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Health and career risks surrounding consumption of dietary supplements

Ciências da Nutrição

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Declaro para os devidos efeitos ter atuado com integridade na elaboração deste Trabalho de Projeto, atesto a originalidade do trabalho, confirmo que não incorri em plágio e que todas as frases que retirei de textos de outros autores foram devidamente citadas ou redigidas com outras palavras e devidamente referenciadas na bibliografia.

João Nuno Alves do Vale Marques:

Trabalho apresentado à Universidade Fernando Pessoa como parte dos requisitos para obtenção do grau de licenciado em Ciências da Nutrição

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List of Abbreviations, acronyms and initials

DS- Dietary Supplement

EFSA- European Food Safety Authority

WADA- World Anti-doping Authority

CYP- Cytochrome P450

Resumo

Objetivos: Este artigo tem como objetivo identificar a existência de substâncias dopantes ou quantidades perigosas de qualquer outro componente, no rótulo dos suplementos alimentares em questão, e fazer uma declaração sobre possíveis implicações de carreira ou saúde para o consumidor.

Metodologia: Várias marcas que possuíam os suplementos divididos em pré-workout e pós-workout foram analisadas, tendo sido selecionados 40 suplementos alimentares com todos os constituintes descritos. Foi realizada uma análise detalhada dos constituintes dos suplementos alimentares baseando-se exclusivamente na descrição dos mesmos da marca

Resultados: Relativamente à cafeína, o grupo pré-workout demonstrou uma maior média (241±86 mg) do que o grupo pós-workout (183±68 mg), e a dose média mínima foi 226±84 mg enquanto que a dose média máxima foi 242±88 mg. Relativamente à creatina, o grupo pré-workout demonstrou uma menor média (3106±1079 mg) do que o grupo pós-workout (4137±4177 mg), e a dose média mínima foi 3167±1728 mg enquanto que a dose média máxima foi 3917±3643 mg. Quanto ao conteúdo em sal, o grupo pós-workout demonstrou maior média (2155±4486 mg) do que o grupo pré-workout (464±605 mg) e a dose média mínima foi 1635±3930 mg enquanto que a dose média máxima foi 1708± 3926 mg.

Extratos de *Citrus aurantium*, Yohimbe, *Garcinia cambogia* e raiz de Maca foram também encontrados em alguns suplementos.

Conclusões: Vários suplementos alimentares continham ingredientes pouco estudados que quando consumidos em conjunto poderiam causar problemas de saúde graves. Apesar de algumas doses de alguns ingredientes não serem preocupantes, as recomendações de consumo no rótulo poderão conduzir em sobredose. Existe uma grande necessidade de um maior controlo e regulamentações mais estritas para produtores de suplementos alimentares.

Palavras-chave: Suplemento alimentar, ingrediente, doping, implicações de saúde.

Abstract

Aims: This article aims to find out if there are any doping substances, or dangerous amounts of any other component, stated on the labels of the analyzed dietary supplements, while also making a statement regarding possible career and health implications towards the consumer.

Methodology: Several brands which possessed its supplements sorted in pre-workout and post-workout were analyzed, having been selected 40 dietary supplements with all of their ingredients described. Further analysis of the dietary supplements was made, based exclusively on each brands description of their supplement.

Results: Regarding caffeine, the pre-workout group displayed higher mean caffeine (241±86 mg) than the post-workout group (183±68 mg), and the minimal mean dose was 226±84 mg meanwhile the maximal mean dose was 242±88 mg. Concerning creatine, the pre-workout group displayed lower mean creatine (3106±1079 mg) than the post-workout group (4137±4177 mg), and the minimal mean dose was 3167±1728 mg meanwhile the maximal mean dose was 3917±3643 mg. As for the salt content, the post-workout group displayed a much higher mean salt (2155±4486 mg) than the pre-workout group (464±605 mg) and the minimal mean dose was 1635±3930 mg meanwhile the maximal mean dose was 1708±3926 mg.

Citrus aurantium extract, Yohimbe extract, *Garcinia cambogia* extract and Maca root extract were also found in some of the analyzed dietary supplements.

Conclusions: Several dietary supplements had untested ingredients that when paired up could cause severe health issues. Although some ingredient doses were not concerning, consumption recommendations in the label could lead to dosage abuse. There is need for tighter control and regulations for dietary supplement producers.

Keywords: Dietary supplement, ingredient, doping, health concerns.

Introduction

From times immemorial the prospect of increased physical performance attained with relative lower effort always seemed appeasable. An individual who looks to outperform himself or just improve his physic almost always engages towards better nutrition. For the ordinary individual, the need for an upgraded diet most of times relies in changing dietary habits and sizing of portions, but for a professional athlete, sometimes this doesn't suffice. Dietary supplements (DS) were visioned for athletes with increased nutritional needs, which a balanced diet could not accomplish alone, but an ever growing market for these products lures fitness pursuers to these relatively unneeded products(1), and its dangers, every day. The definition of dietary supplement is stated in the Dietary Supplement Health and Education Act of 1994 as a product whose goal is to increase the dietary consumption of an individual, while containing one or more of the following constituents: a vitamin; a mineral; a herb or other botanical; an amino acid; a dietary substance to be used by a human to supplement the diet by increasing the total dietary intake; or combination of any ingredient described above. However, this definition combined with poor regulation of the DS market sometimes clashes with doping authorities.

In Europe, European Food Safety Authority (EFSA) is the main regulatory authority on dietary supplements which regulates vitamin and mineral supplements to ensure the safety of consumers (2), but since dietary supplements are considered as a subcategory of food, their producers are not obliged to provide evidence of product safety and efficacy (1). Subsequently, cross-contamination of doping substances and undeclared doping substances on the product label has become a real health problem for athletes and non-athletes. According to Word Anti-Doping Agency (WADA), which is one of the main bodies attached to detection and prevention of doping in athletes, anti-doping rule violations have gone down approximately 16% between 2013 and 2017(3,4). These numbers are somewhat encouraging and seem to shadow the growing reality of DS with very high contamination rates (5–7), which comprehend a total of about 6.4%-8.8% of all anti-doping rule violations (8). This is backed up by many articles and reports, such as a review article in which the studies who analyzed more than two contaminating substances in several DS, found a contamination rate of 12% to 58%. While most of those who only analyzed one or two

contamination substances in several DS, found contamination rates of 100% (6). Another example is the data reported by the respective national anti-doping organizations of Australia, UK and USA. These were chosen as representatives of the amount of data available nationally. Since 2006 to 2013, Australia and USA had 6.4% and 7.7% of all doping infractions associated with supplement use. Since 2005 until 2013, UK had 8.8% of all doping infractions associated with supplement use (8).

It is also known that DS are sold indiscriminately, so the thought of a large proportion of children and adolescents being exposed on a daily basis to substances, which put great strain in several organs, can become unsettling (5,9). This concern is increased even more due to the competitive nature of sports. Since athletes have a greater chance of taking performance-enhancing drugs when in belief that others are taking them, starting a vicious cycle of prohibited substances(10).

Usually, athletes are aware that consuming performance enhancing drugs is cheating, and they often show anti-doping attitudes (10). WADA also has established a strict policy in which an athlete is always responsible for doping when the control proves positive, be it intentional or non-intentional. However, it is always a delicate matter when there is a doping infraction from the consumption of a DS, which never stated having prohibited substances in its label, and for all that is known, was clean. While this scenario is becoming an increasing reality, a large proportion of athletes do not take counsel on this matter from health professionals as much as they should, instead consulting those closest to them, like team mates or their coach (1,5,10).

Since it has been shown by some articles that there are DS which are contaminated with doping substances, often unstated in their label, this article aims to find out if there are any doping substances, or dangerous amounts of any other component, stated on the labels of the analyzed DS, while also making a statement regarding possible career and health implications towards the consumer.

Methods

50 randomly chosen dietary supplements (DS), currently available for online purchase in their brand’s websites, were evaluated for their constituents. All the DS were related to

some sort of physical exercise and were meant to be taken accordingly. Each individual analysis consisted in research of the DS ingredients as labeled in the official brand website. When performing the research, we found that several DS did not describe appropriately their formulation. In fact, 10 different DS were not analyzed and accounted in this article, since all its constituents were not fully described or the amounts of some components were not stated. After refining both dietary brands and supplements, 40 dietary supplements with the full formula available, were selected and divided into pre-workout and post-workout. This division was solely made according to the website's self-categorizing parameters, meaning that each website according to its makers own judgment, sorted which DS were pre or post-workout. Several brands of DS were used as a way to stand out DS differences between brands. The DS brands were Optimum Nutrition, BSN, Biotech USA, Scitech Nutrition, Gold Nutrition, Cellucor, Nutramino, Applied Nutrition, Muscletech, Prozis. BSN and Nutramino were the only brands which only had pre-workout DS. Since the recommended dose differed in some of the DS, and some DS had two recommended doses, initially, only the minimal recommended dose was considered for all the DS, and later on, maximal dosage was analyzed. For each DS the following categories were made to compare each other: recommended dose, energy, caffeine, creatine, amino acids and derivates, macronutrients and derivates (lipids, protein, carbohydrates, and fiber), vitamins, minerals and derivates, vegetable extracts, and other ingredients. Every category was analyzed in milligrams for the exception of the recommended dose and macro nutrients and derivates, which were described in grams. Every category was then analyzed for banned substances according to WADA's list of prohibited substances, and any dangerous amounts of those substances were noted.

Results

After thorough screening, a total of 40 DS were deemed appropriate for further analysis, given that the full formula was completely described. The DS included in this article belonged to 10 different brands with the number of products within brackets: Optimum Nutrition [3], BSN [1], Biotech USA [4], Scitech Nutrition [7], Gold Nutrition [6], Cellucor [3], Nutramino [1], Applied Nutrition [4], Muscletech [8], Prozis [3]. As it was previously stated, the DS were analyzed dividing them into two groups: pre and post-workout.

In Table 1, the description of all DS constituents is plainly exhibited. Relatively to the amino acids content, the post-workout group displayed higher mean number of amino acids and derivates (6) than the pre-workout group (4). Concerning the vitamin content, the post-workout group displayed a higher mean number of vitamins and derivates (4) than the pre-workout group (2). Regarding vegetable extracts in each group, the pre-workout group displayed a higher mean number of these extracts (3) than the post-workout group (1). Lastly, both pre and post-workout groups had the same mean number of uncategorized ingredients (2).

In table 2 and 3, all of the most relevant constituents were thoroughly screened. Each dose hence stated is often a daily dose, but as recommended often by most brands, some DS are to be ingested before or after training or whenever in need of energy. Only 5 DS from the entire sample displayed an alternative dose, to which a maximal and minimal dose was obtained. Regarding caffeine, the pre-workout group displayed higher mean caffeine dose (241±86 mg) than the post-workout group (183±68 mg), despite having significantly more DS within its group, 19 in comparison to 3 respectively. The minimal mean dose was 226±84 mg and the maximal mean dose was 242±88 mg, being the maximal dose of 380 mg found in supplement number 17. Caffeine doses in some DS could be higher than these figures, seen that Green tea extract and other vegetable extracts were often depicted in the ingredient lists, and withhold varying amounts of caffeine, as such it is not possible to account them in previous analysis. Concerning creatine, the pre-workout group displayed lower mean creatine (3106±1079 mg) than the post-workout group (4137±4177 mg). The minimal mean dose was 3167±1728 mg and the maximal mean dose was 3917±3643 mg, being the maximal dose of 20000 mg found in supplement number 37. As for the salt content, antithetically to what was seen in the caffeine dosage distribution within groups, the post-workout group displayed a much higher mean salt (2155±4486 mg) than the pre-workout group (464±605 mg). The minimal mean dose was 1635±3930 mg and the maximal mean dose was 1708±3926 mg, being the maximal dose of 15000 mg found in supplement number 29.

Other ingredients were not statistically analyzed in Table 2, because only a few DS contained them. However, given their importance, some are described next. *Citrus*

aurantium extract was found in 1 pre-workout DS. The underlying dosage of *Citrus aurantium* extract was of 400 mg, representing the only recommended dose stated by its product. As for the Yohimbe extract, it was only found in 3 pre-workout supplements. The minimal mean dose was 25±5 mg and the maximal mean dose was 32±7 mg. The maximal dose was of 40 mg. *Garcinia cambogia* extract was found in one pre-workout DS with a dose of 10 mg. Maca root extract was found in one pre-workout DS with a dose of 200 mg.

Discussion and Conclusions

During the making of this study one of our main goals was to find doping substances or dangerous amounts of any other substance. It was perceived during the DS analysis that the first goal was not fully achieved. It is thought possible, that doping substances could be masked within the "Vegetable Extracts" or "Other Ingredients" categories in Table 1. Unlike the first category, "Other Ingredients" never showed doping red flags in the literature, and therefore we will focus our analysis to the "Vegetable Extracts". In the pre-workout group of the "Vegetable Extracts" category, *Citrus aurantium* extract, Yohimbe extract, *Garcinia Cambogia* extract and Maca root extract were found. Although the first three extracts stated before are not free from being contaminated by prohibited substances, Maca root extract has been said to have a high risk of contamination by the Australian Sports Anti-Doping Authority and is considered a group D supplement (Level of evidence: Banned or at high risk of contamination with substances that could lead to a positive doping test. Not to be used by athletes) by the Australian Institute of Sport (11). All of these plant extracts were found in the pre-workout DS group. These totalize all of the WADA, U.S. Food and Drugs Administration or EFSA unapproved or shunned constituents found in this study.

Although some might think that contamination is only a doping problem, clinical trials say otherwise. 2 patients were admitted in a hospital after consumption of a botanical DS with severe health issues, due to the contamination of the ingredient plantain with Digitalis lanata Ehrhart. This plant was not stated in the label of the consumed DS (12). In several of the reviewed DS, vegetable compounds were found which didn't state all of its components, due to it being a patented formula, such as the Bioperine compound found in 13% of all DS in this study. Since some vegetable constituents were not evaluated and

remain trade secret, this creates a blockade towards clinical trials of those constituents. In some ways this could help hide contaminants in the DS, creating health risks and severe doping problems. The most serious safety concern relative to contamination of DS is the potential for liver damage (13). One must always use authenticated plants to prevent misplacement or misidentification of herbal components and apply good agricultural practices to avoid most contamination problems (13).

Apart from contamination, vegetable extracts can also play a role in drug efficacy. These extracts can act by inhibiting or augmenting the action of certain drug-metabolizing enzymes, hence vegetable extracts in DS can reduce or prolong the half-life of drugs that depend on those enzymes. Increasing serum drug concentrations to toxic levels or reducing its action, both could lead to devastating outcomes. According to preclinical interactions, *Panax Ginseng*, green tea extract, *Ginkgo Biloba* extract, Grape seed and Yohimbe, inhibits some Cytochrome P450 (CYP) enzymes (14). All of the referred plants and extracts were found in several DS in this study.

Synephrine is the main active compound in *Citrus aurantium* extract. Nowadays synephrine is an ingredient used often in DS formulation related to weight loss (15). There are ingredient associations of synephrine with caffeine, salicyn and ephedrine made to boost the weight loss ability of the DS (16). This is somewhat concerning since high increases in blood pressure are seen when synephrine is taken with caffeine (17). An article also assessed the causal relationship between a patient who recently had an ischemic stroke associated with an ephedra-free dietary supplement containing synephrine and caffeine. This dietary supplement was the only vasoactive medication in the patient's recent medical history, leading to the conclusion that it was the cause of the ischemic stroke. This could be a major setback for dietary supplement companies, since many of their products related to weight-loss contain synephrine and caffeine (18). However some authors mention that no serious illness outcomes have ever been related to consumption of synephrine with caffeine, despite its heavy consumption around the world, in several product formulations, and that synephrine only produces cardiovascular effects at doses up to 100mg (19), also some state that the consumption of synephrine alone does not raise blood pressure (17). In this study only one DS had synephrine, in the form of *Citrus aurantium* extract (400 mg),

but this DS also had 350 mg of caffeine in its ingredients, so this DS could eventually induce some unwanted cardiovascular side effects. Potential drug interactions may also pose a health threat to consumers, even more so because products containing synephrine are targeted not only but also towards obese individuals, as thermogenic weight-loss DS, who are more likely to be taking drugs than normoponderal individuals.

Product information clarity was one of the main setbacks in the realization of this study. Several products did not state their full compositions clearly on their labels. Website ingredient quantities had clear dose mistakes and synephrine was no exception. Some dietary supplements are sold as having synephrine in their composition, which in some cases, is not true. On the other hand, those supplements tend to have an increased amount of caffeine. The real amount of synephrine is often less, and mislead by the amounts stated in the supplement label (16). Perhaps this could be seen as an advantage to consumers, since there is evidence that synephrine could be dangerous on certain situations. It would seem wise to restrict the use of these combined ingredients until solid clinical evidence is at hand.

Yohimbe extract or yohimbine is most often used in DS associated with an increase of physical and sexual performance. Although none of the analyzed products in this article were advertised for sexual related purposes, some were indeed made with the prospect of an increased muscle mass, hence increased physical performance. Therefore 8% of all DS contained Yohimbe extract in their composition.

It is already well know that the DS market is valued in many millions, and Yohimbe extract is becoming a trendy ingredient. In 2017, an article analyzed 80 DS in which 12 had non-allowed pharmacologically active substances that were not reported in the label. 3 of these had yohimbine, despite the yet unclear erectogenic effect and several risks associated to yohimbine use (20). In fact yohimbine is displayed ever more often, since in the 3 year release gap between these two articles yohimbine use in DS doubled from 4% to 8%.

The increased use of this ingredient is most concerning, since by using a DS with Yohimbe bark extract according to its consumption suggestion on the label, consumers have a high probability (79%) of consuming different amounts of Yohimbe than those stated on the

label. Most often, the intake of Yohimbe could vary by a factor of 10, leading to the product not wielding the wanted effects due to low dosage, or getting unwanted side effects related to higher than recommended dosage (21). Lower doses of yohimbine do not translate to any changes in blood pressure nor heart rate in normotensive individuals, whilst at 15-30 mg, increased blood pressure and anxiety could be detected. While taking yohimbine during exercise, mean arterial blood pressure, heart rate, norepinephrine and effort sensation all become significantly increased. In patients taking tricyclic antidepressants, 4 mg three times a day is enough to generate hypertension and other health issues in some mental illnesses. Overdose seems to be achieved around 200 mg or higher (22,23).

Taking these considerations into account, even the lowest amount of Yohimbe found in a DS (20 mg) in this study poses a health threat to normotensive individuals, not even to mention the highest doses found (40 mg) towards individuals taking antidepressants while exercising. It is important to state that most of the DS producers probably know that Yohimbe carries some unwanted side effects, and that is why 2/3 of all DS with Yohimbe in this study stated directly to not exceed the maximum dosage within a 24h period. Only a very small portion of DS in this study stated this warning in their label.

Several studies confirm weight management properties in *Garcinia Cambogia* extract, when supplemented to obese or overweight individuals (24,25). In several clinical trials *G.Cambogia* was deemed safe to use in treatment of obesity, and only caused headaches and mild gastrointestinal adverse effects. However, there were 3 cases of hepatotoxicity related to *G.Cambogia* and there is conflicting evidence as far as lower platelet aggregation (25).

Most negative cases were ruled out due to it being because of a multicomponent DS with interactions that might not be related to *G.Cambogia* (24). Nonetheless, it has been proven that *Garcinia Cambogia* displays inhibitory effects on CYP enzymes, particularly in CYP2B6. This inhibitory property was not displayed due to the hydroxycitric acid in the sample, since this component alone did not display the same inhibitory patterns (26). Hydroxycitric acid is considered to be the active ingredient for weight loss in G.Cambogia

extract. Caution is advised when prescribing drugs that use these enzymes during the metabolism.

Despite the relative safety of this ingredient, there have been several disturbing clinical cases that raise suspicion on its use. A patient was presented with abdominal pain and vomiting caused by hepatitis. After excluding all other causes, an herbal Supplement was concluded to have been the highly likely cause. This supplement was found to be 100% pure *G.Cambogia*, and the patient was taking a daily dose of 2800 mg. After the patient stopped taking the supplement all symptoms subsided, and afterwards reappeared when she began to consume the supplement once again (27). The FDA has reported 23 cases of hepatotoxicity related to consumption of hydroxycitric acid. Due to these setbacks, some say it would be wise to avoid the ingredient completely, as it may cause harm to the user and the results regarding weight lowering properties are scarce (25).

The main reason why Garcinia Cambogia extract was flagged in this study was due to its repetitive association with Sibutramine, which is a known doping substance (28). Several athletes have been issued doping bans after taking a *Garcinia Cambogia* DS that either had sibutramine in their composition or were contaminated by it. Sibutramine is a drug intended for the treatment of obesity, which was withdrawn from Europe and the United States given the potential for several cardiovascular problems (29). Only one DS in this study had *Garcinia Cambogia* in its ingredient list. The daily dose of this ingredient was of 10 mg, which even taken several times a day is far from being considered a dangerous amount. However, if a trace of sibutramine is caught in a doping test, this could mean a several year ban from official competitions and in some scenarios a denied possibility for future re-entry in the sport.

Caffeine is without a doubt a major ingredient in most DS. The fact that 91% of all reviewed pre-workout DS had caffeine says how much the supplement industry relies on this ingredient. While only 16% of the post-workout DS featured caffeine, this is completely understandable, since taking caffeine after exercise does not help with recovery and can lead to increased anxiety (30). On the other hand, taking caffeine before physical trials can lead to beneficial ergogenic effects such as increased strength and sprint outcomes during a short time (31) and lower completion time of the set course. Lower

completion time was seen when mean caffeine doses of 4.9 mg/kg were administered to athletes prior to a short but demanding physical trial (32). Although 4 to 6 mg/kg of caffeine per day seems to have no diuretic adverse consequences in healthy adults consuming caffeine regularly, this may not be the same for an athlete who just consumes caffeine before the trial (33).

Since many athletes already know how beneficial caffeine can be to their performance, some eventually become heavily dependent on this substance. The acute intake of caffeine can increase blood pressure, generate heart arrhythmias and neuroendocrine side effects (33). Due to these known side effects, the limit daily recommended caffeine dose is around 400mg/day in adults used to caffeine consumption (33). However, as in other articles (15,34), this is easily surpassed in many DS in this study, where one dose can reach up to 380 mg. The manufacturers also state that the DS is to be taken whenever the user is in need of energy and/or before training, meaning several times a day for athletes who train more than once in a day. This safety inconsistency was similarly seen in other studies, where some of the supplements evaluated had high doses of caffeine which were recommended for everyday use (32). Furthermore, not every product issued health concerns towards abuse of unreasonable ingestion of their products, considering the high amounts of some ingredients in their DS, such as caffeine (34).

Additionally, there are 85 known drugs which interact with caffeine, 11 of these can result in severe interactions (33).

It seems that by following current caffeine dosage guidelines and recommendations on supplementation, there appears to be no major health consequences regarding caffeine ingestion (31).

Creatine is an amino acid compound naturally found within muscle tissue that fundamentally provides energy by converting ADP to ATP. This ingredient grants massive performance improvements when taken, from increased overall mean power and peak mean power outputs (35) to increased time until exhaustion. This might be why in 2014, the National Collegiate Athletic Association reported a high consumption of creatine in male athletes, reaching almost one third of all the athletes in some sports, such as wrestling,

lacrosse, football, baseball and ice hockey (36). The importance and effectiveness of creatine is well represented in the analyzed DS, since this was the most used ingredient, present in 65% of all DS. Meanwhile, it was not fully understood why DS developers would pair so many of their products with caffeine and creatine (17 DS displayed both), since caffeine consumption during creatine loading can lead to decreased creatine beneficial effects, such as better muscle relaxation time, due to a reduction of the functional capacity of the sarcoplasmic reticulum Ca^{2+}ATPase (31,37).

A normal diet contains about 1-2g/day of creatine, which takes up to 60-80% of creatine stores. Dietary supplementation serves to complement this and give the other 20-40% missing (36). Creatine supplementation should be made within two phases, loading phase and maintenance phase. The loading phase is characterized by a much higher concentration of creatine dosage than the maintenance phase. During the loading phase de first 2 days are the ones with biggest creatine absorption (38). Loading phase consists in consumption of 0.3g/kg per day for 5-7 days, followed by maintenance at 0.03g/kg per day for 4-6 weeks (36,38). Creatine loading increases urinary concentrations of toxic substances which can have a harming effect on kidney function (38), however, also during loading phase Creatine has been found to help maintain a good hydration status due to its initial fluid retention phase (36).

As far as dosage is concerned, in the reviewed DS there is heavy discrepancy between the maximal mean creatine dose (3917 mg) and the maximum dose (20000 mg). If the individual taking the DS with the higher dose weighs 70kg, then he would have the ideal daily dose for the loading phase (0.29 g/kg). But since the loading phase is only to last about 5-7 days, then the individual would have to change to another DS with lower creatine dosage. One might think that the maximal mean creatine dose displayed by all the DS is enough for the maintenance phase, but that would represent a 5 times lower dose (0.006 g/kg) than the one needed (0.03 g/kg). So there seems to be some sort of misinformation as far as creatine dosage in current DS developers.

Regarding creatine safety, 0.3g/kg to 0.8g/kg per day poses no health threats (36), meaning that none of the samples reviewed in this study could harm anyone, if taken as stated in the

label. In general it appears that creatine is a relatively safe and effective substance to integrate in a DS (31,36,38,39).

In any sport, sodium is important for water regulation and fluid balance, as well as good muscle function and nerve cell activity. Sodium also plays an important role in the absorption of nutrients. When sweating heavily, sodium loss can be more than 0.5g and require increased intake (40). However, children and adolescents who represent a big portion in many sports communities, consume between 8-8.6g of salt more than the recommended 5g for their age range. The same increased intakes can be seen in adults. Concerningly, an increased salt intake of 1 g/day increases systolic blood pressure by 0.4 mmHg (41).

These increased salt consumptions can eventually take its toll on a person's body. A high dietary salt intake is associated with increased risk of developing cardiovascular diseases, gastric cancer and kidney disease. There has also been made a link between high dietary salt intake and obesity (40). In general, normotensive individuals tend to be inherently resistant to salt induced hypertension; the same might not be said about hypertensive or salt sensitive individuals (42). However a reduced salt intake results in quick decrease of systolic and diastolic blood pressure (41).

Depending on the level and type of physical exercise, a person might need additional salt intake to compensate for sweat losses. In this study it is understandable for why the vast majority of the salt containing DS where in the post-workout group, since in a pre-workout situation sweat mineral losses have not occurred yet. Since it is understood that sweat losses can vary greatly between exercise types, some DS salt values might be too high for the average gym attendant which naturally already consumes too much dietary salt. In fact, the post-workout mean salt might only be adequate for aerobic athletes who train every day for several hours. One of the most alarming salt values of 15g (supplement number 29) which is representative of 3 times the maximum amount of salt intake for normotensive individuals. This excessive salt value might only be useful for some of the harshest competitions known of, as the Tour de France, where an athlete can lose multiple kilograms of body water through sweat within each stage. It is naturally concerning that this product is available for purchase in public locations.

While some might say that doping substances are not necessarily harmful for their users, doping regulations are placed to prevent damage to both the individual and the competitiveness of the sport. That said, in this study the risk of ingesting sibutramine or any other prohibited substance due to contamination is indeed high. Taking this into account, it is unadvised for athletes to take DS without proper opinion from a team doctor or nutritionist.

The amount of possible drug interactions and enzyme inhibition within the ingredients found in this study was staggering, with a high probability of consumption of a DS that leads to some CYP enzymes being inhibited, which in extreme cases can cause an accumulation of a drug to toxic levels. In this degree, mostly all of the possible drug interactions were on the ingredients in "Vegetable extracts" group, so caution in this group of ingredients would be advised when buying a DS. Several dietary supplements also had untested ingredients that when paired up could cause severe health issues. It is also advisable to look at the quantities of certain ingredients, since some may be below recommendations, as creatine content was, or above recommendations, as salt content was. Inspite of this, ingredient doses were not concerning, but consumption recommendations in the label could lead to dosage abuse.

It is known that some athletes truly have need for DS consumption, but it is advisable to try to avoid DS and contact the team nutritionist to make the most of an individual's diet, and only when needed with conjunction with low risk DS such as isogonics and energy gels. Lastly, there is great need for tighter control and regulations for dietary supplement producers.

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Table subtitles

Table 1- Thorough description of all the ingredients contained in the dietary supplements. These have been sorted in several columns describing their recommended dose and content in energy, caffeine, creatine, amino acids, Lipids, protein, carbohydrates, fiber, vitamins, minerals and derivates, vegetable extracts and other ingredients. The table's columns have been divided into 3 separate tables, in order to boost its comprehension.

Table 2- Minimum and maximum dosage portrayed by the DS brands on the most relevant ingredients (Caffeine, Creatine, Yohimbe extract, Citrus aurantium, Salt).

Table 3- Mean and standard deviation of all reviewed DS's recommended dose, caffeine, creatine and salt content within the minimum and maximum dosage shown in Table 2. This analysis was also divided into pre-workout and post workout.

Table 1- List of all the DS's ingredients.

Product	Recomended dose	Energy(kcal)	Caffeine	Creatine	Amino acids
Pre-Workout Supplements					
1	10 g	10	175mg	3000mg	250mg Tyrosine + 1500mg Beta-Alanine + 750mg Citrulline
2	13g	5	300mg	4000mg	1500mg Arginine + 1600mg Beta-Alanine + 1500mg Citrulline
3	9.5g	3	150mg	1500mg	300mg Tyrosine + 2000mg Arginine + 2000mg Beta-Alanine + 1025mg Citrulline
4	4g	2.4			690mg Carnitine + 418mg Arginine + 1010mg Beta-Alanine + 505mg Citrulline
5	9.5g		300mg		383mg Carnitine + 2000mg Glutamine + 500mg Arginine + 100mg Theanine + 1000mg Citrulline + 900mg Taurine
6	30g		350mg	5473mg	560mg Carnitine + 1910mg Glutamine + 1000mg Tyrosine + 4100mg Arginine + 10mg Alanine + 1400mg Beta-Alanine + 800mg Citrulline
7	20g		300mg	3929mg	300mg Carnitine + 1000mg Tyrosine + 4200mg Argnine + 500mg Beta-Alanine + 200mg Citrulline + 200mg Taurine
8	7g		200mg	2641mg	100mg Carnitine + 500mg Arginine + 520mg Beta-Alanine

9	50g	154	150mg	4000mg	3000mg Arginine + 3000mg Beta-Alanine + 1000mg Leucine + 500mg Isoleucine + 500mg Valine + 100mg Citrulline + 1000mg Taurine
10	22g		250mg	3800mg	4800mg Arginine + 3500mg Citrulline + 1000mg Taurine
11	16g	5	300mg	2000mg	400mg Tyrosine + 6000mg Citrulline + 1000mg Taurine
12	10.5g	5			1500mg Arginine + 4000mg Citrulline
13	60g	17	200mg		2000mg Arginine + 2000mg Beta-Alanine
14	10.5g	1	200mg	3250mg	2000mg Beta-Alanine + 4000mg Citrulline + 200mg Taurine
15	15g	3	250mg	3000mg	250mg Tyrosine + 3000mg Arginine + 2000mg Beta-Alanine + 5000mg Citrulline + 250mg Taurine
16	21g	35	350mg	3000mg	3200mg Beta-Alanine + 125mg Theanine + 4000mg Citrulline + 1000mg Taurine
17	6g		160mg	1500mg	1600mg Beta-Alanine + 75mg Theanine + 1500mg Citrulline
18	10g	20	350mg		1000mg Carnitine + 3200mg Beta-Alanine + 100mg Theanine + 1000mg Taurine
19	18g		300mg		3200mg Beta-Alanine + 8000mg Citrulline + 1000mg Taurine
20	15g		150mg	3000mg	1995mg Beta-Alanine + 750mg Taurine + 1250mg Arginine AKG + 2891mg Citrulline
21	6.5g		160mg	1000mg	1600mg Beta-Alanine + 1000mg Arginine AKG + 130mg Tirosine
Post-Workout Supplements					

22	10g	15			5000mg BCAA blend
23	334g	1250		1000mg	500mg Glutamine + 500mg Glutamine peptides
24	9.4g	3	200mg	1020mg	1770mg Arginine + 590mg L-arginine alpha ketoglutarate + 1704mg Beta-Alanine + 2045mg Citrulline + 1180mg Taurine
25	11.5g	7	250mg	1760mg	250mg Tyrosine + 1000mg Arginine + 1600mg Beta-Alanine + 3600mg Citrulline + 1000mg Taurine
26	162g	588		5763mg	50mg Carnitine + 800mg Glutamine + 50mg Phenylalanine + 800mg Arginine + 300mg Alanine + 200mg Beta-Alanine + 500mg Leucine + 250mg Isoleucine + 250mg Valine + 40mg Ornithine + 50mg Lysine + 2000mg Taurine
27	140g	447		4858mg	100mg Carnitine + 1500mg Glutamine + 500mg Phenylalanine + 500mg Tyrosine + 1000mg Arginine + 1000mg Alanine + 2000mg Beta-Alanine + 1500mg Leucine + 100mg Isoleucine + 900mg Valine + 1500mg Threonine + 1500mg Taurine
28	50g	186		1056mg	295mg Glutamine + 190mg Alanine + 250mg Taurine + Aminoacid mix (5% Alanine, 2.5% Arginine, 10.4% Aspartic Acid, 2.2% Cisteine, 16.9% Glutamine, 1.8% Glicine, 1.7% Histidine, 6% Isoleucine, 10.5% Leucine, 9.1% Lysine, 2.1% Methionine, 3.2% Fenilalanine, 6% Proline, 5.2% Serine, 6.9% Threonine, 1.7% Tryptophan, 2.9% Tyrosine, 5.9% Valine
29	78g	282			3700mg Glutamine + 2700mg Leucine + 1500mg Isoleucine + 1500mg Valine
30	52g	205			2300mg Isoleucine + 2300mg Valine

31	320g	1225			6600mg Leucine + 3800mg Isoleucine + 3700mg Valine
32	75g	305		2300mg	2700mg Leucine + 1400mg Isoleucine + 1500mg Valine + 500mg Taurine
33	11.7g			7000mg	
34	9g				4000mg Leucine + 1000mg Isoleucine + 1000mg Valine
35	100g	353			480mg Methionine + 3970mg Glutamine + 310mg Glycine + 480mg Cysteine + 660mg Phenylalanine + 310mg Tryptophan + 570mg Tyrosine + 460mg Arginine + 2420mg Aspartate + 1100mg Alanine + 2330mg Leucine + 1410mg Isoleucine + 1300mg Valine + 370mg Histidine + 1010mg Serine + 1210mg Proline + 2110mg Lysine + 1470mg Threonine
36	10g	30	100mg		50mg Methionine + 500mg Glutamine + 50mg Phenylalanine + 75mg Tyrosine + 125mg Arginine + 3000mg Leucine + 1000mg Isoleucine + 1000mg Valine + 25mg Histidine + 200mg Lysine + 125mg Citrulline + 50mg Threonine + 1000mg Taurine
37	48g	150		5000mg	500mg Alanine + 500mg Leucine + 250mg Isoleucine + 250mg Valine + 1000mg Taurine
38	1.7g			1500mg	
39	11g			6000mg	
40	80g	299			3200 Glutamine + 1600mg Leucine + 800mg Valine + 800mg Isoleucine

Product	**Lipids**	**Protein**	**Carbohydrates**	**Fiber**	**Vitamins**
Pre-Workout Supplements					
1			2g		2mg Thiamin + 20mg Niacin + 10mg Pantothenic acid + 2mg Piridoxin + 0.2mg Folic acid + 0.01mg Cyianocobalamin + 500mg Calciferol
2			1g		30mg Niacin + 10mg Pantothenic acid + 200mg Ascorbic acid
3	Under 0.5g		Under 0.5g		1.22mg Thiamin + 5mg Niacin + 1.24mg Piridoxin + 225mg Ascorbic acid
4			0.2g		4.04mg Niacin + 1.6mg Piridoxin + 81mg Ascorbic acid
5					200mg Ascorbic acid
6					0.21mg Riboflavin + 100mg Niacin + 0.21mg Piridoxin + 0.0075mg Biotin+ 0.82mg D-Biotine + 0.03mg Folic acid
7			4.6g		35mg Niacin + 0.0075mg Biotin + 0.03mg Folic acid
8					0.03mg Folic acid

9	Under 0.5g	4.5g	31g		
10					
11			Under 1g		
12			Under 1g		259mg Ascorbic acid
13					1mg Piridoxin + 0.001mg Cyianocobalamin
14					80mg Niacin + 0.1mg Cyianocobalamin
15			0.63g		60mg Niacin + 0.05mg Cyianocobalamin
16			1g		
17					
18					
19			Under 1g		
20					1.4mg Piridoxin
21					240mg Ascobic Acid + 24mg Niacin + 0.46mg Piridoxin + 0.13mg Folic Acid + 0.0037mg Cobalamin
Post-Workout Supplements					

22			4g		9mg Ascorbic acid
23	4g	50g	254g		1.5mg Retinol + 4.8mg Thiamin + 4mg Riboflavin + 50mg Niacin + 25mg Pantothenic acid + 5mg Piridoxin + 0.3mg Biotin + 0.04mg Folic acid + 0.01mg Cyianocobalamin + 60mg Ascorbic acid + 0.005mg Calciferol + 25.8mg Tocopherol
24			0.8g		10mg Niacin + 0.8mg Piridoxin
25			1g		8mg Niacin + 5.5mg Pantothenic acid + 1.2mg Piridoxin + 80mg Ascorbic acid
26	6.2g		55g		81mg Ascorbic acid
27	3g	42g	63g	2500mg	2.4mg Niacin + 0.03mg Folic acid
28	2.5g	17.5g	22g		0.03mg Folic acid
29	0.5g	1.4g	52g	1400mg	1.7mg Retinol + 24mg Niacin + 9mg Pantothenic acid + 21mg Piridoxin + 0.075mg Biotin + 0.3mg Folic acid + 0.004mg Cyianocobalamin + 120mg Ascorbic acid + 18mg Tocopherol

30	3.3g	40g	3.8g	400mg	
31	6.9g	67g	222g	4200mg	48mg Niacin + 4.2mg Piridoxin + 0.0045mg Cyianocobalamin + 58mg Ascorbic acid + 26mg Tocopherol
32	4.5g	30g	36g	800mg	0.919mg Retinol + 1.8mg Thiamin + 1.8mg Riboflavin + 18mg Niacin + 1.8mg Piridoxin + 0.092mg Folic acid + 0.0015mg Cyianocobalamin + 55mg Ascorbic acid + 0.0015mg Calciferol + 0.113mg Vit. K + 9.2mg Tocopherol
33					0.0125mg Calciferol
34					3mg Piridoxin + 0.005mg Cyianocobalamin
35	2.47g	23.01g	60.72g	113mg	500mg Ascorbic acid
36					
37			38g	2000mg	5.25mg Piridoxin + 0.0002mg Cyianocobalamin + 125mg Ascorbic acid
38					
39					

40	0.88g	17.60g	55.20g		128mg Ascorbic Acid + 0.64mg Retinol + 0.004mg Calciferol + 0.0096 mg Tocopherol + 1.12mg Riboflavin + 0.88mg Thiamin + 12.8mg Niacin + 1.12mg Piridoxin + 0.16mg Folic Acid + 0.002mg Cyianocobalamin + 0.04mg Biotin + 4.8mg Pantothenic Acid

Product	**Minerals and derivates**	**Vegetable Extracts**	**Other ingredients**
Pre-Workout Supplements			
1		25mg (AstraGin -Astragalus membranaceus Extract and Panax notoginseng Extract)	100mg Citrus Biofavonoids Complex
2	0.170mg Sodium + 160mg Potassium + 70mg Calcium	150mg Longan Extract(fruit) + 26mg Yohimbe Extract(bark)	250mg Calcium Glycerophosphate + 250mg Magnesium Glycerophosphate
3	20mg Salt		
4		12mg Green tea leaves extract + 11mg chlorogenic acid	10mg CoQ10

5		250mg Green tea extract + 250mg Beets extract + 86g Cocoa seed extract + 50mg AstraGin	Citicolina + L-Glutathione
6	0.006mg Chromium + 56mg Magnesium + 10mg Calcium(AKG)	10mg Garcinia cambogia extract(Sibutramine) + 400mg Citrus aurantium extract (synephrine) + 10mg Bacopa monnieri extract + 10mg ginger extract + 10mg guarana extract + 100mg grape seed extract + 10mg sour melon extract + 10mg BioPerine® Piper	92.5mg Choline + 4000mg Maltodextrin + 1650mg Sodium bicarbonate + 224mg magnesium carbonate + 0.053mg Chromium Picolinate + 206mg choline bitartrate + 10mg HMB + 10mg Calcium piruvate + 10mg CoQ10 + 10mg D-ribose + 10mg L-malic acid + 10 mg Alpha lipoic acid
7	56mg Magnesium	200mg Green tea extract + 20mg grape seed extract	10mg Alpha lipoic acid + 50mg L-ornithine + 50mg Sodium bicarbonate + 5mg Bioperine (Piperine)
8		50mg Rhodiola Rosea extract	10mg Alpha-ketoglutaric acid + 10mg Maltodextrin
9	540mg Sodium + 1400mg Salt + 0.012mg Chromium	100mg Ginseng extract + 50mg grape seed extract + 50mg ginger extract	2000mg Sodium bicarbonate + 100mg Alfa Lipoic acid + 0.1mg Chromium Picolinate
10		200mg Maca root extract + 125mg Guarana extraxt	
11		62.5mg Theacrine + 1mg Rauwolfia vomitoria extract + 0.05mg Huperzine A	3200mg Carnosyn Beta-Alanine + 200mg A-GPC
12		150mg Grape seed extract	1.5g Nitrosigine + 30mg trans-Resveratrol
13			

14	0.319mg Salt	100mg Theacrine	
15	171mg Sodium + 426mg Salt	50mg Astragin	5mg Bioperine
16		2500mg Betaine anhydrous + 200mg Hawthorn extract + 100mg Hovenia dulcis extract + 30mg Yohimbe extract	1500mg Nitrosigine + 150mg VasoDrive-AP(casein hydrolysate) + 200mg Choline
17	15mg Calcium	50mg Rhodiola extract + 20mg Yohimbe extract	
18		500mg ViNitrox (grape extract and apple extract) + 400mg C. canephora robusta extract + 250mg grape extract + 100mg Black currant extract + 100mg Goji extract + 40mg Theacrine + 40mg Grains of paradise extract	
19	390mg Sodium + 60mg Calcium	250mg Grape extract + 100mg Nutmeg extract + 100mg Jujube extract + 75mg Skullcap extract + 75mg Theacrine	30mg Choline + 150mg VasoDrive-AP(casein hydrolysate) + 400mg Adenosine 5'-triphosphate disodium + 62.5mg A-GPC
20		150mg Paullinia Cupana seed extracts +75mg Panax ginseng root extract + 7.5mg Salvia miltiorrhiza + 3.8mg Ophiopogon japonicus + 15mg Pinus massoniana + 4.50mg Ginko biloba	15mg Quercetin
21			

Post-Workout Supplements			
22	100mg Sodium + 100mg Potassium + 60mg Magnesium	250mg Bakers yeast beta glucan + 200mg Rhodiola extract	
23	430mg Sodium + 940mg Potassium + 5mg Iron + 0.12mg Chromium + 140mg Magnesium + 0.075mg Molybdenum + 2mg Manganese + 1mg Copper + 0.07mg Selenium + 15mg Zinc + 0.15mg Iodine + 460mg Phosphorus + 630mg Calcium		250mg Choline + 250mg Inositol + 5mg PABA
24	4mg Salt + 5.9mg Zinc		
25	Under 1mg Salt	164mg Betaine hydrochoride	71mg Choline citrate
26	380mg Salt + 360mg Potassium + 58.9mg Magnesium + 20mg Calcium(AKG)		82000mg 6-Carb Matrix (Wheat flour, Maltodextrin, Palatinose, Dextrose, Frutose, Waxy corn starch) + 238mg Magnesium carbonate + 10mg Alpha lipoic acid + 5mg Bioperine
27	1000mg Salt + 445mg Potassium + 0.012mg Chromium + 57.3mg Magnesium + 1.5mg Zinc + 10mg	500mg Avena sativa extract + 100mg Coleus forskohlii extract + 100mg Sour melon extract + 25mg Bromelain + 25mg	1500mg Calcium HMB + 100mg Calcium piruvate + 10mg Alpha lipoic acid + 5mg Bioperine

	Calcium(AKG)	Papain	
28	140mg Salt		
29	195mg Sodium + 15000mg Salt + 0.162mg Chromium + 192mg Magnesium + 1.5mg Zinc + 225mg Calcium + 155mg Chloride	37.5mg Grape seed extract + 23mg Ginkgo biloba	23mg Alpha lipoic acid acid
30	198mg Sodium + 490mg Salt + 162mg Phosphorus + 247mg Calcium	173mg Bromelain + 173mg Papain	260mg Lactase
31	1179mg Sodium + 2950mg Salt + 2925mg Potassium + 118mg Magnesium + 1.8mg Zinc + 978mg Phosphorus + 623mg Calcium		
32	80mg Salt + 0.016mg Chromium + 7.9mg Manganese + 2.4mg Zinc		46mg Glucoronolactone + 92mg Alpha lipoic acid + 92mg enzimatic complex
33	360mg Calcium		3g HMB

34			
35	400mg Sodium + 1000mg Salt + 600mg Potassium 113mg + Magnesium + 240mg Calcium		
36	100mg Sodium + 18mg Potassium	25mg Green tea extract	50mg Coconut water + 50mg Watermelon juice + 160mg Sodium Chloride + 40 mg Dipotassium phosphate
37	35mg Sodium + 24mg Potassium + 32.5mg Magnesium		100mg Alpha lipoic acid
38			
39	120mg Sodium + 0.1mg Chromium	2500mg Betaine anhydrous + 800mg CinDura (Cinnamomum tamala leaf extract and Garcinia mangostana fruit rind extract)	5.3mg Bioperine
40	780mg Salt + 480.8mg Potassium + 232mg Magnesium + 310.4mg Sodium	500mg Prunus Cerasus + 500mg Lythraceae punica granatum + 250mg Curcumin complex	1.52mg HMB + 30mg Lactowise + 56mg Digestive enzime complex(alpha-amylase, neutral amylase, celulase, lactase, lipase)

Table 2- Minimum and maximum recommended dosage and its translation in dosage related to the most relevant ingredients.

	Recomended dose (g)											
Product	Minimum recommended	Maximum recommended	Caffeine Min (mg)	Caffeine Max (mg)	Creatine Min (mg)	Creatine Max (mg)	Yohimbe extract Min (mg)	Yohimbe extract Max (mg)	Citrus aurantium extract Min (mg) (synephrine)	Citrus aurantium extract Max (mg) (synephrine)	Salt Min (mg)	Salt Max (mg)
Pre-Workout Supplements												
1	10	10	175	175	3000	3000						
2	13	13	300	300	4000	4000	26	26				
3	9.5	19	150	300	1500	3000					20	40
4	4	4	43	43								
5	9.5	9.5	300	300								
6	30	30	350	350	5473	5473			400	400		
7	20	20	300	300	3929	3929						
8	7	7	200	200	2641	2641						

9	50	50	150	150	4000	4000					1400	1400
10	22	22	250	250	3800	3800						
11	16	16	300	300	2000	2000						
12	10.5	10.5										
13	60ml	60ml	200	200								
14	10.5	10.5	200	200	3250	3250					0.319	0.319
15	15	15	250	250	3000	3000					426	426
16	21	21	350	350	3000	3000	30	30				
17	6	12	160	380	1500	3000	20	40				
18	10	10	350	350								
19	18	18	300	300								
20	15	15	150	150	3000	3000						
21	6.5	6.5	160	160	1000	1000						
Post-Workout Supplements												
22	10	10										
23	334	334			1000	1000						
24	9.4	9.4	200	200	1020	1020					4	4
25	11.5	11.5	250	250	1760	1760					1	1
26	162	162			5763	5763					380	380
27	140	140			4858	4858					1000	1000

28	50	50			1056	1056					140	140
29	78	78									15000	15000
30	52	52									490	490
31	320	320									2950	2950
32	75	75			2300	2300					80	80
33	11.7	11.7			7000	7000						
34	6 tablets	7 tablets										
35	100	200									1000	2000
36	10	10	100	100								
37	48	192			5000	20000						
38	1.7	3.4			1500	3000						
39	11	11			6000	6000						
40	80	80										

Table 3- Mean and standard deviation associated with minimum and maximum dosage for all DS divided in pre-workout and post-workout.

	Recommended dose		Caffeine (mg)		Creatine (mg)		Salt (mg)	
	Min	Max	Min	Max	Min	Max	Min	Max
Pre-workout DS by minimum and maximum	15±10	16±10	232±85	250±88	3006±1174	3221±1042	462±656	467±651
Pre-workout total	16±10		241±86		3106±1079		464±605	
Post-workout DS by minimum and maximum	84±73	97±81	183±86	183±90	3387±1685	4887±3613	2105±3469	2205±3676
Post-workout total	90±102		183±68		4137±4177		2155±4486	