Caffeine and Ephedrine

Physiological, Metabolic and Performance-Enhancing Effects

Faidon Magkos and Stavros A. Kavouras

Laboratory of Nutrition and Clinical Dietetics, Department of Nutrition and Dietetics, Harokopio University, Athens, Greece

Abstract

Preparations containing caffeine and ephedrine have become increasingly popular among sports persons in recent years as a means to enhance athletic performance. This is due to a slowly accumulating body of evidence suggesting that combination of the two drugs may be more efficacious than each one alone. Caffeine is a compound with documented ergogenicity in various exercise modalities, while ephedrine and related alkaloids have not been shown, as yet, to result in any significant performance improvements. Caffeine-ephedrine mixtures, however, have been reported in several instances to confer a greater ergogenic benefit than either drug by itself. Although data are limited and heterogeneous in nature to allow for reaching consensus, the increase in performance is a rather uniform finding as it has been observed during submaximal steady-state aerobic exercise, short- and long-distance running, maximal and supramaximal anaerobic cycling, as well as weight lifting. From the metabolic point of view, combined ingestion of caffeine and ephedrine has been observed to increase blood glucose and lactate concentrations during exercise, whereas qualitatively similar effects on lipid fuels (free fatty acids and glycerol) are less pronounced. In parallel, epinephrine and dopamine concentrations are significantly increased, whereas the effects on norepinephrine are less clear.

With respect to pulmonary gas exchange during short-term intense exercise, no physiologically significant effects have been reported following ingestion of caffeine, ephedrine or their combination. Yet, during longer and/or more demanding efforts, some sporadic enhancements have indeed been shown. On the other
hand, a relatively consistent cardiovascular manifestation of the latter preparation is an increase in heart rate, in addition to that caused by exercise alone. Finally, evidence to date strongly suggests that caffeine and ephedrine combined are quite effective in decreasing the rating of perceived exertion and this seems to be independent of the type of activity being performed. In general, our knowledge and understanding of the physiological, metabolic and performance-enhancing effects of caffeine-ephedrine mixtures are still in their infancy. Research in this field is probably hampered by sound ethical concerns that preclude administration of potentially hazardous substances to human volunteers. In contrast, while it is certainly true that caffeine and especially ephedrine have been associated with several acute adverse effects on health, athletes do not seem to be concerned with these, as long as they perceive that their performance will improve. In light of the fact that caffeine and ephedra alkaloids, but not ephedrine itself, have been removed from the list of banned substances, their use in sports can be expected to rise considerably in the foreseeable future. Caffeine-ephedra mixtures may thus become one of most popular ergogenic aids in the years to come and while they may indeed prove to be one of the most effective ones, and probably one of the few legal ones, whether they also turn out to be one of the most dangerous ones awaits to be witnessed.

Athletes have always been seeking the competitive edge to improve performance and win. Dietary manipulations remain one viable alternative for achieving this goal, especially among elite athletes who share a favourable genetic endowment and train at the limit of what can be considered sustainable. Such attempts are clearly evident in the anecdotal fad diets of ancient Greek athletes, as well as in the contemporary dietary practices during training and competition for virtually any kind of sport. Along this line, the field of ergogenic aids has expanded tremendously in recent years and numerous such compounds, including potential energy sources, metabolites, recovery aids and drugs, are currently available alone or in combination and promise enhanced endurance, power, strength and speed.

Among the various ergogenic aids, only a few have scientifically documented efficacy; rather, most are used by athletes on the basis of personal testimonies of unknown truthfulness and anecdotal reports of questionable validity. In addition, some formulations may carry significant risks of adverse health effects and their use is tightly regulated or even completely banned from sports. One exception is caffeine, and more recently, the combination of caffeine with ephedra alkaloids. The purpose of this article is to provide an overview of the acute effects of combined caffeine plus ephedrine ingestion on several parameters of athletic performance and also to discuss some of the metabolic and physiological effects of such drug preparations during exercise in humans.

1. Use in Sports and Legislation

1.1 Caffeine

Caffeine consumption depends on many factors, such as natural source, age, sex, nutritional status, fitness level, peer behaviour and habituation. Use of caffeine in sports is mainly driven by its perceived ergogenic efficiency, but caffeine is also inexpensive, has little or no acute adverse effects on health, and is a socially acceptable drug. Approximately 27% of Canadian high-school students have scientifically documented efficacy; rather, most are used by athletes on the basis of personal testimonies of unknown truthfulness and anecdotal reports of questionable validity. In addition, some formulations may carry significant risks of adverse health effects and their use is tightly regulated or even completely banned from sports. One exception is caffeine, and more recently, the combination of caffeine with ephedra alkaloids. The purpose of this article is to provide an overview of the acute effects of combined caffeine plus ephedrine ingestion on several parameters of athletic performance and also to discuss some of the metabolic and physiological effects of such drug preparations during exercise in humans.

1. Use in Sports and Legislation

1.1 Caffeine

Caffeine consumption depends on many factors, such as natural source, age, sex, nutritional status, fitness level, peer behaviour and habituation. Use of caffeine in sports is mainly driven by its perceived ergogenic efficiency, but caffeine is also inexpensive, has little or no acute adverse effects on health, and is a socially acceptable drug. Approximately 27% of Canadian high-school students have scientifically documented efficacy; rather, most are used by athletes on the basis of personal testimonies of unknown truthfulness and anecdotal reports of questionable validity. In addition, some formulations may carry significant risks of adverse health effects and their use is tightly regulated or even completely banned from sports. One exception is caffeine, and more recently, the combination of caffeine with ephedra alkaloids. The purpose of this article is to provide an overview of the acute effects of combined caffeine plus ephedrine ingestion on several parameters of athletic performance and also to discuss some of the metabolic and physiological effects of such drug preparations during exercise in humans.

At the time this review was written, the proposed new global list of banned substances had not been drawn up. The new list is now available at the World Anti-Doping Agency (WADA) website: the World Anti-Doping Code – the 2004 Prohibited List – International Standard (http://www.wada-ama.org/docs/web/standards_harmonization/code/list_standard_2004.pdf). Caffeine, pseudoephedrine and phenylpropanolamine have been removed from the list, while ephedrine use remains restricted with a 10 mg/L urinary concentration limit.
and US adolescent athletes\[^{14}\] have been reported to make use of caffeine for the specific purpose of improving performance. Furthermore, 68% and 64% of >2000 US college-student athletes surveyed in 1985 and 1989, respectively, consumed the drug but claimed to do so for social reasons only.\[^{15}\] In competitive sports, there is only one described incidence of the use of caffeine suppositories by the US Cycling Team in the 1984 Olympic Games,\[^{16}\] while disqualification cases due to caffeine abuse are extremely scarce.\[^{17}\] For instance, in two recent doping cases, a US sprinter was stripped of a bronze medal in the 60m at the 1999 World Indoor Championships after a positive caffeine test and a female runner from Suriname lost her gold medal in the 800m at the 2003 Pan American Games over the same offense.\[^{18}\] It is believed, however, that use of stimulants in general\[^{19}\] and caffeine in particular\[^{20,21}\] among both professional and amateur athletes is much more widespread.

Until recently, caffeine was a restricted compound in sports, with a 12 mg/L urinary concentration limit set by the International Olympic Committee (IOC).\[^{18,22}\] However, oral doses up to 9 mg/kg ingested approximately 1 hour prior to exercise result in postexercise urine levels that are generally below the IOC’s cut-off point,\[^{23,24}\] while the likelihood to exceed 12 mg/L increases significantly with higher caffeine doses, e.g. 13 mg/kg.\[^{24}\] Fear that the IOC limit in urine might be violated has probably kept consumption of caffeine by athletes at generally low and safe amounts. Amazingly, however, the drug is about to be taken off the proposed new global list of banned substances, to be drawn up by the World Anti-Doping Agency.\[^{18}\] The usefulness of the IOC cut-off has been questioned several times in the past\[^{21,25}\] and caffeine use by athletes has repeatedly given rise to significant ethical concerns.\[^{21,25,26}\] The decision of sport governing bodies to legalise caffeine, however, is a diametrically opposite response to the concerns of the scientific community and seems hardly logical. In light of this development, use of caffeine among sportspersons can be expected to rise considerably in the foreseeable future.

It is also important to note that many athletes perceive the ergogenic effects of a given substance in a ‘linear’ fashion, i.e. the greater the dose the greater the benefit. It would not be surprising, therefore, if some individuals resort to consuming much larger amounts of caffeine than the recommended ‘optimum’ dose, which lies between 3 and 6 mg/kg.\[^{12,27}\] Nevertheless, plasma caffeine concentrations rise in a dose-dependent manner at rest and during exercise, and an oral dose of 9 mg/kg results in peak plasma levels of approximately 70–80 µmol/L.\[^{28}\] This is just below 100 µmol/L, which is considered the upper limit above which caffeine’s metabolism saturates (although saturation may occur at even lower concentrations)\[^{29}\] and is approximately 2.5-fold lower than the toxic range in humans (i.e. 200 µmol/L).\[^{30}\] Unrestricted use of caffeine by athletes may result in consumption of multi-fold higher doses, and one cannot rule out the possibility of manifestation of serious acute adverse health effects, especially among caffeine-naive individuals.

### 1.2 Ephedrine

Ephedrine and related compounds (pseudoephedrine and phenylpropanolamine) are structurally similar to amphetamines; they are widely used alone, or in combination with caffeine, as weight loss adjuncts or ‘fat burners’ among both athletes and non-athletes.\[^{31-33}\] A recent meta-analysis of published studies concluded that such preparations may indeed be effective for short-term weight loss.\[^{34}\] Information on the use of ephedra alkaloids in sports, however, is scarce. It has been reported that ephedrine, pseudoephedrine and phenylpropanolamine, as a group, accounted for 31% (35 out of 113) of the positive samples detected among 2066 urine specimens collected from competitors in 17 different sports during the period 1986–91.\[^{35}\] In the 1972 Olympic Games, a 16-year-old US athlete was compelled to return his gold medal due to ephedrine use prior to competition and despite claiming that he had made use of the drug for treatment of his asthma as prescribed by his physician.\[^{36}\] More recently, a Romanian teenage gymnast had her all-around gold medal taken away at the 2000 Olympic Games in Sydney, after her doctor gave her a cold remedy containing pseudoephedrine.\[^{18}\] Urine concentrations >10 mg/L for ephedrine\[^{37}\] and >25 mg/L for pseudoephedrine\[^{38}\] are considered positive by most sport governing bodies at present. Besides urinal-
ysis, hair analysis techniques are also being developed as useful adjuncts to conventional drug testing for identifying doping cases with ephedrine.\textsuperscript{[39]}

Of interest, in a recent survey, anonymous questionnaires were distributed to 511 clients entering five commercial fitness centres in the US.\textsuperscript{[40]} Twenty-five percent of men and 13% of women attendees reported ephedrine use within the previous 3 years; extrapolation from these results (109 subjects or 21.3%) to a national level would translate into approximately 2.8 million US recreational athletes and fitness enthusiasts making use of the drug.\textsuperscript{[40]}
The latest National Collegiate Athletic Association (NCAA) study of substance use habits of college-student athletes,\textsuperscript{[41]} involving 21225 individuals from 713 NCAA member institutions, has also revealed a number of interesting findings. It was shown that ephedrine use increased from 3.5% in 1997 to 3.9% in 2001 and this was especially true among female athletes. The frequency of use varied from 0% (gymnastics, rifle) to 5.5% (lacrosse) among men, and from 0% (skiing) to 11.8% (ice hockey) among women.\textsuperscript{[41]} The main reasons stated for using ephedrine were to improve athletic performance (23.6%), as an appetite suppressant or weight-loss aid (21.7%), for health reasons in general (21.5%) and to improve appearance (20.3%).\textsuperscript{[41]}
Also, use of the drug appears now to start for the majority of student athletes prior to college, i.e. in high school, contrary to what was observed in 1997, when ephedrine use began after college.\textsuperscript{[41]}

Several authors have expressed their concern over ephedrine and pointed out recreational\textsuperscript{[25]} and adolescent\textsuperscript{[42]} athletes as subsets of the population especially prone to consuming the drug. Interestingly, however, ephedrine-related alkaloids like pseudoephedrine and phenylpropanolamine, but not ephedrine itself, are also soon to be legalised in sports.\textsuperscript{[18]} hence, foretelling an expansion of their use among professional athletes as well. The combination of caffeine and ephedra alkaloids may thus become one of the most popular ergogenic aids among athletes in the years to come. These two drugs also coexist in many commercially available dietary supplements and, in several cases, this is without being clearly declared on the labels.\textsuperscript{[43]}

Ephedrine and pseudoephedrine share comparable pharmacokinetics, reaching peak plasma concentrations approximately 2.4 hours after oral ingestion, i.e. slightly later than caffeine.\textsuperscript{[44]} The pharmacokinetic disposition of all these compounds in plasma can be well described by a single-compartment model with a typical rise-then-fall pattern, i.e. it follows first order, linear kinetics.\textsuperscript{[44]} Half-lives for elimination from the plasma compartment are also similar, ranging from 4.5 to 8 hours for ephedrine, from 4.5 to 10 hours for pseudoephedrine and from 3.5 to 8 hours for caffeine.\textsuperscript{[44]} These figures are in accordance with published values reported for each compound alone,\textsuperscript{[29,33,45,46]} implying that no significant pharmacokinetic interaction between the three drugs takes place when ingested in combination.\textsuperscript{[44]}

2. Performance Enhancement

2.1 Caffeine

The ergogenic effects of caffeine are well documented. Since the initial studies by Rivers and Webster,\textsuperscript{[47]} a number of reports have shown that ingestion of the drug may enhance exercise performance. Work by the Costill laboratory\textsuperscript{[48-50]} renewed interest in caffeine in the late 1970s, whereas Graham and Spriet\textsuperscript{[23]} and Spriet\textsuperscript{[51]} in the early 1990s demonstrated beyond doubt that ingestion of the drug may result in substantial improvements in endurance. Almost 20 review articles dealing specifically with the ergogenicity of caffeine under various exercise modes have been published during the last 15 years,\textsuperscript{[12,17,21,25-27,52-63]} and their findings will not be reproduced here. The most consistent observation is that caffeine can increase time to exhaustion during submaximal exercise bouts lasting approximately 30–60 minutes. Speed and power output during such activities may also improve. Aerobic endurance during shorter events (5–25 minutes) has been reported to be either enhanced or unaffected by prior caffeine ingestion. Positive effects are less frequently observed during shorter-term and more intense bouts, while the same holds true for incremental exercise. Finally, the limited data available suggest that caffeine may enhance some aspects of the neuromuscular function in vivo in humans.\textsuperscript{[63]} Although the exact biochemical mechanisms underlying the ergogenic effects of caffeine are not fully understood,\textsuperscript{[12]} a
number of cellular actions that could potentially contribute to or account for these effects have been identified. [29, 64]

2.2 Ephedra Alkaloids

Evidence for a performance-enhancing effect of ephedrine is equivocal. In fact, and despite being perceived by the public as an ergogenic agent, most studies have not demonstrated any kind of improvement in athletic performance following ingestion of ephedra alkaloids at doses generally considered to be safe, i.e. up to 120mg. [37, 65, 66] Foltz et al. [67] were some of the first to describe the effects of ephedrine-containing preparations on performance during high-intensity exercise in four medical students. Many years later, Sidney and Lefcoe [68] carried out an elaborate study with 21 healthy males, where the effects of a low dose of ephedrine (24mg) on several parameters of exercise capacity were examined. Ephedrine ingestion did not influence muscle strength, endurance, power, anaerobic capacity, speed, reaction time, hand-eye coordination or recovery from effort. [68]

Another investigation evaluated the effects of pseudoephedrine ingestion (120mg), taken approximately 2 hours prior to testing, on exercise performance during a 40km cycle ergometry time trial, and on skeletal muscle function as measured during isometric contractions before and after exercise in ten male cyclists. [69] For the cycling test, times ranged from 53.8 to 69.7 minutes after drug ingestion and from 53.1 to 65.9 minutes after placebo ingestion; mean times after pseudoephedrine (58.7 ± 1.5 minutes) and placebo (58.1 ± 1.4 minutes) were not significantly different. [69] Likewise, neither maximum voluntary contraction (MVC) nor time to fatigue were affected by drug ingestion, either before or after exercise [69]. Corroborating these findings, Swain et al. [70] studied 20 male cyclists, ten of whom received typical doses of phenylpropanolamine (0.33 or 0.66 mg/kg) and the remaining ten were given pseudoephedrine (1 or 2 mg/kg). There were no significant improvements in time to exhaustion during a bicycle ergometry test in either group, regardless of drug dose. [70]

In a more recent investigation, the effects of pseudoephedrine (120mg) ingested approximately 2 hours before testing were examined in ten male and nine female volunteers. [38] The subjects completed a number of battery tests to evaluate skeletal muscle function, including MVC measurements, a 60-second intermittent isometric handgrip protocol and dorsi-flexion testing of the right ankle; they also completed a 30-second maximal cycling test to determine anaerobic power output. [38] No effects of drug treatment on any of these performance parameters were observed. [38]

Apparently, isolated use of ephedra alkaloids at recommended doses does not seem to enhance athletic performance under a variety of different exercise modalities. However, in their brief communication, Walton et al. [71] observed an ergogenic effect in eleven male athletes, who were given pseudoephedrine (120mg) approximately 2 hours prior to testing, which included measurements of the neuromuscular function of the quadriceps muscle (twitch torque, MVC, post-tetanic torque), submaximal cycling ergometry (time to exhaustion at 80% of maximal oxygen uptake [ \( \dot{V}O_2 \text{max} \) ], and a series of two Wingate tests. These investigators reported a greater (p = 0.04) absolute and relative mean power output during the Wingate and a strong trend (p < 0.11) towards increased MVC after drug ingestion. [71] Another study was undertaken to determine whether a higher than therapeutic dose of pseudoephedrine (180mg) would produce any ergogenic effects during short-term maximal exercise. [72] Twenty-two male athletes were recruited and were given pseudoephedrine or placebo 45 minutes prior to testing, which included isometric knee extension, muscle motor unit activation measurements, bench press at 70% and 100% of one repetition maximum (1RM), and a 30-second ‘all-out’ cycle test. [72] Pseudoephedrine increased peak torque by 8.6% over placebo during knee extension (321.1 ± 62.0 vs 295.7 ± 72.4Nm, respectively), but did not affect muscle activation; the drug did not influence weight-lifting performance at either 70% or 100% of 1RM and did not affect total work production during the 30-second cycle ride; however, it did increase peak power by 2.8% during the latter test (1262.5 ± 48.5 vs 1228.4 ± 47.1W, respectively). [72]

These findings and those from previous studies could imply that a threshold dosage level may exist for the ergogenic effects of ephedra to manifest. Alternatively, the drug may be effective in increas-
drine-related alkaloids, but not ephedrine itself, is about to become unrestricted in sports. It should be noted here that pseudoephedrine is approximately 2.5-fold less potent than ephedrine on an equal weight basis; hence, for instance, a 120mg dose of the former is equivalent to a 48mg dose of the latter. Alternatively, ephedrine doses equal to 0.8–1.0 mg/kg (as those used in the studies described later in this section) are equivalent to pseudoephedrine doses of 2–2.5 mg/kg.

In the first of the studies examining the effects of caffeine-ephedrine mixtures on athletic performance, ingestion of a combined dose of caffeine (5 mg/kg) plus ephedrine (1 mg/kg) resulted in an approximate 38% improvement in time to exhaustion compared with placebo during submaximal cycle ergometry exercise (figure 1a). This effect was greater than that of caffeine or ephedrine alone, the latter two being not significantly different from placebo, and was also preserved with lower drug doses that minimised adverse effects (figure 1b). The same investigators undertook two field trials where they also demonstrated an ergogenic effect of the combination treatment. In the first study, nine male runners performed the Canadian Forces Warrior Test, which consists of 3.2km of running performance only during specific types of activity and only under certain circumstances. The first possibility, however, is not supported by more recent data. Chester et al.[73] had eight male runners perform an exercise session consisting of 20 minutes of submaximal running at 70% of VO2max, followed by a 5km time trial on the treadmill, under pseudoephedrine (60mg four times daily, i.e. 240 mg/day), phenylpropanolamine (25mg four times daily, i.e. 100 mg/day) or placebo conditions; treatments were administered over the 36-hour period prior to testing.[73] There were no differences in time to complete the runs between any of these trials.[73]

2.3 Caffeine-Ephedrine Mixtures

As exemplified in sections 2.1 and 2.2, although caffeine alone can be ergogenic under many circumstances, ephedra alkaloids by themselves are probably not. The recent surge of interest has been fuelled by several contemporary reports indicating that combined use of caffeine and ephedrine may be of greater ergogenic benefit than each compound alone.[25,63] This combination seems timelier now than ever before, since the use of caffeine and ephedrine-related alkaloids, but not ephedrine itself, is about to become unrestricted in sports.[18] It should be noted here that pseudoephedrine is approximately 2.5-fold less potent than ephedrine on an equal weight basis; hence, for instance, a 120mg dose of the former is equivalent to a 48mg dose of the latter.[69] Alternatively, ephedrine doses equal to 0.8–1.0 mg/kg (as those used in the studies described later in this section) are equivalent to pseudoephedrine doses of 2–2.5 mg/kg.

In the first of the studies examining the effects of caffeine-ephedrine mixtures on athletic performance, ingestion of a combined dose of caffeine (5 mg/kg) plus ephedrine (1 mg/kg) resulted in an approximate 38% improvement in time to exhaustion compared with placebo during submaximal cycle ergometry exercise (figure 1a). This effect was greater than that of caffeine or ephedrine alone, the latter two being not significantly different from placebo, and was also preserved with lower drug doses that minimised adverse effects (figure 1b).[74] The same investigators undertook two field trials where they also demonstrated an ergogenic effect of the combination treatment. In the first study, nine male recreational runners performed the Canadian Forces Warrior Test, which consists of 3.2km of running...
Fig. 3. Effects of caffeine (CAF) and ephedrine (EPH) alone or in combination (C+E) on anaerobic exercise performance during the Wingate test. Sixteen male volunteers ingested placebo (PL), CAF 5 mg/kg, EPH 1 mg/kg or C+E (CAF 5 mg/kg and EPH 1 mg/kg). After 90 minutes of rest they performed the 30-second Wingate cycle test. Values for power output are shown as mean ± standard error. * p < 0.05 for EPH and C+E vs CAF and PL. [78]

running while wearing ‘fighting order’ weighing approximately 11kg. [76] The trials were performed in sets of two runs, i.e. two tests were done 24 hours apart, with placebo or caffeine (375mg) plus ephedrine (75mg) being ingested alternatively during the first or the second day. Run times were significantly reduced by approximately 4.5% when caffeine and ephedrine were ingested 2 hours prior to exercise compared with placebo (14.6–14.8 vs 15.3–15.5 minutes, respectively). [76] In the second study, ten male and two female recreational runners performed a 10km race while wearing the same 11kg gear, approximately 1.5 hours after ingesting placebo, caffeine (4 mg/kg), ephedrine (0.8 mg/kg) or a combination of the two drugs (4 mg/kg caffeine and 0.8 mg/kg ephedrine). [77] In this case, time to complete the run for the ephedrine trials (45.5 ± 2.9 and 45.7 ± 3.3 minutes for ephedrine alone and ephedrine-caffeine, respectively) was significantly reduced by approximately 2% compared with the non-ephedrine trials (46.0 ± 2.8 and 46.8 ± 3.2 minutes for caffeine alone and placebo, respectively); this was attributed to an apparent increase in pace (approximately +0.5 km/h) over the last 5km of the run (figure 2). [77]

The combined drug treatment seems to be of ergogenic benefit not only during submaximal short- and long-term exercise, but in various other exercise modalities as well. For instance, Bell et al. [78] demonstrated a small (1–2%) but significant increase in power output during the 30-second Wingate test following ingestion of ephedrine alone or in combination with caffeine, compared with caffeine alone or placebo; this effect was only evident early during the ride (figure 3). In another experiment, time to exhaustion and oxygen deficit during a maximal accumulated oxygen deficit (MAOD) test were increased by 7–8% following administration of caffeine (alone or with ephedrine) compared with ephedrine alone or placebo; however, accumulated oxygen consumption (˙VO2) was not significantly affected (figure 4). [78] In both instances, therefore, ingestion of the caffeine-ephedrine mixture was associated with significant improvements in performance, regardless of the relative contribution of each drug to the ergogenic effect of the combined preparation.

A recent study from the same laboratory [79] (see also Pasternak et al. [80]) examined the effects of caffeine and ephedrine, alone or in combination, on muscular endurance during a weight-lifting circuit consisting of three supersets, each comprising leg press followed by bench press. Again, compared with the non-ephedrine trials (caffeine alone and placebo), ephedrine ingestion, either alone or with caffeine, resulted in significant increases in the
Effects of caffeine (CAF) and ephedrine (EPH) alone or in combination (C+E) on anaerobic exercise performance during the maximal accumulated oxygen deficit (MAOD) test. Eight male volunteers ingested placebo (PL), CAF 5 mg/kg, EPH 1 mg/kg or C+E (CAF 5 mg/kg and EPH 1 mg/kg). After 90 minutes of rest they performed the MAOD test, i.e. supramaximal cycling at 125% of \( \dot{V}O_2 \text{peak} \). Values are shown as mean ± standard error. *\( p < 0.05 \) for CAF and C+E vs EPH and PL. [78] 

\( \dot{V}O_2 = \) oxygen consumption; \( \dot{V}O_2 \text{peak} = \) peak oxygen consumption.

Collectively, these data lend strong support to the premise that both aerobic and anaerobic performance is improved, although to a variable degree, after ingestion of a combination of caffeine plus ephedrine. Still, available research is extremely limited and quite heterogeneous in nature, thus any conclusions remain tentative. While there seems to be little doubt that caffeine-ephedrine mixtures can improve athletic performance relative to placebo, the putative additional effect of ephedrine, on top of that caused by caffeine alone (i.e. caffeine-ephedrine vs caffeine alone) is less consistent and needs further investigation. The two drugs act independently and probably additively rather than interactively, i.e. there seem to be no synergistic effects. [74,77,78,81,82] It is of interest to note that groups of subjects participating in the above-mentioned experiments consisted of individuals who were regular coffee drinkers, or had variable habitual caffeine consumption and who did not abstain from caffeine-containing products prior to testing for a period longer than 24–48 hours. [74-79] Thus, it seems that caffeine habituation and perhaps the development of tolerance to some caffeine-induced physiological effects (e.g. cardiovascular stimulation and catecholamine release), [83] do not impair the ergogenic potential of the mixed treatment. This is in agreement with the results for the ergogenic nature of isolated caffeine use [84] and attests to the general consensus that caffeine habituation and withdrawal have no major influence of the performance-enhancing ability of the drug. [12,63]
3. Hormonal Response

Studies examining the hormonal response to the ingestion of caffeine, ephedrine or their combination have generally been limited to catecholamines (epinephrine and norepinephrine) and monoamines (dopamine). In most circumstances, epinephrine levels were increased throughout exercise in the caffeine trials (alone or with ephedrine) compared with ephedrine alone or placebo. It seems that caffeine-induced increases in plasma epinephrine are independent of the type of exercise, since they have been observed during either submaximal steady-state bouts or anaerobic bouts such as the Wingate and the MAOD tests. In both instances, however, the drugs led to higher epinephrine concentrations already before exercise initiation, i.e. after the initial period of rest following drug ingestion. Apparently, therefore, individuals under the caffeine and caffeine-ephedrine treatments commenced exercise with higher epinephrine levels, so it is not clear whether a catecholaminergic effect was manifested also during exercise or merely reflected a residual effect of the drugs at rest. A very interesting response was reported by Bell et al. in their study involving 10km of running at above 90% of peak oxygen consumption (VO₂peak). These investigators observed that caffeine alone enhanced epinephrine concentrations, whereas ephedrine alone attenuated this response; as a result, the combined ingestion of both drugs had no effect on the time course of plasma epinephrine, which was strikingly similar to that after placebo ingestion (figure 6).

The results for norepinephrine are quite mixed. During submaximal steady-state exercise lasting approximately 15 minutes, norepinephrine levels were unaffected by caffeine, ephedrine or their combination; still, they were higher at exhaustion in the two ephedrine trials. On the other hand, during the first 30 minutes of a 10km run, norepinephrine concentrations were greater for the caffeine and the caffeine-ephedrine treatments compared with ephedrine alone and placebo. Moreover, during the Wingate cycle ride, norepinephrine was similarly increased by both caffeine and ephedrine, and their combination was additive (i.e. caffeine-ephedrine > caffeine alone = ephedrine alone > placebo). No effect of either drug or their combination, however, was evident during the MAOD cycle test. Whether the variability in norepinephrine responses could rest on the different exercise modalities or on other factors is unknown at present. Overall, ingestion of caffeine and ephedrine combined seems to be able to

---

**Fig. 5. Effects of caffeine (CAF) and ephedrine (EPH) alone or in combination (C+E) on weight-lifting performance. Thirteen males ingested placebo (PL), CAF 4 mg/kg, EPH 0.8 mg/kg or C+E (CAF 4 mg/kg and EPH 0.8 mg/kg). After 90 minutes of rest, they performed a weight-training circuit consisting of three supersets, each comprising leg press (at 80% of 1RM to exhaustion) followed by bench press (at 70% of 1RM to exhaustion) with 2 minutes of rest in between. Values for the number of repetitions during leg press (a) and bench press (b) are shown as mean ± standard error. * p < 0.05 for EPH and C+E vs CAF and PL. ** 1RM = 1 repetition maximum.
produce sporadic increases in plasma norepinephrine, at least during some exercise types. In contrast, much more consistent findings have been reported for dopamine: ingestion of ephedrine alone or ephedrine plus caffeine has uniformly resulted in markedly increased dopamine concentrations compared with caffeine alone or placebo treatments; this was regardless of the type of exercise, i.e. aerobic or anaerobic and submaximal or maximal (figure 7). [74,77,78]

Considering the potential contribution of each individual drug to these effects, acute administration of caffeine has been associated with higher epinephrine concentrations at rest and during exercise of various modalities and only rarely has this not been observed (for review see Magkos and Kavouras[63]). On the contrary, caffeine-induced increases in norepinephrine levels are seldom observed.[63] A recent investigation by Graham et al.,[85] however, found that muscle norepinephrine spillover during exercise more than doubled after caffeine ingestion compared with placebo. With respect to dopamine, the limited available studies indicate no effects of caffeine either at rest[83,86,87] or during exercise,[87] although one study reported an increase in dopamine levels after caffeine ingestion during the recovery period from exercise.[87] Unfortunately, studies examining the isolated use of ephedra alkaloids during exercise in humans have not measured hormonal concentrations.

In summary, it seems that ingestion of caffeine-ephedrine mixtures leads to increased epinephrine concentrations at rest and during exercise, and this is probably due to the caffeine content of the preparation. Significant increases in dopamine levels during exercise are also observed, but by contrast, these seem to result from the ephedrine component of the mixture. Norepinephrine responses are quite variable. Both drugs may enhance norepinephrine turnover, but each one alone only modestly; a combination of the two, however, probably potentiates this effect.

4. Substrate Metabolism

Unfortunately, very limited information is available with respect to substrate shifts during exercise following ingestion of caffeine-ephedrine mixtures. The most well characterised metabolite response is probably that of lactate. Plasma lactate concentrations have been reported to increase after ingestion...
Caffeine-Ephedrine Mixtures and Exercise

of caffeine plus ephedrine; this is a rather uniform finding, as it has been observed during a steady-state submaximal run lasting approximately 15 minutes,[74] an aerobic 10km time trial lasting approximately 45 minutes[77] and an anaerobic 30-second Wingate cycle test.[78] It seems that the two drugs have additive effects and both account for the increase in lactate levels, although caffeine may contribute to a greater extent.[74,77,78] In accordance with this hypothesis, Graham[12] recently outlined that caffeine ingestion alone has very often been observed to increase blood lactate during exercise. On the contrary, isolated use of ephedra alkaloids has consistently not induced any change in lactate concentrations during various exercise modes, such as prolonged aerobic cycling,[69] submaximal steady-state running,[73] 'all-out' anaerobic cycling[38,72] or isometric handgrip exercise.[38] There is only one report of a tendency (p < 0.15) for pseudoephedrine to increase blood lactate levels at the end of the Wingate test,[71] a finding that is not supported by others.[38,72]

A similar pattern of response as that for lactate has also been observed in the case of blood glucose. Ingestion of caffeine-ephedrine mixtures has been associated with higher concentrations of glucose during various exercise modes compared with ingestion of either compound alone or placebo.[74,77,78] In this case, the two drugs seem to contribute equally to the hyperglycaemic effect observed after their combined use.[74,77,78] Still, although caffeine alone may sometimes lead to increased blood glucose levels compared with placebo, generally it exerts no such effect.[12] Likewise, the only study that measured glucose concentrations during exercise after pseudoephedrine, phenylpropanolamine or placebo ingestion found no significant differences between the treatments.[73] Therefore, a synergistic effect

![Graphs showing effects of caffeine (CAF) and ephedrine (EPH) alone or in combination (C+E) on dopamine levels during various exercise types.](image-url)

**Steady-state cycling**: see figure 1 for details on the experimental protocol. § p < 0.05 for C+E vs CAF and placebo (PL); * p < 0.05 for EPH and C+E vs CAF and PL.[74] Long-distance running: see figure 2 for details on the experimental protocol. * p < 0.05 for EPH and C+E vs CAF and PL (reproduced from Bell et al.,[77] with permission). Wingate test: see figure 3 for details on the experimental protocol. * p < 0.05 for EPH and C+E vs CAF and PL.[78] MAOD test: see figure 4 for details on the experimental protocol. * p < 0.05 for EPH and C+E vs CAF and PL.[78] All values are shown as mean ± standard error. MAOD = maximal accumulated oxygen deficit.
cannot be ruled out in the case of blood glucose when caffeine and ephedrine are ingested in combination.

With respect to free fatty acid (FFA) and glycerol concentrations, the limited information available suggests that no significant alteration occurs after ingesting a mixture of caffeine plus ephedrine, beyond that caused by exercise itself or by each drug separately. During steady-state running at 85% of VO_{2peak}, FFA concentrations were similar between placebo, ephedrine and caffeine plus ephedrine trials, but in all three treatments, FFA levels were approximately 100–150 µmol/L lower than in the caffeine-only trial, both prior to and during exercise. On the contrary, during a time trial involving running as fast as possible (at above 90% of VO_{2peak}), FFA levels were similar for all conditions at the beginning of exercise, but were sporadically increased in the ephedrine-containing trials (ephedrine and caffeine-ephedrine) compared with the non-ephedrine ones (caffeine and placebo).

Similarly, plasma glycerol has been reported either to increase or remain unchanged after consumption of caffeine plus ephedrine. In both instances, however, ingestion of caffeine alone led to significantly higher glycerol concentrations than ephedrine alone or placebo. Although these findings are difficult to interpret, it is probably caffeine that brings about any changes in circulating lipid fuels observed following ingestion of caffeine-ephedrine mixtures. Isolated use of caffeine has been associated with increased FFA concentrations, yet this has been observed much more frequently at rest than during exercise; the effects of the drug on glycerol levels are less clear, with both increases and no changes being reported (reviewed in Magkos and Kavouras). On the other hand, it is disappointing to note the almost complete lack of studies measuring FFA and/or glycerol concentrations during exercise following ingestion of ephedra alkaloids alone; however, in those who did, no significant effects were reported.

5. Cardiovascular Effects

Ingestion of preparations containing caffeine and ephedrine approximately 1.5–2 hours before commencing exercise has repeatedly been shown to result in an increase in heart rate (HR) above that caused by exercise alone and this has been observed during either steady-state submaximal exercise lasting 10–30 minutes, or during short-distance and long-distance time trials. A similar but transient increase in HR has also been observed during submaximal (50% of VO_{2peak}) exercise in a hot (40°C) and humid (30% relative humidity) environment, following ingestion of the two drugs. A question remains, however, as to whether this response is due to caffeine, ephedrine or both. During running at 85% of VO_{2peak}, the combination of caffeine with ephedrine and to a lesser extent, caffeine alone, significantly increased HR above that recorded in the other two trials (ephedrine alone and placebo). When running at >90% of VO_{2peak}, however, treatment with ephedrine (alone or with caffeine) produced a slight but significant increase in the mean HR response throughout exercise (176 ± 12 beats/min) compared with the non-ephedrine trials (caffeine alone and placebo, 174 ± 13 beats/min).

There are no studies available regarding the effects of caffeine-ephedrine mixtures on the pressor response to exercise. Jacobs et al. recently observed an increase in systolic, but not diastolic blood pressure (BP) just before commencing a weight-lifting circuit, following ingestion of ephedrine (alone or with caffeine) compared with caffeine alone and placebo. However, no data on BP during exercise were reported. In an earlier communication, the same group measured BP responses over a 48-hour period involving only activities of daily living (no specific exercise), under placebo, caffeine (375mg), ephedrine (75mg) or a combination of the latter two treatments. They, too, observed that systolic BP increased the most after the caffeine-ephedrine treatment, reaching hypertensive values after 1 hour (138 ± 11mm Hg); each drug alone also produced a significant increase in systolic BP (132 ± 10 and 126 ± 10mm Hg after ephedrine and caffeine, respectively) compared with placebo (118 ± 8mm Hg). The pattern of response at the 1-hour mark was caffeine-ephedrine > ephedrine = caffeine > placebo, but at 8 hours and thereafter, systolic BP had returned to baseline. The three drug treatments also produced similar and significant increases in diastolic BP, but these were considerably smaller in magnitude and duration.
Studies into the effects of ephedra alkaloids alone on HR and BP prior to or during exercise and recovery have generally provided mixed results, with either increases or no alterations being observed. The results for the isolated use of caffeine are more homogeneous, with the majority of evidence showing no effect on HR during exercise and an increase in BP, although some have also reported an increase in HR. It seems, therefore, that both drugs are able to influence HR and/or BP during exercise, albeit modestly. Ephedrine, however, probably contributes to a greater extent to the uniform increases in HR observed during submaximal aerobic exercise after ingestion of caffeine-ephedrine mixtures.

6. Pulmonary Function and Gas Exchange

Measurements of pulmonary gas exchange during short-term submaximal steady-state exercise in humans, following ingestion of caffeine-ephedrine mixtures, have generally revealed no significant effects on VO₂, carbon dioxide release (VCO₂) or minute ventilation (VE). In one study, all variables increased progressively during exercise, but there were no differences between the various drug treatments and placebo; timecourse curves were almost super-imposable (figure 8). Similar results have been obtained regardless of whether a high or a low caffeine-ephedrine dose was administered. However, during a time trial consisting of 10km of running, VO₂, VCO₂ and VE were inconsistently affected by treatment: ingestion of ephedrine (alone or with caffeine) only tended to increase VO₂ and did increase VCO₂ after 9km of running, whereas VE was significantly greater for the caffeine-only trial at 15 minutes into exercise, and for the caffeine-ephedrine trial at the 9km time point. Also, during submaximal exercise at 50% of VO₂peak in a hot and humid environment, lasting approximately 2 hours, the combination of caffeine plus ephedrine has been shown to result in increased VO₂ and VE relative to placebo/control treatments.

Looking into the isolated effects of each drug, ephedra alkaloids have not been shown to result in any consistent and/or significant alterations in the pulmonary function and gas exchange during exercise in humans, irrespective of the type of alkaloid (ephedrine, pseudoephedrine, phenylpropanolamine) and the mode of exercise (steady-state sub-
Fig. 9. Effects of caffeine (CAF) and ephedrine (EPH) alone or in combination (C+E) on rating of perceived exertion (RPE) during exercise. Eight recreationally active male volunteers ingested placebo (PL), CAF 5 mg/kg, EPH 1 mg/kg or C+E (CAF 5 mg/kg and EPH 1 mg/kg). After 90 minutes of rest they performed a 5-minute warm-up at 50% ofVO₂peak and then cycled to volitional exhaustion at 85% ofVO₂peak. Subjects were asked to rate their perceived exertion on the Borg scale. Values are shown as mean ± standard error. * p < 0.05 for C+E vs CAF and PL.[74]

maximal, incremental, time trials).[36,68,70,73,91] Only one study could be identified where pseudoephedrine (180mg) was reported to enhance lung function, as witnessed by significant post-exercise increments in the forced vital capacity (FVC), i.e. the volume expired from maximum inspiration to rapid forced maximum exhalation, and the forced expiratory volume in 1 second (FEV₁); the forced expiratory ratio at the first second (FER₁), however, calculated as the ratio of FEV₁ to FVC and used as a measure of airway resistance, was not different.[72] With respect to the pulmonary gas exchange during exercise following acute caffeine administration, evidence abounds but is rather heterogeneous in nature: some studies observed an increase in exercise VO₂ after caffeine ingestion.[49,92,102,106-109] whereas others reported no effects on VO₂, VCO₂, or VE.[48,84,85,87,97,99,110-113]

7. Psychophysiological Correlates

In addition to putative actions in the periphery, both caffeine and ephedra alkaloids have considerable stimulatory effects on the CNS.[114,116] Ephedrine, pseudoephedrine, phenylpropanolamine and caffeine act on peripheral and central neurons, and exert their effects either by binding directly to cell surface receptors or by increasing release and/or inhibiting reuptake of neurotransmitters, which are then available to bind to and activate receptors.[117] Alteration of brain neurotransmitter function leading to reduced sensation of effort, for instance, may be a plausible mechanism by which caffeine-ephedrine mixtures could enhance athletic performance. In fact, the subjective feeling of effort during sub-maximal steady-state exercise, as measured by the rating of perceived exertion (RPE), has been shown to be less after ingestion of caffeine and ephedrine combined, than after ingestion of each drug alone or placebo; this coincided with delayed onset of fatigue under the caffeine-ephedrine treatment (figure 9).[74] Also, the reduction in RPE does not seem to depend on the exact dose of caffeine and ephedrine in the mixture.[75]

It was reported recently that RPE during a time trial involving 10km of running was similar between placebo, caffeine, ephedrine, and caffeine plus ephedrine treatments, and this was despite the fact that pace was significantly higher in the ephedrine trials (alone or with caffeine) compared with the non-ephedrine trials (caffeine and placebo).[77] From a simplistic point of view, this means that subjects under ephedrine were able to run faster, i.e. exercise
at a higher intensity, and yet, perceive this effort as less intense. Although these findings imply that it is the ephedrine component that is responsible for the reduced sensation of effort following ingestion of caffeine-ephedrine mixtures, studies examining the isolated effects of ephedra alkaloids have failed to support this notion.\textsuperscript{[36,68,70,73,91]} On the other hand, caffeine alone may indeed be able to reduce\textsuperscript{[48,97,101,102,109,118,119]} or strongly tend to reduce\textsuperscript{[93,120]} RPE during various exercise modalities, although not uniformly.\textsuperscript{[87,99,100,113,121]}

Of interest are the results reported in the initial study by Ivy et al.,\textsuperscript{[49]} where nine trained cyclists ingested placebo or caffeine (250mg before and 250mg during exercise) and then performed 120 minutes of isokinetic cycling at 80 rpm. In this type of cycle ergometry, speed is fixed and resistance is variable, thus work production is also variable. It was shown that RPE was similar between the caffeine (12.3 ± 0.34) and the placebo (13.3 ± 0.20) trials, despite total work produced being significantly greater (+7.4%) under the drug treatment.\textsuperscript{[49]} This finding was subsequently confirmed by others\textsuperscript{[96,122]} and is equivalent to that reported by Bell et al.\textsuperscript{[77]} for caffeine plus ephedrine, referred to earlier in this section. Recently, caffeine alone was shown to be effective in decreasing RPE during high-intensity exercise (80% of VO\textsubscript{2max}: 14.7 ± 2.2 vs 15.6 ± 2.3 for caffeine and placebo, respectively) but not during moderate-intensity exercise (50% of VO\textsubscript{2max}: 8.8 ± 1.2 vs 8.6 ± 1.1, for caffeine and placebo, respectively).\textsuperscript{[102]} This implies that the drug may become increasingly capable of reducing sensation of effort as more strenuous activity is being performed. Collectively, it is difficult to weigh the relative contribution of caffeine and ephedrine in the reduction of RPE during exercise after ingestion of caffeine-ephedrine mixtures, but it is clear that such a CNS-related mechanism is operational \textit{in vivo} and could indeed be responsible for the ergogenic effects of the combined drug treatment.

8. Conclusion

In light of the fact that caffeine and ephedrine-related compounds such as pseudoephedrine and phenylpropanolamine are about to legalised in sports,\textsuperscript{[18]} their use by professional athletes can be expected to rise considerably in the foreseeable future. The decision of sport governing bodies to remove caffeine and ephedra alkaloids from the list of banned substances is unexpected, since caffeine is one of the few ergogenic aids with documented efficiency.\textsuperscript{[12,63]} but also, its combination with ephedrine, as outlined in this article, may be even more efficacious in increasing athletic performance than each drug separately. This has been demonstrated in various different exercise types, including submaximal steady-state aerobic exercise, short- and long-distance running, maximal and supramaximal anaerobic cycling, and weight lifting (see section 2.3). The fact that use of ephedrine \textit{per se} will still be restricted is probably of little significance, since, for instance, pseudoephedrine at 2.5-fold higher doses is believed to exert similar effects.\textsuperscript{[69]} The above point notwithstanding, studies into the potential ergogenicity of mixtures containing caffeine and ephedra alkaloids like pseudoephedrine and phenylpropanolamine have not been conducted to date. Relevant research in this field, therefore, is clearly warranted.

Besides performance, caffeine-ephedrine preparations tend to increase blood lactate and glucose concentrations during exercise compared with ingestion of each drug alone or placebo. Whether this could reflect an accelerated rate of carbohydrate metabolism remains unknown at present, but it seems that the two drugs interact in a way to bring about these increases. Sporadic enhancements of FFA and glycerol levels may also be observed, but these are generally modest in nature. On the other hand, caffeine-ephedrine mixtures have been shown to result in marked hormonal responses, such as increased epinephrine concentrations, probably due to caffeine, increased dopamine concentrations, probably due to ephedrine, and perhaps increased norepinephrine concentrations, probably as a result of an additive or synergistic effect between the two drugs. With respect to pulmonary function and gas exchange during short-term intense exercise, no physiologically significant effects have been reported. On the other hand, gas exchange may be enhanced by caffeine plus ephedrine during longer and/or more demanding efforts. This possibility is supported by available studies from the obesity literature, showing that combination of the two drugs increases resting metabolic rate.\textsuperscript{[123-125]} A relatively
consistent cardiovascular manifestation is an increase in HR after the combined ingestion of caffeine and ephedrine, in addition to that caused by exercise itself. Finally, evidence to date strongly suggests that caffeine-ephedrine mixtures are effective in decreasing the sensation of effort (i.e. RPE) during various exercise modalities. Although this may seem to result from the ingestion of caffeine rather than ephedrine, an additive or synergistic effect cannot be ruled out, bearing in mind the multiple CNS-related actions of both drugs.[114-117] For instance, increased dopamine availability after ingestion of caffeine plus ephedrine could readily enhance brain dopaminergic activity, thus suppressing brain 5-hydroxytryptamine synthesis and metabolism; theoretically, this could reduce the limiting for performance influence of central fatigue.[120]

It is evident that scientific knowledge regarding the physiological, metabolic and performance-enhancing effects of caffeine-ephedrine mixtures during exercise in humans is quite limited and heterogeneous in nature. These aspects of study are still in their infancy and additional research is needed to fully understand and characterise them. As use of caffeine and ephedra alkaloids by athletes is about to become unrestricted, it is imperative to elucidate how these drugs work and what potential ergogenic benefits they confer. However, before engaging in the use of such preparations, one should also be aware of the considerable health risks they might entail.[127-129] Serious cardiovascular and CNS events, including hypertension, palpitations, tachycardia, chest pain, stroke, cerebral vascular accidents, myocardial infarction, seizures, and other psychiatric and autonomic symptoms are only a few; permanent disabilities and even death have been documented in several cases.[18,34,130-134] Still, athletes have great perseverance and a very long history of using compounds and techniques potentially jeopardising their health, and most often, the perceived ergogenic benefits overshadow the documented adverse effects. It is the authors’ opinion that this will also be the case for caffeine-ephedra mixtures.

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. The authors have no conflicts of interest that are directly relevant to the content of this article.

References


© 2004 Adis Data Information BV. All rights reserved. Sports Med 2004; 34 (13)
67. Foltz EE, Ivy AC, Barborka CJ. The influence of amphetamine (benzedrine) sulfate, desoxyephedrine hydrochloride (pervi- tin), and caffeine upon work output and recovery when rapidly exhausting work is done by trained subjects. J Lab Clin Med 1943; 28: 603-6


103. Naughton LR. Two levels of caffeine ingestion on blood lactate and free fatty acid responses during incremental exercise. Res Q Exerc Sport 1987; 58: 255-9


105. Bell DG, McLellan TM. Exercise endurance 1, 3, and 6h after caffeine ingestion in caffeine users and nonusers. J Appl Physiol 2002; 93 (4): 1227-34


128. Marcus DM, Grollman AP. Ephedra-free is not danger-free [letter]. Science 2003; 301 (5640): 1069-71


133. Charatan F. Ephedra supplement may have contributed to sportsman’s death [letter]. BMJ 2003; 326 (7387): 464


Correspondence and offprints: Dr Stavros A. Kavouras, Laboratory of Nutrition and Clinical Dietetics, Department of Nutrition and Dietetics, Harokopio University, 70 El. Venizelou Avenue, 176 71 Athens, Greece. E-mail: skav@hua.gr