellular pathways report that NAC supplementation may impair intrinsic responses and recovery of muscles [61,77]. Thus, further researches are necessary.

Ubiquinones - Ubiquinones are lipid-soluble antioxidants able to prevent lipid peroxidation and play an important role in recycling vitamin E [62]. Coenzyme Q10 (CoQ-10) represents the most predominant form of uquinones in humans. Some studies documented a positive relationship between exercise capacity and CoQ-10 plasma concentration in physically active males. Diaz-Castro et al. reported that a 3-day CoQ-10 supplementations (5 capsules of 30 mg of CoQ10) decreased oxidative stress and muscle damage in a group of runners before a constant run (50 km) that combined several degrees of high effort (mountain run and ultra-endurance), in permanent climbing [79]. In another study, a 12-day CoQ-10 supplementation (300 mg/day CoQ10) reduced oxidative stress markers and improved physical performance of young swimmers by increasing maximal treadmill time [80]. Two older intervention studies reported that 30 days of supplementation with 100 mg/day of CoQ-10 was able to increase endurance capacity and/or endurance performance in sedentary and athletes [81-82]. On the contrary, some studies failed to demonstrate an ergogenic property for CoQ-10, while other showed an impaired performance in high-intensity and endurance tests after supplementation with CoQ-10 [83].

In conclusion, current data regarding supplementation with CoQ-10 during exercise training are inconsistent. EFSA rejected the claims about the role of CoQ-10 in the improvement of physical endurance and performance since a cause and effect relationship has not been established [84].

Lipoic acids - α-Lipoic acid is an endogenous thiol and co-factor of α-dehydrogenase complexes. In cells, lipoic acid is reduced to dihydro-lipoic acid (DHLA), an important agent in recycling vitamin C during oxidative stress [85]. Supplementation with α-lipoic acid enhances muscle phosphocreatine levels, muscle total creatine concentrations, and consequently has a potential enhancing effect on short-term exercise [83]. However, its effects on exercise performance are unknown. A recent study performed on a group of sixteen healthy young males reported that the intake of α-lipoic acid (1200 mg daily for 10 days prior to exercise) was able to reduce oxidative stress, enhance erythropoietin release and reduce muscle damage after running eccentric exercise [86]. Zembron-Lacny and coworkers documented that α-lipoic acid supplementation (600 mg/day, for 8 days) was able to modulate a pro-antioxidant response to the muscle-damaging exercise in trained men [87].

In conclusion, there are insufficient data to document the role of α-lipoic acid supplementation in physical performance.

Polyphenols and polyphenol-rich foods - Polyphenols are a big family of bioactive compounds widely distributed in whole plant foods. Despite their rapid and low absorption in human body, these compounds have potent antioxidant properties and are involved in the modulation of several important cell signaling pathways. Numerous *in vitro* and *in vivo* studies documented the capacity of polyphenols, in a variety of forms and doses, to positively affect markers of oxidative stress [88]. In this regard, recent studies performed in our laboratories showed that the consumption of polyphenol-rich foods such as blueberries counteracted endothelial dysfunction and reduced DNA oxidative damage in healthy subjects and in those with cardiovascular risk factors [89-91]. However, the role of polyphenols and polyphenol-rich foods on physical performance has not been deeply investigated. Chang et al. [92] reported that consuming a high-polyphenol diet (200 g/day of purple sweet potato leaves) for 7 days can modulate antioxidant status and decrease exercise-induced oxidative damage and pro-inflammatory cytokine secretion in healthy untrained young men after a running exercise. McAnulty et al. [93] showed that the administration of 150 g/day blueberries for 6 weeks, and a portion of 375 g of blueberry, 1 h prior to 2.5 h of running at about 72% maximal oxygen consumption, significantly decreased serum levels of free radicals in athletes in a hot environment. Lafay et al. [94] documented that a 30-day supplementation with 400 mg/day of a grape extract, containing oligomeric proanthcyanidins, enhanced physical performance in elite male athletes during physical exercise. A recent meta-analysis of 11 different studies on the role of quercetin supplementation on endurance performance showed that, although an improvement of endurance exercise performance and endurance exercise capacity was observed following supplementation (median dose 1000 mg/day), the changes were not significantly different from placebo [95]. Recently, Yarahmadi et al. [96] reported that 6-week supplementation with anthocyanin pills (100 mg/day) was able to improve some indices of exercise performance in a group of athletes.

Concerning the use of polyphenol-rich juice (including pomegranate, chokeberry and cherry juice) as supplements in exercise studies, the evidence cannot support the role of these products in the improvement of endurance performance [69].

An increasing interest is rising towards the effects of polyphenols and polyphenol-rich foods in the context of muscle damage and performance recovery after muscle micro-damage. In comparison to endurance performance studies, trials on this topic seem more promising. For example, Pilaczynska-Szczesniak and colleagues reported that the consumption of 150 mL/day of chokeberry juice (providing 34 mg of anthocyanins) for 30 days, was able to limits the exercise-induced oxidative damage by enhancing the endogenous antioxidant defense system [97]. Bowttel et al. [98] showed that the consumption of a cherry juice (60 mL/day containing 300 mg of anthocyanins), for 7 day before and 48 h after intensive exercise, improved the recovery of isometric muscle strength and attenuated oxidative damage, induced by the damaging exercise, in a group of 10 well-trained male overnight-fasted athletes. Trombold et al. [99] documented that a 7-day supplementation with pomegranate juice (providing approximatively 200 mg of anthocyanins and 60 mg of ellagic acid) attenuated weakness and reduced soreness of the elbow flexor but not of knee extensor muscles in a group of resistance trained men after eccentric exercise.

In conclusion, polyphenols can have beneficial effects on sport performance by decreasing oxidative stress; these effects can be obtained by introducing an amount of polyphenols easily reached through the diet (e.g. consumption of five or more servings of fruit and vegetables) without the need of specific ergogenic products. However, their role in the modulation of endurance performance is not clearly understood and should be further investigated. Preliminary evidence suggest to address the research on recovery from muscle micro-damage in order to gain better insight.

Other substances

In addition to the supplements previously described that showed some positive ergogenic effect, there are several substances that lack scientific rationale or have been clearly demonstrated to be ineffective in promoting an ergogenic effect. This is, for example, the case of glutamine and isoflavones.

Glutamine - L-glutamine, the most abundant non-essential amino acid in the body, has shown to increase cell volume, stimulate protein and glycogen synthesis [100-101]. Theoretically, glutamine supplementation should increase muscle mass and enhance gains in strength during training. However, there is no compelling evidence to support l-glutamine supplementation as a potential ergogenic product in terms of increasing lean body mass, muscular performance or repair skeletal muscle tissue in adults performing strenuous exercise [102].

Isoflavones - Isoflavones are non-steroidal phytoestrogens that showed promising results in preventing declines in bone mass in post-menopausal women [103]. Recently, it has been theorized that two isoflavone exctracts (ipriflavone and methoxyisoflavone) can increase strength and muscle mass during resistance-training. Despite these potential benefits, no research has supported these claims in human models. Wilborn et al. [104] showed that 8-week supplementation (800 mg/day of methoxyisoflavone) failed to affect body composition or training adaptations, influence the anabolic/catabolic hormone status or general markers of catabolism in resistance-trained males.

HEALTH RISKS

Few considerations about risks related to the intake of sport supplements are needed.

It is self evident that any medical condition that may contraindicate the use of specific substances must be taken into consideration when deciding to take supplements. Furthermore, athletes and sport practitioners should have clear in mind that dietary supplements should not be used to justify poor food habits. Many athletes, in fact, have a low level of nutritional knowledge and no access to qualified professionals for nutritional counseling. Furthermore, many supplements, such as vitamins and minerals, are considered completely safe being part of the habitual diet, while very high intake for a long time could have negative effects. For example, a Norwegian study reported that high dosages of Vitamins C and E (1000 mg vitamin C and 235 mg of vitamin E (alpha-tocopherol) per 10 weeks) inhibited the adaptation to strength training in young, healthy volunteers [105].

The daily vitamin and mineral intake through the diet and the amount consumed with common fortified foods, such as cereals, drinks and yoghurts should also be taken into consideration. Most public institutions involved in nutrition determined tolerable Upper Levels or Safe Upper Levels of intake for vitamins and minerals in order to reduce the risk of overconsumption. However, these levels derive generally from few data and lack of consideration about individual variability and sensitivity.

The interaction between supplements is another aspect not always adequately considered; while some compounds work in synergy, others may interact to provide negative outcomes. For all these reasons, caution should be exercised.

In addition, there are also health risks associated with poor manufacturing practice and with the presence of contaminants. Notwithstanding efforts to counteract this problem, some preparations for athletes may be contamined with harmful or banned substances. To address this concern, the Food and Drug Administration issued rules requiring manufacturers to follow "current good manufacturing practices" and to ensure that dietary supplements are produced in a "quality manner, do not contain contaminants or impurities, and are adequately labeled" [106].

Finally, it should be remarked that the effects of supplement use on growth and development of children and adolescents remain unclear and thus, the use of supplements by this population should be always discouraged.

CONCLUSIONS

In conclusion, nutritional supplements advertised as ergogenic substances are highly accessible and commonly used by athletes at all levels. However, it is extremely important to underline that sport supplements are not for everyone and oversight of qualified specialists is needed to suggest whether and how to use them. This aspect is particularly critical when considering young athletes who are highly vulnerable to pressures from the media and the prospect of playing sport at increasingly elite levels. Despite the efforts of some scientific and sporting organizations to educate professional as well as amateur athletes about supplement efficacy, safety and legality, much remains to do in order to provide as much accurate information as possible. In fact, most of these athletes take supplements and stimulants available online, believing to attenuate fatigue and increase muscle mass and sport performance without knowing the potential health risks of a wrong supplementation. The level of scientific evidence remains the most important approach to identify the effectiveness and safety of each product, and the research has the important role to enforce scientific substantiation proving a cause and effect relationship. Companies should develop scientifically based products by supporting applied research, market the results of studies and provide products' dosage instructions and other directions for use to help consumers in making informed decisions.

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Table 1: Intake of ergogenic substances and supplements in a group of individuals attending gyms (n=451).

Substance	% total	% female	% male
Vitamins	53.4	53.1	54.6
Weight loss supplements	9.5	10.5	7.4
Protein and amino acids derivates	12.4	7.8	19.6
Diuretics	4.0	4.7	3.0
Stimulants	17.8	20.7	13.5
Anti-infiammatories	70.1	78.9	55.8
Sedatives	8.3	8.6	8.0
Erythropoietin	1.0	0.4	1.8
Anabolic agents	0.7	0.4	1.2

Table adapted from Leone & Pesce [9].

Table 2: Supplements' function according to athletes

Objectives	Substances
Muscle growth and repair	Protein powder and hydrolysate, amino acids and essential amino acids, β-hydroxy β-methylbutyrate
Fat reduction	Pyruvate, caffeine, carnitine
Exercise metabolism	Carbohydrate, caffeine, bicarbonate, creatine
Promoting recovery	Whole protein powders, protein isolates and hydrosylates, protein-carhohydrate bars and drinks, ginseng
General health	Vitamins, minerals, evening primrose oil
Immune function	Echinacea, antioxidants, zinc, lycopene
Central nervous system stimulation	Taurine, caffeine, guarana
Replacement of meal	Liquid meals, sport bars, carbohydrate gels
Fluid and electrolytes	Sports drinks, electrolyte supplements

Table adapted from Maughan et al. [10].

Table 3: Factors to consider when assessing a research paper on sport supplements

Factors	Considerations
Participants	Are they similar to the athletes/sport practitioners the supplement is suggested to? Are they comparable for age, gender and training status?
Type of performance test	Is the test valid and reliable?
Control of the study	Is the study well controlled? Does it account for diet, training and sleep?
Study design	Is the study placebo-controlled and double blinded? Was the statistical power correctly calculated? Is the study acute or chronic?
Supplement	Have the active components been analyzed and quantified? Has the supplement been tested for contaminants, particularly banned substances?
Funding source	Has funding source been correctly declared?

Table adapted from Braun et al. [12].

Table 4: Categorization of some sport supplements based on available literature

	Sport foods	Performance enhancement supplements	Muscle building and repair supplements
Apparently effective	Carbohydrate or protein based drinks, powders, bars Carbohydrate-electrolite based drinks, powders, bars	Caffeine Creatine Sodium bicarbonate Sodium citrate	
Possibly effective		Amino acids Essential amino acids Branched chain amino acids β-hydroxy β-methylbutyrate (HMB)	Branched chain amino acids Essential amino acids β-hydroxy β-methylbutyrate (HMB) Leucine
Too early to tell		Medium chain triglycerides	α -ketoglutarate
Apparently ineffective		Glutamine Ribose Inosine Chromium L-carnitine	Glutamine Boron Chromium Conjugated linoleic acids Isoflavones

Table adapted from Kreider et al. [11].

Table 5: EFSA panel scientific opinion on the substantiation of health claims related to some supplements and physical performance

Nutrient/substance	Claim	Condition of use of the claim	Health relationship	EFSA opinion reference
Carbohydrate-electrolite solutions	Carbohydrate-electrolyte solutions contribute to the maintenance of endurance performance during prolonged endurance exercise	In order to bear the claim carbohydrate-electrolyte solutions should contain 80 350 kcal/L from carbohydrates, and at least 75 % of the energy should be derived from carbohydrates which induce a high glycaemic response, such as glucose, glucose polymers and sucrose. In addition, these beverages should contain between 20 mmol/L (460 mg/L) and 50 mmol/L (1,150 mg/L) of sodium, and have an osmolality between 200-330 mOsm/kg water	Maintenance of endurance performance	[13]
Carbohydrate-electrolyte solutions	Carbohydrate-electrolyte solutions enhance the absorption of water during physical exercise	In order to bear the claim carbohydrate-electrolyte solutions should contain 80 350 kcal/L from carbohydrates, and at least 75 % of the energy should be derived from carbohydrates which induce a high glycaemic response, such as glucose, glucose polymers and sucrose. In addition, these beverages should contain between 20 mmol/L (460 mg/L) and 50 mmol/L (1,150 mg/L) of sodium,	Enhancement of water absorption during exercise	[13]

		and have an osmolality between 200-330 mOsm/kg water		
Carbohydrates	Carbohydrates contribute to the recovery of normal muscle function (contraction) after highly intensive and/or long-lasting physical exercise leading to muscle fatigue and the depletion of glycogen stores in skeletal muscle	The claim may be used only for food which provides carbohydrates which are metabolized by humans (excluding polyols). Effect is obtained with the consumption of carbohydrates, from all sources, at a total intake of 4 g per kg body weight, at doses, within the first 4 hours and no later than 6 hours, following highly intensive and/or long-lasting physical exercise leading to muscle fatigue and the depletion of glycogen stores in skeletal muscle. The claim may be used only for foods intended for adults who have performed highly intensive and/or long-lasting physical exercise leading to muscle fatigue and the depletion of glycogen stores in skeletal muscle		[14]
Creatine	Creatine increases physical performance in successive bursts of short-term, high	The claim may be used only for food which provides a daily intake of 3 g of creatine. In order to bear the claim information shall be	Increase in physical performance during short-term, high intensity, repeated	[15]

	intensity exercise	given to the consumer that the beneficial effect is obtained with a daily intake of 3 g of creatine. The claim may be used only for foods targeting adults performing high intensity exercise	exercise bouts	
Vitamin C	Vitamin C contributes to maintain the normal function of the immune system during and after intense physical exercise	The claim may be used only for food which provides a daily intake of 200 mg vitamin C. In order to bear the claim information shall be given to the consumer that the beneficial effect is obtained with a daily intake of 200 mg in addition to the recommended daily intake of vitamin C	Function of the immune system during and after extreme physical exercise	[16]
Caffeine	Caffeine contributes to an increase in endurance performance	In order to obtain the claimed effect, caffeine should be consumed at doses of 3 mg/kg body weight one hour prior to exercise. The target population is adults performing endurance exercise.	Increase in physical performance during short-term endurance activities	[17]
Caffeine	Caffeine contributes to an increase in endurance capacity	In order to obtain the claimed effect, caffeine should be consumed at doses of 3 mg/kg body weight one hour prior to exercise. The target population is adults performing endurance	Supports exercise performance (reduction in perceived exertion, improve time to exhaustion and exercise capacity)	[17]

		exercise.		
Caffeine	Caffeine contributes to a reduction in the rated perceived exertion/effort during exercise	In order to obtain the claimed effect, caffeine should be consumed at doses of 4 mg/kg body weight one hour prior to exercise. The target population is adults performing endurance exercise.	Supports exercise performance (reduction in perceived exertion, improve time to exhaustion and exercise capacity) and reduces perception of effort	[17]