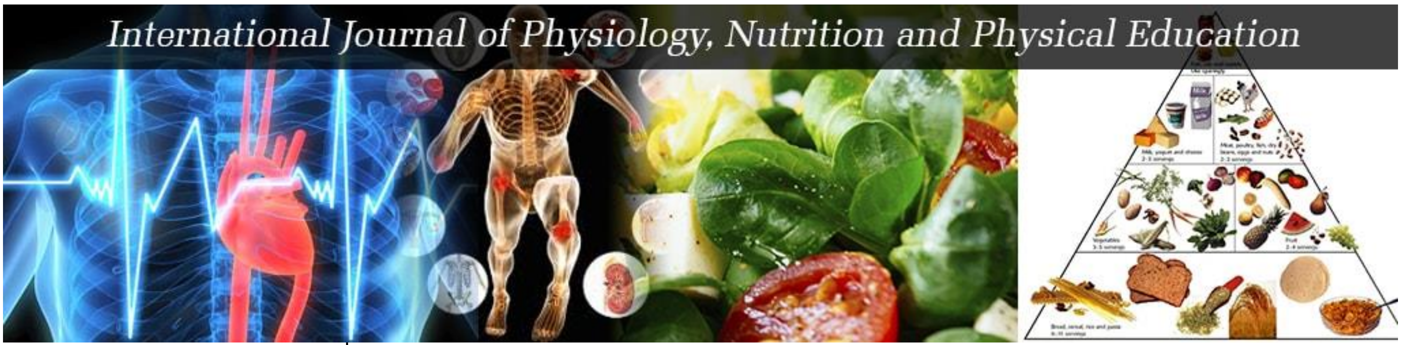

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The role of caffeine consumption on individuals' health and athletic performance: An overview

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Abstract
Caffeine is considered a very popular, extensively ingested substance among the general population and athletes or recreational exercisers. This narrative review seeks to present the most recent scientific literature on the role of caffeine consumption on individuals' health and athletic performance. There are favorable relations between coffee use and liver outcomes (e.g. cirrhosis, fibrosis, liver cancer, and chronic liver disease) and a wide range of other health outcomes, while, there are no decisive deleterious relations with any health outcomes, except for pregnancy. The ergogenic effects of caffeine are significant after consumption of doses 3 to 6 mg/kg/body weight, 15 to 60 min pre-exercise (it depends on the form), mainly due to the Central Nervous System. Caffeine may enhance the re-synthesis of glycogen during the recovery phase from exercise. Caffeine has beneficial effects in several features of exercise such as extended aerobic-type activities, fixed-term activities, brief duration activities, high-intensity prolonged exercise as in team sports, and strength/power activities. It does not cause harmful changes in urination, water loss, sweating rate, and fluid balance. In periods of sleep deprivation, it can improve vigilance and alertness. Among the most commonly incorporated side effects of caffeine, ingestion is anxiety and heart palpitations.

Keywords: Caffeine, health, athletic performance, nutrition aid, recommendations

1. Introduction

Athletes and recreational exercisers consume nutritional supplements in the idea that they will make available their energy reserves, promote exercise training adjustments and competitive performance, maintain intense exercise training by promoting recovery, protect their health and consume an effective and convenient source of nutrients [1]. Caffeine is considered a very popular, extensively ingested nutritional ergogenic aid. Research data on its physiological effect on athletic performance and health is extensive and researchers today continue to explore, define and extend existing scientific knowledge. Published scientific data in areas of interest such as its effect on strength, endurance, team sports, rehabilitation, and hydration is huge and in many cases contradictory [2]. It is considered that the improvement in aerobic endurance exercise due to its administration may be due to inhibition of phosphodiesterase (increases lipolysis) or to the activation of the adrenal gland and the increase in the activity of epinephrine (lipolytic hormone) [3-5]. To better understand the potential effect of caffeine as a whole, it is essential to analyze both its chemical structure and how the substance is normally be assimilated into the body [6]. Caffeine, in addition to the ingredient in coffee and tea, is found in chocolate, sports drinks, as well as in some medicines [6]. Except for water, coffee and tea are the widely consumed beverages, globally. According to statistics in North America and Europe, almost 90% of adults are regular users of caffeinated beverages. The average daily caffeine intake per person is almost 200 mg or 2.4 mg/kg body weight (BW) (corresponding to about 2 cups of coffee) and is considered to be the most widespread and consumed active pharmacological ingredient in the world [7]. Although caffeine consumption per day has not changed in the previous decades, current scientific results proposed that the mean total daily caffeine consumption is lower than caffeine intake recommendations (3 mg/kg BW for children, and 400 mg for adults) [8]. Moreover, among adolescents and young exercising individuals, there is a rapid increase in the intake of commercial products containing caffeine, such as energy drinks, chewing gum, energy gels, and other foods [9, 10]. The effects of caffeine on individuals' health, exercisers or not, is a very old area of research, and it stable remains to be a dietary ingredient of great interest in public health, as speculated by widespread research data [11-14]. Simultaneously, there is a dedicated concern of research in better knowledge of the potential effect of caffeine intake on several types of athletic performance [15–17].

Accordingly, the present narrative review scopes to present the recent scientific data on the potential beneficial effect of caffeine intake on health and athletic performance in both exercised and non-exercised individuals, as well as current recommendations for safe administration.

2. Materials and Methods

In the current narrative review, we conducted a systematic search of the electronic databases PubMed, MEDLINE, and EMBASE, using title words, terms, and abstract words such as "exercise", "athletes", "athletic performance", "health", "nutrition supplements", "ergogenic aids", and "caffeine". Moreover, we assess review articles, as well as references from original articles and relatively books. Exercise training, athletic performance, health, and caffeine were used as keywords. We considered necessary research included the abovementioned terms that were published from January 1985 to December 2021, in the English language. Scientific articles were included if they presented data on caffeine intake in athletes, reviewed their probable effectiveness in terms of health and/or athletic performance, or described in detail its mechanism of action, administration protocols, side-effects, safety, and public recommendations. We examined all article's titles and abstracts meet requirements, and full-text studies were retrieved if the inclusion criteria were doubtful.

3. Results and Discussion

3.1 Metabolism of the substance

Creatine's major pharmacologically active ingredient is the alkaloid purine included in the xanthine family (1, 3, 7-trimethyloxanthin). Caffeine is contained via the stomach, small intestine, and large intestine [3, 5]. Its absorption depends on the food present in the stomach and the concentration of caffeine in the food ingested [3, 5]. Caffeine is distributed throughout the body and brain. Caffeine is both fat-soluble and water-soluble. Because of its lipophilic nature, the substance penetrates the cerebral blood circulation, while it can reach the fetus and does not accumulate in the body [3, 5]. Its metabolism in the liver is attributed to the enzyme CYP1A2. Caffeine is broken down into paraxanthine, theophylline, and theobromine. Specifically, the breakdown of the substance takes place in the liver with the help of cytochrome P450, where it is metabolized to three separate substances: (a) paraxanthine, which enhances lipolysis, resulting in increased glycerol levels and free fatty acids (FFA) in the blood plasma, while also increasing the amounts of Ca^{++} in skeletal muscle; (b) theobromine, that enlarges blood vessels and gently enlarges urine production and; (c) theophylline, that relaxes smooth muscle bronchi [18, 19]. The abovementioned metabolites are more extended metabolized and excreted in the urine. The time it takes for the metabolism and excretion of caffeine depends on several factors [18, 19]. Particularly, it is slower when: (a) concomitant alcohol consumption occurs, (b) in Asians, (c) in men, (d) in newborns, (e) in pregnant women, and (f) when there is liver damage [20]. On the contrary, the metabolism is lower and faster together with cigarettes (smoking), in Caucasians, women, and children [20]. Caffeine is quickly contained by the body when consumed from a food or supplement, comes into view in the blood after 5 to 15 min and at its highest concentration (peak) between 40 and 80 min, after consumption [21, 22]. Caffeine in plasma reaches levels of about 15 to 20 μmol/L after low dose intake (3 mg/kg BW), ~40 μmol/L at a moderate dose (6 mg/kg BW), and ~60-70 μmol/L at a high dose (9 mg/kg BW). It has a half-life of about 3 to 5 hours that allows it to interact with other tissues and functions of the body. It is well-known that caffeine and its metabolites are excreted in the urine, in an amount of about 3 to 10% [21, 22]. Due to its uptake by the tissues as well as its elimination through the urinary system, the amount circulating in the blood is reduced by 50-75% after 3-6 hours of consumption. Therefore, the clearance of the substance is proportional according to its absorption and metabolism [21, 22].

3.2 Mechanisms of action

Caffeine exerts its effect on improving athletic performance through many mechanisms, the main ones of which are:

1. **Adenosine antagonist-affects the Central Nervous System (CNS):** Scientific data proposed that its most significant mechanism of action is that of acting as an adenosine antagonist at its receptors, thus affecting the central nervous system. In particular, owing to its chemical similarity to adenosine, it blocks adenosine receptors, thereby inhibiting its competitive action in the brain, activating noradrenaline neurons and affecting the release of dopamine-associated dopamine. Caffeine can block cerebral blood flow as it competes with adenosine receptors in blood vessels, therefore decreasing adenosine-regulated vasodilation and, as a result, reducing the blood flow in heart tissue [23].
2. **Increases lipid oxidation:** Enhanced lipolysis results in reduced dependence on glycogen use. Caffeine changes the preference for energy substrates from glycogen to fat by improving the activity of hormone-sensitive lipase (HSL) and blocking the action of glycogen phosphorylase [18]. The increased concentration of FFA in the blood leads to a greater uptake of FFA into the muscle. Their increased oxidation results in a reduction in carbohydrate oxidation [23-24]. Reducing carbohydrate oxidation can save muscle or liver glycogen stores so that a person can exercise more time at the same intensity or a higher intensity for the same distance. Oxidation of fatty acids increases in people who receive caffeine while this effect decreases infrequent users of the substance [23, 24]. Decaffeination in caffeine reduces its lipolytic action. The potential effect of caffeine on athletic performance might be more linked to the effect of the substance on the CNS [2, 20].
3. **Acts as a non-selective antagonist of the phosphodiesterase enzyme inhibitor:** Phosphodiesterase hydrolyzes cyclic adenosine monophosphate (cAMP), inhibiting cAMP cleavage. CAMP enhances lipolysis by activating hormone-sensitive lipase (HSL) and is an essential molecule for activating epinephrine [18]. Also, it activates protein kinase A, which in turn can phosphorylate several other enzymes involved in lipid and glucose metabolism. Therefore, it is possible that caffeine, by activating the metabolism of glucose and lipids more, promotes athletic performance [20].
4. **Improves the accumulation of glycogen in muscle after exercise:** Caffeine enhances recovery by

augmenting the rate of muscle glycogen resynthesis after exercise training. Research by Pedersen *et al*. (2008) revealed that co-administration of caffeine (8 mg/kg BW) with carbohydrates augmented its rate after muscle glycogen accumulation as compared to carbohydrate intake in well-trained athletes after strenuous exercise [25, 26]. To better understand the specific issue is needed to additional investigation in trained and untrained individuals and at different periods (e.g. during exercise or rehabilitation). Caffeine when included in the post-exercise carbohydrate diet appears to be able to enhance glycogen recomposition [2].

5. **Mobilizes intracellular calcium:** Caffeine may improve the release of Ca from the sarcoplasmic reticulum and may slow down its reuptake [27]. Through this mechanism, caffeine can enhance the contractile power of the muscle in submaximal contractions. Intracellular Ca promotes the activation of endothelial nitric oxide synthase, which increases nitric oxide [27]. Nitric oxide is normally produced in the human body and causes blood vessels to dilate, improving blood flow to the muscles, resulting in increased endurance, recovery time, and energy for a high level of performance [2]. A number of the ergogenic effects of caffeine could, at least in part, act as regulators, acting on the neuromuscular system and enhancing the contractile force.
6. **Increases the secretion of β-endomorphins:** A potential mechanism by which caffeine intake affects athletic performance is by enhancing the secretion of β-endomorphins. Research has shown that caffeine administration (6 mg/kg BW) enlarged plasma concentrations of β-endomorphine in athletes who cycled for 2 hours at 65% of VO_2peak as compared to the placebo group [28]. Increasing the plasma concentration of β-endomorphins during exercise, due to their analgesic properties, might lead to a reduction in pain perception. Conclusively, caffeine can influence both the CNS and skeletal muscle. Caffeine appears to have a combined effect on athletic performance, through both the central and peripheral (muscular) systems. The effect of the substance on athletic performance also depends on many factors such as the condition of the individual, the sport (e.g. type, intensity, duration), and the dose of the substance [31].

4. Health effects

Caffeine intake was often associated with more advantages than harm for a wide range of health consequences taken into consideration the doses were consumed (e.g. low vs. high, any vs. none etc). Caffeine causes CNS stimulation, vasoconstriction, increased urination and sodium excretion, activation of adipose tissue lipolysis, increased gastric fluid secretion, and increased muscle contractility [2]. From the above effects, the stimulation of the CNS, the activation of lipolysis, and the increase of the contractility of the muscles have ergogenic implications [2, 8]. As will be discussed below, the main mechanism by which caffeine improves athletic performance is related to its direct effect on the CNS, in such a way as to reduce fatigue during exercise and activate muscles. Positive effects include increased alertness and vigilance, reduced fatigue, less risk of cardiovascular disease (CVD) and diabetes, and enhanced metabolic rate [8, 11]. On the contrary, the harmful effects include stress and addiction, higher blood pressure and vasoconstriction, and the mobilization of dieresis [2].

4.1 Cognitive Performance

Caffeine augments individuals' alertness in fatigue or rest, in a dose-related manner [29-30]. It is considered that moderate doses could be favorable while increased doses could result in anxiety and perhaps, in non-sleep individuals or non-users of caffeine, impair cognitive performance [31]. Caffeine presents a proven advantageous effect on vigilance tasks. Specifically, its beneficial effects are more common in sleep-deprived and rested individuals, probably because it reverses increases in alertness related to extended upkeep of attention [32-36]. Also, caffeine promotes cognitive processes such as reaction and attention time [29, 30, 37]. Scientific data proposed that chronic caffeine consumption has a beneficial effect on memory, probably via its neuroprotective effects, while, its acute effects on memory are not as reliable and may be influenced by task (e.g. boring or not) [38, 39]. Moreover, there is no clear evidence related to its potential effects on higher-order executive functions, mainly, because of its difficulty to assess. In conclusion, it seems that moderate doses of caffeine intake enhance mood, vigilance, and learning.

4.2 Pregnancy

It is well-known that in pregnancy, the half-life of caffeine is about 8 to 16 hours longer than usual meaning that it could affect both mother and fetus [40, 41]. Additionally, it seems that steroid hormones slow caffeine metabolism in pregnancy [42]. Thus, because of the potential effects of caffeine intake on brain development, the above concern should be of great concern in pregnancy for safety issues. Moreover, scientific data proposed that caffeine clears out very slowly during early infancy, resulting in potentially long-lasting effects, mainly in the infancy brain [43].

4.3 Relief of pain

Caffeine used for several years to treat pain since its vasoconstricting action, less important than adenosine receptor antagonism, is correlated to reduced pain. Scientific results showed that acute caffeine intake (300 to 500 mg) can decrease pain and puncture headaches [44-46].

4.4 Cardiovascular Effects

Caffeine intake stimulates a small increase in systolic and diastolic blood pressure, while, it could be affected heart rate (e.g. tachycardia or bradycardia), and the release of neuroendocrine hormones (e.g. epinephrine, norepinephrine, renin) [47]. In addition, caffeine consumption in high-doses could cause cardiac arrhythmias due to the mechanism of adenosine receptors blockade [48]. The existing effects differ among habitual and non-habitual users and by dose, while the severity of the threats depends on several other factors such as medical conditions, the quantity of the ingredients consumed the time, the length of consumption, and others. Several studies proposed that typical caffeine doses consumption provoke modest changes in heart rate and blood pressure and a minor rise in sympathetic activity [48-51].

4.5 Vascular System Effects

It is believed that caffeine intake can improve endothelial cell function as it increases intracellular concentrations of calcium, leading to increased stimulation of the endothelial cells to produce NO causing vasodilation [52]. Also, caffeine binds to the vascular muscle cell receptors and causes vasoconstriction [53]. Lamdar *et al*. (2009) speculated that caffeine consumption without delay before or during exercise could be harmful and can augment the risk for ischemia in the myocardium [54]. However, another study incorporated decreased myocardial blood flow with caffeine consumption immediately before exercising [55]. The vasoconstrictive effect could be more distinct in individuals who consumed high amounts of caffeine (e.g. energy drinks) or in caffeine-naïve individuals.

4.6 All-cause mortality

Review and meta-analysis study examining the possible effect of caffeine intake (in a dose-response analysis) on all-cause mortality revealed that intake of one more cup of coffee, daily, was associated with almost 4% decreased risk of all-cause mortality [56]. In parallel, another meta-analysis proposed that high caffeine consumption (seven cups per day) was associated with a decreased risk of all-cause mortality by 10%, although the greater observed decrease in risk was found with the intake of three cups per day, as compared to no consumption [57]. The above results did not differ between the sexes [57]. Moreover, in the comparison between low and high intake of decaffeinated coffee, the same meta-analysis showed a significant association with decreased all-cause mortality, resulting in greater advantage at three cups of coffee per day [57].

4.7 Cancer

The results of a meta-analysis by Grosso *et al*. (2016) only among non-smokers, revealed a lower risk of cancer mortality by 2% for a 1 cup daily augmentin coffee intake [57]. Another meta-analysis proposed a decreased incidence of cancer for any vs. no coffee intake by 13%, high vs. low coffee intake by 18%, and one extra cup per day by 3% [58]. The results from the same study among smokers, showed an increase in the risk of cancer mortality associated with coffee consumption, reaching statistical significance above 4 cups per day [58]. Furthermore, a recent meta-analysis concluded that high vs. low coffee intake is associated with decreased risk of melanoma, liver cancer, oral cancer, prostate cancer, and endometrial cancer in a dose-related benefit manner [59]. High as compared to low coffee intake was associated with a harmful effect on lung cancer (OR 1.59, 95% CI 1.26, 2.00), while the same is evident for any vs. none (OR 1.28, 95%CI 1.12, 1.47) [60-61]. However, the harmful effect was deteriorated after adjustment for smoking, and was disappeared among never smokers [60, 61]. A meta-analysis examined the potential association of coffee consumption on several other cancers such as colon, thyroid, breast, bladder, pancreatic, and pancreatic revealed no statistically significant association between any vs. no coffee consumption [59].

4.8 Gastrointestinal and liver

It is considered that coffee intake was associated with a lower risk for several liver conditions. A meta-analysis by Liu *et al*. (2015) showed that coffee consumers were less possible by 39% to develop cirrhosis than no consumers. Also, the same study concluded that low or moderate coffee consumers had 34% lower probabilities of hepatic cirrhosis than no consumers, while, high coffee intake might significantly decrease the risk for hepatic cirrhosis by 47% than non-consumption [62]. Another recent meta-analysis proposed that the risk of nonalcoholic fatty liver disease in patients who were coffee consumers was lower by 29% in comparison with patients who did not consume [63]. Moreover, consumption of two extra cups of coffee was associated with a 35% lower risk of mortality from cirrhosis [64]. The results of a meta-analysis incorporated that coffee consumers had a 27% lower risk of advanced hepatic fibrosis than non-consumers, while it seems that the protective effect on hepatic cirrhosis and fibrosis also occurred in patients with chronic hepatitis C virus and alcoholic liver disease [62]. In similar, other data proposed a reduced risk of liver fibrosis by almost 30% among nonalcoholic fatty liver disease patients who consumed coffee as compared to no consumers [63]. A meta-analysis examining the probable association between coffee intake and gallstone disease concluded that coffee intake is associated with a decreased risk of gallstone disease, in a dose-related manner when the intake increased from two to six cups, daily [65].

4.9 Neurological concerns

There are no findings that associate coffee consumption with cognitive decline or dementia, while it proposed a significant opposite association between the highest caffeine intake and the risk for Alzheimer's disease [66]. Two meta-analyses proposed that coffee intake was associated with a decreased risk of Parkinson’s disease, even after adjustment for several confounders [67, 68]. Also, recent scientific data indicated that coffee intake is associated with a reduced risk for depression [69, 70].

4.10 Metabolic factors

There is a plethora of evidence that coffee intake was linked to a decreased risk of type-2 diabetes, in a dose-response manner, while, the results were stable for decaffeinated and caffeinated coffee [71]. Moreover, the same meta-analysis revealed that the risk was lower for each dose of higher intake from one to six cups [71]. Regarding the potential effect of caffeine consumption on metabolic syndrome, a meta-analysis showed a lower risk by almost 10% for high as compared to low consumption [72]. The current knowledge indicates that the highest coffee consumption is associated with a 30% lower risk of urolithiasis as compared to no consumption, while it suggested that coffee intake exhibited an inverse dose-response relationship with urolithiasis [73]. Moreover, a meta-analysis proposed a significant lowering effect on serum urinary acid for caffeine consumption, while, it also revealed that 1 cup per day or more coffee intake was associated with a lower risk of gout, for both genders [74].

5. Effect on Athletic Performance

5.1 Caffeine and mental performance in exercise

Caffeine is an efficient ergogenic supplement for people who are both in special military units and/or in those who experience frequent stress (e.g. long periods of sleep deprivation) [75-77]. Caffeine in these situations promotes concentration and readiness [75-77]. A meta-analysis among studies relevant to the military, mental fatigue in sport, and aerospace populations showed that the consumption of energy drinks (including caffeine) showed a small advantageous effect on reaction time, while caffeine intake did not affect accuracy [78]. It also seems that caffeine can benefit endurance athletes both physically and mentally [2]. Regarding the mental effect of caffeine in high-intensity short-term exercise, the results are contradictory [2]. In conclusion, although the research is limited, it seems that the administration of the substance can have a positive effect on physical activities that require high mental performance.

5.2 Effects of caffeine on perceived fatigue during and after exercise

A meta-analysis by Doherty & Smith (2005) planned to explore the effect of caffeine administration on the assessment of perceived fatigue (RPE) showed that the caffeine intake group reduced perceived fatigue during exercise by 5.6%, and improved exercise performance by 11%, as compared to the placebo group. Also, the regression analysis showed that the RPE values reported during exercise could represent approximately 29% of the variation in athletic performance improvement [79]. Another recent meta-analysis speculated that the consumption of caffeine in a low/moderate dose before and/or during exercise training be able to enhance mood, self-reported energy, and attention; while, it might also get better reaction time, memory, and fatigue [80]. In summary, caffeine reduces perceived fatigue during exercise, which may partly explain the substance's ergonomic effect on performance, as athletes could exercise for longer.

5.3 Effect of caffeine on endurance performance

Caffeine is the most widely used ergogenic aid among active individuals and athletes in an extended range of physical activities and sports concerning aerobic endurance. It is considered that caffeine intake benefits several endurance-type sports such as running, cycling, swimming, and skiing [2]. Also, it is well known that almost three to four elite athletes on endurance-type exercise use caffeine as an ergogenic aid before or during athletic events [2]. A review study investigated the effect of caffeine on endurance sports of a specific duration and in a particular duration>5 minutes, found that the average improvement in performance due to the administration of the substance was 3.2 ± 4.3% (0.3 - 17.3%) [81]. According to the same results, the high variability of the results may be due to the time of taking the substance, the form/dose, and the addiction of the person to the substance [81]. Another meta-analysis examined 56 endurance time trials (mainly in cycling athletes), revealed a percent difference in performance between the caffeine group and the placebo group by 3.0 to 16% [82]. Also, in a meta-analysis that included 40 double-blind studies of aerobic, anaerobic, and mixed exercise, the results showed that caffeine improved the test result by 12.3% compared to placebo, while, in aerobic tests, the result was more improved compared to either anaerobic or mixed exercise [79]. Moreover, in the studies in which the time to exhaustion was examined, higher improvements were found compared to the studies that included other tests [79]. Finally, a meta-analysis by Southward *et al*. (2018) speculated that moderate doses (3–6 mg/kg) of caffeine intake had an advantageous effect on endurance performance by 2.3 ± 2.6% and in mean power output of 2.9 ± 2.2% as compared to placebo [83]. In brief, caffeine intake may have an ergogenic effect by 2 to 4% for endurance athletes when consumed before or during exercise in moderate amounts (3-6 mg/kg BW).

5.4 Effect of caffeine on high-intensity strength training

Caffeine intake of moderate dose (4-6 mg/kg BW) may have a beneficial effect on either intermittent or short-term exercise and in high-intensity exercise, mainly in trained individuals [2]. The training and condition of the athletes can improve certain psychological adjustments which in combination with the administration of the substance lead to the enhancement of the performance [83]. The high variability in the performance of the untrained individuals may obscure the favorable effect of the administration [20]. Research into the effect of the substance on strength-training activities suggests that the administration may help high-trained power and strength athletes [20]. It is of interest the absence of significant findings of lower body strength relative to upper body athletic performance. A review study examining caffeine's ability to improve athletic performance in anaerobic exercise (e.g. team sports, sprinting, and resistance exercise), found that 11 of the 17 studies had significant improvements in strength and power after administration, as compared to the placebo group [84]. The positive effect was more apparent in professional athletes who were not regular caffeine consumers. Furthermore, six of the 11 studies revealed significant benefits of caffeine in resistance training [84]. A most recent meta-analysis found that caffeine intake of low doses (1 to 2 mg/kg BW) had significant ergogenic effects on muscular endurance and strength, and on mean velocity, highlighting the minimum ergogenic doses of caffeine [85]. Moreover, a meta-analysis exploring the effects of caffeine intake on the rate of force development (RFD) found a significant ergogenic effect of small-to-moderate and moderate-to-high caffeine doses on RFD, even if the effects were larger with higher caffeine doses [86]. Also, recent findings proposed a significant ergogenic effect of caffeine supplementation on muscle maximum strength and endurance in the bench press exercise [87]. Additionally, it seems that alternating caffeine sources such as gel, chewing gum, and coffee had an ergogenic effect for resistance exercise performance when consumed 10 to 30 min before exercise [88]. To sum up, moderate doses of the substance (3-6 mg/kg BW) may be beneficial, although the exact mechanism that explains the ergogenic effect of caffeine in short-term, high-intensity exercise is not well established.

5.5 Caffeine and sport performance

Although several studies in the laboratory suggest that caffeine consumption might improve athletic performance, it is not quite clear if these advantages transfer to sport-specific performance. There are several studies performed among athletes participating in individual and team sports that speculate that caffeine ingestion may improve athletic performance in several sports tasks, however, there are plenty of studies that reported no significant effects [2, 17-20]. A most recent meta-analysis in this field found that caffeine consumption improved athletic performance in specific team-sport skills, total body impacts, countermovement jump, and handgrip strength, while, no effects were considered on agility, squat jumps, and the ratings of perceived exertion, in women athletes [89]. Briefly, the scientific data support the ergogenic effect of caffeine intake on an extensive range of sport-specific tasks, athletes and exercisers should keep in mind the associated side-effects and the individual response before using it in competition.

5.6 Effect of gender and systematic caffeine consumption on its ergogenic action

Research exclusively on women is somewhat limited and extremely diverse. Scientific studies that investigated the role of caffeine supplements in endurance, high-intensity exercise, or the effect of the substance on strength in trained women are minimal, especially compared to scientific articles that assessed the dynamics among men. Specifically, research has been conducted on rowing, treadmill walking, and aerobic dance among recreational athletes with moderate-intensity aerobic exercise [90-92]. The results show that a moderate dose of caffeine can be effective in enhancing athletic performance in female athletes. A most recent meta-analysis of studies performed in women suggests the caffeine habituation and physiological responder status might contribute to caffeine's efficacy, with a possible plateau in the dose-response relationship of athletic performance improvement [93]. Also, the scientific research suggests a different response to the administration of the substance concerning its effect on athletic performance by non-systematic users than users. Specifically, a study by Bell et McLellan, (2002) in which caffeine (5 mg/kg BW) or placebo was administered to users (n=13) and non-caffeine users (n=8), found that all people who consumed caffeine (5 mg/kg) had better performance than placebo groups, but the improvement was higher in non-users of the substance, and in addition, the effect of the substance in non-users was still present 6 hours after ingestion [94].

6. Caffeine: Form, Dose, and Exercise

Caffeine intake through a cup of coffee may be less effective in athletic performance than consumption in an anhydrous form [20, 95]. Drinking coffee before the anhydrous caffeine supplement does not change its ergogenic effect when given in low to moderate doses [20, 95]. Coffee contains many biologically active ingredients; however, it is not well-known whether all of these compounds are beneficial to athletic performance. Based on limited scientific findings, caffeinated coffee has better results in athletic performance than decaffeinated coffee [2, 95]. Individual response is essentially a very relevant issue that concerns all nutritional aids and depends on many factors. Therefore, these variables (dose, type, tolerance, age, training level, etc.) must be taken into account when giving caffeine to an athlete's training program. It seems that high-dose caffeine (9 mg/kg) can stimulate the CNS to such an extent that the usual positive ergogenic responses are bypassed. A study by Spriet LL (2014), examined the effects of administration of 3, 6, and 9 mg/kg BW in the endurance performance of 8 trained endurance runners, who did not consume caffeine for 48 hours, and exercised until ~85% of VO_2max on a floor ergometer, showed that endurance performance was enhanced by 22% and 11% after ingestion of 3 and 6 mg/kg caffeine, over the placebo group, and not significant after the highest dose of 9 mg/kg caffeine [96]. A recent meta-analysis explored the potential effect of both sports drinks with caffeine and energy drinks with caffeine showed that there were effective in enhancing several aspects of athletic performance when the number of drink offers was a minimum of 3 mg/kg BW [97]. It seems that as a result of their composition, caffeinated sports drinks could be more efficient during long-duration exercise, while, energy drinks might be more appropriate before exercise [97]. In another systematic review, some results incorporated a positive effect of caffeine mouth rinsing on exercise performance, while, others showed no improvements or only suggestive benefits [98].

6.1 Caffeine and diuresis at rest and exercise

Caffeine has been accused of having a diuretic effect on athletes and therefore, in theory, increased pre-workout water loss could impair athletic performance, especially in hot humid environments (probably due to reduced sweating rate and consequent higher body temperature). However, scientific data have not shown changes in sweating rate, blood volume, or body temperature after caffeine consumption [20]. Acute caffeine intake can increase urine volume, causing fluid balance concerns during exercise [22, 99]. A meta-analysis by Zhang *et al*. (mean total dose of 300 mg) aimed at evaluating possible diuresis induced by substance administration during exercise recorded an average increase in urine volume of 109±195 mL or 16.0±19.2% for caffeine consumption compared to intake of the same amount of decaffeinated beverage [100]. Further analysis of the results showed that exercise is a powerful regulator of diuresis and that women were more sensitive to the diuretic effect of the substance than men [100]. Another review study proposed that acute consumption of caffeine in high doses (250–300mg) could result in a short-term stimulation of urine output in persons who have been deprived of caffeine ingestion for a long time (days or weeks) [101]. In conclusion, caffeine exerts a slight diuretic effect which is reversed by exercise. Potential concerns about fluid loss associated with caffeine intake are unwarranted, especially when swallowing precedes exercise.

6.2 Caffeine and hydration

It is suggested that caffeine intake causes an acute state of dehydration [20]. Nevertheless, caffeine consumption at rest and during exercise are two completely different scenarios. The results of relevant research indicate that the intake of caffeine only or in combination with water or a sports drink does not increase the temperature of the trainees and does not weaken the heat dissipation [102, 103]. The results also suggest that caffeine (6 mg/kg) increases urine flow and electrolyte excretion through sweat, but these effects are not adequate to cause dehydration or affect electrolyte levels in the blood even when the exercise (duration 120 min) is done in a warm environment [2]. Therefore, there is no adverse effect on fluid balance during exercise that could adversely affect performance [100]. In the question, if there is a disagreement for caffeine-induced diuresis at rest, the scientific literature does not report any noteworthy adverse effects of caffeine on sweat loss [104]. A study in which 50 men consumed 4X200 ml of coffee/day or water for 3 days and measured physical activity and food and fluid intake, found no changes in body mass, urine volume, and hydration indices but also in hematological indicators [103]. The authors concluded that coffee when consumed in moderation has the same hydrating properties as water [103]. Also do not forget that by drinking coffee, we receive not only caffeine but also water! Scientific research incorporated that if one drinks only caffeinated beverages the loss of water is insignificant [105]. In short, with a glass of coffee, one is hydrated just like with a glass of water.

7. Administration protocol and practical recommendations

The current knowledge related to caffeine supplementation is widespread. It is noticeable that caffeine is ergogenic in performance sports, but it is more specifically related to the athlete's condition, as well as the duration, intensity, and kind of exercise. Therefore, after considering the recent literature, the following recommendations can be drawn [2, 8, 10, 20]:

- In most studies caffeine is given 60 minutes before exercise to ensure optimal absorption.
- It can improve performance even when consumed 15 to 30 minutes before exercise.
- It is effective for strengthening various types of exercise when consumed in low to moderate doses (3 to 6 mg/kg BW).
- There is no additional benefit when consumed in higher doses (≥ 9 mg/kg BW).
- Caffeine is stronger when consumed in anhydrous form (e.g. powder), compared to coffee.
- *Practical recommendations*
- Lower doses can be just as effective in performance as

higher doses without adverse effects.
- After a period of no use, resuming its intake may have the same ergogenic effect as before or even better.
- It can be consumed gradually in low doses and during 3-4 days, before intense exercise to avoid side effects.
- Caffeine can also improve mental aspects of performance, such as concentration when an athlete is not sleeping well.
- It should not be tested for the first time before a major race.
- Athletes and coaches should also consider that age, weight, gender, substance tolerance, and dose alone can all affect its ergogenic effect on athletic performance [2, 8, 10, 20, 106].

7.1 Caffeine safety and side effects
Caffeine from 1962-1972 and 1984-2003 was on the banned list of the World Anti-Doping Authority (WADA), with a concentration>12 μg/ml in the urine to be considered doping. Caffeine is ergogenic at doses lesser than those resulting in a urinary concentration of 12 μg/ml, and elevated doses appear to have no further effect on athletic performance. The penalties ranged from warnings to 2 years of suspension (maximum penalty, usually 2-6 months). One of the reasons it was removed from the banned list was that because it is ubiquitous in food and beverages, a limit could lead to athletes being penalized possibly due to dietary caffeine intake. In addition, caffeine is metabolized at different rates in individuals and therefore urinary concentrations can vary considerably and are not always correlated with the dose taken. Nowadays the International Olympic Committee (IOC) has set a limit of 15 μg/ml of urinary caffeine. Caffeine 9-13 mg/kg ~1 hour before exercise will "catch" the maximum allowable limit [107]. Its consumption and concentration in the urine depend on factors such as gender, weight, etc. Therefore, consumption of 6-8 cups of filtered coffee which contains about 100 mg per cup will result in the maximum allowable concentration in the urine [107]. According to the IOC, post-race urinary concentrations>15 μg/ml are considered illegal. The WADA does not consider caffeine to be banned but has included it in its monitoring program to control abuse. Until now, the most frequently incorporated side-effects in the scientific literature, mainly after consumption of caffeine in very high doses (>500-600 mg or 4-7 cups/day) are anxiety, heart palpitations, headaches, hindered sleep quality, and insomnia [2].

8. Conclusions
Caffeine in its many forms (e.g. powder, gel, sports drinks, and coffee) is a common substance that acts as an ergogenic supplement and as a health aid. Its use is frequent among fitness and athletic populations. Caffeine acutely improves many features of athletic performance in most studies. Also, caffeine has been explored for potential associations with a wide range of health outcomes. The most proven beneficial associations are between coffee consumption and liver outcomes (e.g. cirrhosis, fibrosis, liver cancer, and chronic liver disease), while its consumption is also usefully associated with a wide range of other health outcomes. Moreover, it seems that there are no definitive harmful associations with any health outcomes, except for pregnancy. Caffeine exerts its ergogenic aid when consumed in doses of 3–6 mg/kg/BW commonly 60 min pre-exercise. Regarding its effects on athletic performance (a) it is mainly through its beneficial effect on the CNS; (b) may enhance the re-synthesis of glycogen during the recovery phase from exercise; (c) is ergogenic for prolonged aerobic exercise, as well as for increasing performance in fixed-term activities; (d) is beneficial for high-intensity prolonged exercise as in team sports, but improvement is more important in athletes; (e) its effect on strength/power activities are advantageous not only in athletes but also in amateur sports; (f) does not cause increased urination to the extent that it adversely affects performance during exercise; (g) does not cause changes in sweating rate, total water loss, or fluid balance that could adversely affect athletic performance, even under heat stress conditions; (i) during periods of sleep deprivation, it can improve alertness and vigilance, which is beneficial for athletes during strenuous exercise that requires constant focus. Among the most commonly incorporated side-effects, primarily after consumption of caffeine in very high doses, are anxiety and heart palpitations.

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