Dietary supplements

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For the athlete training hard, nutritional supplements are often seen as promoting adaptations to training, allowing more consistent and intensive training by promoting recovery between training sessions, reducing interruptions to training because of illness or injury, and enhancing competitive performance. Surveys show that the prevalence of supplement use is widespread among sportsmen and women, but the use of few of these products is supported by a sound research base and some may even be harmful to the athlete. Special sports foods, including energy bars and sports drinks, have a real role to play, and some protein supplements and meal replacements may also be useful in some circumstances. Where there is a demonstrated deficiency of an essential nutrient, an increased intake from food or from supplementation may help, but many athletes ignore the need for caution in supplement use and take supplements in doses that are not necessary or may even be harmful. Some supplements do offer the prospect of improved performance; these include creatine, caffeine, bicarbonate and, perhaps, a very few others. There is no evidence that prohormones such as androstenedione are effective in enhancing muscle mass or strength, and these prohormones may result in negative health consequences, as well as positive drug tests. Contamination of supplements that may cause an athlete to fail a doping test is widespread.

Keywords: bicarbonate, caffeine, carnitine, creatine, dietary supplements, drugs, nutrition.

Introduction

Talent is undoubtedly the most important attribute of the elite performer, but it is difficult to define. Other factors that characterize the elite athlete include a sustained effective training programme, a range of psychological and cognitive characteristics, resistance to injury and effective nutrition support. At a time when the world standard in sport is moving to ever-higher levels, the athlete who wants to make it to the top and to stay there must explore all possible means of securing an advantage.

As training programmes become ever more demanding, every possible advantage must be seized, and nutrition is an obvious area that can make a difference. The foods that an athlete chooses can make the difference between success and failure. Although wise food choices will not make a champion out of the athlete who does not have the talent or motivation to succeed, an inadequate diet can prevent the talented athlete from making it to the top. A varied diet eaten in an amount sufficient to meet the energy needs of the athlete in training should provide all the essential nutrients in adequate amounts, but not all athletes eat a varied diet and the total food intake may at times be restricted. Because nutritional deficiencies may be difficult to detect in their early stages, athletes are often tempted to take individual nutrients in a concentrated form to guard against the possibility of a deficiency developing. To cater for the demand for specialist nutritional supplements for athletes, an enormous multinational industry has grown up, encouraged by a popular culture of supplement use among the general population in the belief that this can in some way compensate for poor food choices and the increased stresses of modern life. This supplement culture has extended to include an enormous diversity of compounds that extends beyond nutritional components to embrace more exotic edible compounds.

The following sections will review the various categories of nutritional supplements that are used by athletes and will present evidence for or against the use of selected supplements. Some recent comprehensive publications have reviewed a wide range of individual supplements (Antonio and Stout, 2001; Talbott, 2003).
In this review article, we do not attempt to review all of the available information on even a few of the hundreds (perhaps thousands) of different supplements in widespread use, but instead focus on some of the general issues associated with supplement use, using examples to highlight specific issues. Further information on some of these supplements will be found in some of the other reviews contained in this issue.

The use of any nutritional supplement that is effective in improving performance inevitably raises ethical issues. Ergogenic aids are banned by the governing bodies of sport for one of two reasons: on the grounds that they pose threat to the health of the individual, or because they confer what is seen to be an ‘unfair’ advantage. These issues must always be borne in mind when considering the use of any supplement.

The scope of supplement use

Limited information is available on the extent of dietary supplement use among athletes. The global market for supplements in 2001 was estimated at US$46 billion, with the US supplement market in 2000 being estimated at US$16.7 billion (Financial Times, 19 April 2002). Athletes account for a significant fraction of the total market and a wide range of products are aimed at both the active population and at those engaged in competitive sport.

Many surveys of supplement use in athletes have been published, with a meta-analysis of 51 published surveys involving 10,274 male and female athletes showing an overall prevalence of use of 46% (Sobal and Marquart, 1994). Prevalence of use, however, varies widely among sports and among athletes of different ages, standards of performance and cultural background. In some sports, especially strength and power sports, supplement use is the norm. A report of supplement use among 100 Norwegian national-level competitors from various sports revealed that 84% surveyed used some form of micronutrient supplement (Ronsen et al., 1999). Most athletes in this survey took multiple supplements, although many had nutritional habits that were described as ‘unsatisfactory’, implying that these athletes might have benefited more from attention to the foods they ate.

Only a few surveys have attempted to quantify the frequency or amount of supplement use, but it appears to be common for athletes to exceed the recommended doses of supplements. This may be because of a feeling that ‘more is better’ or because team-mates or opponents are known to use higher doses. In some cases, for example creatine, the dose recommended by some suppliers may be far higher than the maximum effective dose. On the other hand, the amount of supplement in some preparations may be far less than the amount used in laboratory studies of efficacy, especially where expensive ingredients are concerned. Estimates of use by individual athletes suggest that some may ingest very large numbers of different supplements on a regular basis and that the amounts used may be far in excess of those shown to be safe. Most people believe that ‘natural’ supplements are harmless, but high intakes of many of these supplements on a long-term basis may be harmful. Iron, zinc and other metallic elements are frequently consumed in amounts that are known to be harmful. It would appear that athletes – and often also those who advise them – are usually unaware of the risks.

Most surveys have failed to examine the reasons for supplement use by athletes, information that is fundamental to any effort to change the behaviour of athletes. In one study, attitudes to dietary supplement use were assessed in 1737 young (14–19 years) male and female (58% male, 42% female) high school athletes (Perko, 2000). Coaches, parents, physicians, athletic trainers and peers all influenced the decision to take supplements. There was a good relationship between behaviour and perceived normal behaviour, but knowledge about the effects of supplements was poor. Other surveys have found no association between the prevalence of supplement use and gender, race, marital status, educational background, dietary habits or training status. Commonly cited reasons for supplement use include:

- to compensate for an inadequate diet;
- to meet abnormal demands of hard training or frequent competition;
- to benefit performance;
- to keep up with team-mates or opponents;
- recommended by coach, parent or other influential individual.

However, even when athletes are informed on the basis of biochemical measurement of nutrient status that their diet is adequate or that the status of their body stores is normal (e.g. iron), the use of supplements persists, suggesting that the decision to use supplements is not a rational one.

Improving strength and power: promoting tissue growth and repair

The use of dietary supplements seems to be particularly prevalent among athletes in strength and power sports, with some surveys showing that all athletes from these events were using one or more supplements. A wide range of supplements are sold as ‘anabolic’ or ‘anti-
catabolic' agents, with either direct or indirect effects on protein synthetic pathways in muscle. Proposed mechanisms of action include a mass action effect on synthetic pathways by increasing amino acid availability, stimulation of hormone release or potentiation of hormone action, an increase in cell volume, or by acting as an adaptogen (i.e. promoting adaptation to training). Supplements on sale in this broad category include amino acids, boron, chromium, chrysin, colostrum, creatine, hydroxymethylbutyrate (HMB), ornithine alphaketoglutarate, protein, tribulus terrestris, vanadium and zinc.

Although protein products are by far the largest selling products in this group, sales of creatine (a product that is not used except in sports nutrition) and of some other products are also substantial. For most of these supplements, there are few supporting data – indeed, few experimental data at all. In many cases, there are suggestions from in vitro studies of effects that may be relevant, but there is no experimental evidence from studies on healthy humans.

**Proteins and amino acids**

The use of high-protein diets has a long history in sports nutrition and such diets were reportedly popular with athletes in the Olympics of ancient Greece. There is good evidence that protein requirements are increased by hard training and it is often recommended that the protein intake of strength athletes should be 50–100% greater than that of their sedentary counterparts (Tarnopolsky, 2001). Athletes often insist that much higher amounts of protein are necessary to increase muscle mass, but the literature does not support this supposition. This apparent inconsistency may be explained by Millward's adaptive metabolic demand model, which proposes that the body adapts to changes in intake occurs only very slowly (Millward, 2001). With high protein intakes, there is an up-regulation of protein degradation and amino acid oxidation. The athlete consuming a high protein diet who acutely reduces protein intake will experience a loss of lean tissue until a new equilibrium has been achieved.

Whether protein supplements are necessary is a separate issue, and this is discussed by Tipton and Wolfe (2004). It is clearly possible to achieve very high protein intakes by choosing appropriate foods, but it is also true that many high protein foods have a high fat content. Knowledge about the composition of foods among athletes is not generally good, which means that a restricted choice of foods is almost inevitable. Protein supplements offer athletes the possibility of achieving their desired protein intake without an unacceptable increase in fat intake and without major changes to their eating habits.

In the case of some amino acids, there are data from clinical studies involving severely stressed individuals (by trauma, burn injury or surgery) showing that supplementation may reduce the extent of muscle wasting that occurs, but this catabolic state is hardly relevant to the healthy athlete trying to increase muscle mass. Individual amino acids claimed to promote muscle growth include glutamine, branched-chain amino acids, leucine, lysine, arginine and ornithine. There is little evidence to support the benefit of supplementation of any of these amino acids for athletes eating a normal diet. Although high doses of arginine, ornithine and lysine may result in increased circulating growth hormone and insulin concentrations, these have not been shown to result in changes in lean body mass or in muscle function (Merimee et al., 1969). The changes in growth hormone that result are transient and small relative to the normal fluctuations that occur and are also small relative to the increases that result from even a short period of very high-intensity effort.

**$\beta$-Hydroxy-$\beta$-methylbutyrate**

A relatively recent addition to the plethora of nutritional supplements is $\beta$-hydroxy-$\beta$-methylbutyrate (HMB), a metabolite of leucine. Although the mechanism of action of HMB is unknown, it has been hypothesized that it either acts by decreasing muscle proteolysis or by improving cell integrity by providing substrate for cholesterol synthesis (Nissen and Sharp, 2003). In previously untrained individuals, HMB may increase lean body mass and strength more than resistance training alone (Nissen et al., 1996; Gallagher et al., 2000a; Panton et al., 2000). Direct measures of muscle membrane integrity have not been made, but intake of HMB has been reported to reduce blood concentrations of creatine kinase during resistance training in previously untrained individuals (Nissen et al., 1996; Gallagher et al., 2000a; Panton et al., 2000). In addition, Nissen et al. (1996) reported that HMB intake reduced urinary excretion of 3-methylhistidine, a finding that is consistent with a decrease in muscle proteolysis. In trained individuals and elite power athletes, however, HMB intake does not appear to enhance lean body mass or strength (Kreider et al., 1999; Slater et al., 2001; Ransone et al., 2003) or anaerobic exercise capacity (O'Connor and Crowe, 2003). $\beta$-Hydroxy-$\beta$-methylbutyrate also does not appear to affect markers of catabolic status or muscle membrane integrity in well-trained individuals (Kreider et al., 1999; Paddon-Jones et al., 2001; Slater et al., 2001).
A recent meta-analysis on studies of both trained and untrained individuals (Nissen and Sharp, 2003) reported that HMB intake increases lean body mass by 0.28% per week and strength by 1.40% per week compared with resistance training alone. Effect sizes for these improvements were small (0.15 and 0.19 for lean mass and strength, respectively). Taken together, these findings suggest that HMB may have some value for athletes beginning a resistance training programme. β-Hydroxy-β-methylbutyrate has been reported to reduce the accumulation of creatine kinase in the blood of runners after a 20-km time-trial (Knitter et al., 2000), and may reduce blood lactate accumulation during endurance exercise (Vukovich and Dreifort, 2001). Although HMB appears to be a safe supplement (Gallagher et al., 2000b; Nissen et al., 2000), its relative expense (US$1.8–2.4 per day) and the limited likelihood of a beneficial effect suggest that it may not have much to offer the athlete.

**Trace elements**

Several single elements are also promoted as anabolic agents. Chromium plays a role in insulin sensitivity and insulin is a potent anabolic hormone. Exercise may increase urinary chromium excretion, raising concerns among athletes that deficiency may occur. There are limited data on the effects of chromium supplements in athletes, with published studies of chromium supplementation showing an increase, decrease or no change in body mass. The best-controlled studies, however, show no effect on muscle mass or strength (Clarkson and Rawson, 1999; Nissen and Sharp, 2003). In addition, concern has recently been expressed that chromium, if taken as the picolinate salt, may not be entirely safe, with several adverse effects having been reported (Vukovich, 2001).

Vanadium is also advertised as a promoter of the action of insulin, and there are limited animal data to support this. Human data, however, show no effect of supplementation on body composition or strength in resistance-trained athletes (Fawcett et al., 1996). There is some debate as to whether boron is an essential element in human nutrition, but boron supplementation is claimed to increase circulating testosterone, with the prospect for an anabolic action. This result, however, was obtained in post-menopausal women who had been fed a low-boron diet (Nielson et al., 1987), and there are no studies showing that boron feeding results in muscle hypertrophy in normally nourished individuals with normal endocrine function. Administration of boron supplements to a group of male bodybuilders had no effect on circulating free or total testosterone or on muscle size or strength (Ferrando and Green, 1993).

**Prohormones and related compounds**

A variety of precursors of testosterone and nandrolone (19-nortestosterone) – together referred to as prohormones – are sold as dietary supplements: these include in particular androstenedione (‘andro’) and 19-norandrostenedione. These are not legal in those countries where they are classified as prescription-only drugs, and are banned in Olympic sports. Nonetheless, their use is permitted in some sports, including baseball, where they have been promoted by successful players, and they are readily available via the internet or from countries where their sale is not restricted. Recent research in this area has focused on dehydroepiandrosterone (DHEA), androstenedione, androstenediol and 19-norandrostenedione. The rationale for taking these supplements is that these androgens are only one or two chemical reactions away from testosterone.

Dehydroepiandrosterone is formed primarily in the adrenal glands, and is found in high concentrations in the blood, but its physiologic roles(s) are unclear; it can also be converted to androstenedione (Geller, 1985) or androstenediol (Schindler and Aymar, 1975). The intake of DHEA does not increase blood testosterone in men or augment gains in muscle size and strength due to resistance training (Brown et al., 1999; Wallace et al., 1999). While replacement doses of DHEA in ageing women increase both serum testosterone and dihydrotestosterone (DHT) concentrations (Morales et al., 1994), the effect of DHEA intake on serum sex hormones, muscle size and muscle strength in young healthy women is not known.

In men, the intake of 100–200 mg of androstenedione or androstenediol does not affect blood testosterone concentrations (King et al., 1999; Wallace et al., 1999; Ballantyne et al., 2000; Earnest et al., 2000). The effect of higher doses of androstenedione on blood testosterone is not clear (Leder et al., 2000). Chronic intake of 200–300 mg androstenedione or 200 mg androstenediol per day does not result in greater gains in muscle size and strength during resistance training than training alone (King et al., 1999; Broeder et al., 2000). Norandrostenedione and norandrostenediol have also been shown not to raise blood concentrations of nandrolone (19-nortestosterone) or to affect body composition or strength in young healthy men (Dehennin et al., 2002; van Gammeren et al., 2002). In middle-aged (30–60 years) men, 300 mg of either androstenedione or androstenediol per day raises blood free testosterone by approximately 35%. In healthy young women, the effect of androstenedione intake is not clear. One study reported that the intake of 100 mg androstenedione increases blood total testosterone to concentrations typically observed in young healthy men (Kicman et al., 2003). In another study, however, blood
testosterone was elevated after the intake of 300 mg of androstenedione, but remained at levels less than one-half of normal values for young men (Brown et al., in press). Although the effect of androstenedione on muscle size and strength in women has not been studied, the likely virilization and other possible side-effects of androstenedione use in women suggest that women should not take this supplement.

Since androstenedione is similar in structure to testosterone, it is reasonable to hypothesize that androstenedione might be an anabolic agent, independent of any effect on testosterone concentrations. However, androstenedione does not increase muscle protein synthesis in vivo (Rasmussen et al., 2000) and does not increase satellite cell proliferation or differentiation in vitro (Vierck et al., 2003).

The intake of androstenedione and androstenediol decreases blood concentrations of high-density lipoprotein cholesterol in males (Brown et al., 2000a,b, 2001a,b), corresponding to a 10–15% increase in the risk for cardiovascular disease. In all participants, ingested androstenedione and androstenediol appeared to be preferentially converted to oestrogens and DHT, rather than to testosterone. Dihydrotestosterone is associated with male pattern baldness and benign prostate hypertrophy. Elevated concentrations of oestrogens have been linked to pancreatic cancer and gynaecomastia (breast growth). Increased blood concentrations of androstenedione may increase the risk of pancreatic and prostate cancer, and may promote behavioural changes.

Because the liver removes a significant amount of androgen that is taken orally, it is possible that an androgen that is taken by allowing a pill to dissolve under the tongue may be more readily converted to testosterone. Androstenediol taken in this form increases blood total testosterone by 125% (Brown et al., 2002). Whether this product enhances muscle size or strength remains to be determined. Finally, androstenedione and other prohormones undergo extensive metabolism to other steroids. Recent reports suggest that athletes taking these steroids are at risk for positive drug tests (Catlin et al., 2000; Uralets and Gillette, 1999).

In summary, ‘testosterone prohormones’ taken orally do not significantly raise blood testosterone in young men and do not increase muscle size or strength. These supplements may pose significant health risks and may result in positive drug tests.

**Herbal supplements**

Many herbal supplements are claimed to increase testosterone concentrations and hence have an anabolic action. These include tribulis terrestris, chrysin, indole-3-carbinol, saw palmetto, gamma-oryzanol, yohimbine, smilax and mummio. All of these claims are based on in vitro data. Attempts have been made to formulate combinations of some of these herbal extracts with androstenedione and androstenediol to minimize aromatization to oestrogens and reduction to DHT. Recently, it has been shown that a formulation containing tribulus terrestris, chrysin, indole-3-carbinol and saw palmetto, together with androstenedione or androstenediol and DHEA, does not increase serum testosterone or augment the increases in muscle size and strength achieved through strength training alone (Brown et al., 2000a,b, 2001a,b). These human data suggest that these herbal extracts are of no value.

**Weight loss and fat loss**

Supplements in this category are used by athletes who need to limit body mass, and especially body fat, in weight category, weight-sensitive or aesthetic sports.

**Carnitine**

The supply of plasma free fatty acids to the exercising muscle is important for determining the relative contributions of fat and carbohydrate to oxidative metabolism, but a number of other steps are recognized as being involved in fat oxidation. Fatty acid uptake into the cell and translocation across the mitochondrial membrane are also key steps. Carnitine combines with fatty acyl-coenzyme A (acyl-CoA) in the cytoplasm and allows that fatty acid to enter the mitochondrion. The first step is catalysed by carnitine palmitoyl transferase 1 (CPT1) and the trans-membrane transport is facilitated by acylcarnitine transferase. Within the mitochondrion, the action of carnitine palmitoyl transferase 2 (CPT2) regenerates free carnitine and the fatty acyl-CoA is released for entry into the β-oxidation pathway.

Within the mitochondrion, carnitine also functions to regulate the acetyl-CoA concentration and the concentration of free CoA. Free CoA is involved in the pyruvate dehydrogenase reaction as well as in the process of β-oxidation and thus plays a key role in the integration of fat and carbohydrate oxidation. It has been proposed that an increased availability of carnitine within the mitochondrion might allow the cell to maintain a higher free CoA concentration, with a stimulatory effect on oxidative metabolism.

Because of the key role of carnitine in the oxidation of both fat and carbohydrate, it has been proposed that carnitine supplementation may improve exercise performance. On the basis of this logic, carnitine is widely sold in sports shops as a supplement for endurance athletes. It is also sold as a weight loss product with
claims of increased fat oxidation. There is, however, no good evidence that carnitine deficiency occurs in the general population or in athletes. Carnitine is present in the diet in red meat and dairy products, so it might be thought that individuals who follow a vegan lifestyle might be at increased risk of deficiency, but carnitine can also be synthesized from lysine and methionine in the liver and kidney. Measurement of the effects of exercise and diet on muscle carnitine concentrations in humans (muscle accounts for about 98% of the total body carnitine content) has only been carried out relatively recently, and there have been few attempts to measure the effects of supplementation on muscle carnitine. Barnett et al. (1994) and Vukovich et al. (1994) reported that short-term supplementation with carnitine (4–6 g day\(^{-1}\) for 7–14 days) had no effect on muscle carnitine concentrations or on the metabolic response to exercise. Even when fatty acid mobilization was stimulated by high fat meals or heparin, there was no effect of carnitine supplementation on fat oxidation (Vukovich et al., 1994).

In contrast to these negative findings, there are published reports suggesting that carnitine supplementation can increase the contribution of fatty acids to oxidative metabolism and thus promote the use of body fat stores. In a comprehensive review of the literature, Spriet (1997) identified eight studies that examined the effects of supplementation on the metabolic response to endurance exercise, and found that three of those studies reported an increased rate of fat oxidation. There is more recent evidence to support this, with one study showing an increased oxidation of 13C-labelled palmitate after 10 days of carnitine supplementation (Muller et al., 2002). This finding alone is not, however, evidence that weight loss and a reduction in body fat content will result.

Most of the products that have been shown to be effective in promoting weight loss contain ingredients prohibited by doping regulations and also raise questions about safety. Combinations of caffeine (sometimes in the form of guarana), ephedrine (sometimes as herbal ephedra) and aspirin (sometimes as naturally occurring salicylates) have been shown to be more effective than any of these ingredients in isolation, but both caffeine and ephedrine can cause positive doping results and ephedrine has been associated with a significant number of positive doping results. There also appear to be significant health risks associated with the use of ephedrine (Bent et al., 2003) and the use of these products is strongly discouraged.

**Promoting energy supply**

One view of exercise-induced fatigue is that it occurs when the rate of ATP hydrolysis in the active muscles exceeds the rate at which ATP can be regenerated. It follows that the onset of fatigue can be delayed and exercise performance improved if a higher rate of ATP resynthesis can be maintained. Supplements that are claimed to improve performance by increasing energy supply and delaying fatigue include bicarbonate, caffeine, carnitine, creatine, guarana, hornet juice, iron, magnesium, pyruvate and ribose. It must be emphasized at the outset that not all of these claims are supported by experimental evidence. There is reason to believe that some athletes may benefit in some circumstances from the use of bicarbonate, caffeine, creatine and iron. Caffeine will be discussed later in this review and is also discussed by Spriet and Gibala (2004).

**Bicarbonate**

For exercise that results in fatigue within a few minutes, anaerobic glycolysis makes a major contribution to energy metabolism. Although glycolysis allows higher rates of ATP resynthesis than can be achieved by aerobic metabolism, the capacity of the system is limited, and fatigue is inevitable when high rates of anaerobic glycolysis occur. The metabolic acidosis that accompanies glycolysis has been implicated in the fatigue process, either by inhibition of key glycolytic enzymes, by interfering with calcium transport and binding, or by a direct effect on the actin–myosin interaction. Therefore, it is intuitively attractive to believe that induction of alkalosis before exercise, an increase in the muscle buffering capacity, and an increased rate of efflux of hydrogen ions from the active muscles all have the potential to delay fatigue and improve exercise performance. Many studies have looked at the effects of metabolic alkalosis (usually induced by ingestion of sodium bicarbonate or sodium citrate) on the performance of high-intensity exercise, but the results are by no means consistent or conclusive (Maughan, 1999; McNaughton, 2000).

In one study designed to simulate athletic competition, trained non-elite (best 800-m time about 2 min 5 s) middle-distance runners performed a simulated 800-m race. In the alkalotic condition, they ran almost 3 s faster than in the placebo or control trials (Wilkes et al., 1983). A more recent report indicated similar improvements (3–4 s) over a distance of 1500 m in runners who completed simulated races in about 4 min 15 s (Bird et al., 1995). Although these effects on performance might appear small, they are of considerable significance to the athlete, for whom an improvement of even a fraction of a second in these events is considered to be a major achievement.

The reasons for the conflicting effects reported in the published literature are not altogether clear, but are at
least in part due to variations in the intensity and duration of the exercise tests used, the nature of the exercise task, the dosage of sodium bicarbonate administered and the time delay between bicarbonate administration and the beginning of the exercise test (i.e. the amount of metabolic alkalosis induced). Performance has been monitored over exercise durations ranging from a few seconds to more than 1 h, and during continuous, incremental and intermittent dynamic exercise as well as during sustained isometric contractions.

There is no clear pattern of exercise duration between those studies where a positive effect was observed and those where no effect was seen. In most studies, a dose of 0.3 g of sodium bicarbonate or citrate per kilogram of body weight has been used to induce alkalosis, and this has usually been administered orally in solution or in capsule form. Such a dose has usually resulted in an increase of 4–5 mmol·l\(^{-1}\) in the plasma buffer base 2–3 h after administration, although the time-course of changes in acid–base status was not carefully followed in most of these studies. Horswill et al. (1988) examined the effects of ingesting 0.1–0.2 g bicarbonate·kg\(^{-1}\) BW (where BW = body weight) on cycle ergometer sprint performance over 2 min. They found no improvement in performance even though the blood bicarbonate concentration was elevated; on the basis of these results, they suggested that a dose of less than 0.3 g·kg\(^{-1}\) BW might be ineffective in improving exercise performance. McKenzie et al. (1986), however, reported that a dose of 0.3 g·kg\(^{-1}\) BW was no more effective than one half this dose.

There are potential problems associated with the use of high doses of bicarbonate. Vomiting and diarrhoea are frequently reported as a result of ingestion of even relatively small doses of bicarbonate, thus limiting any improvement in performance among those individuals susceptible to gastrointestinal problems. There are anecdotal reports of athletes using this intervention, which is not prohibited by the rules of sport, being unable to compete because of the severity of these symptoms. Although unpleasant and to some extent debilitating, these effects are not serious and there seem to be no long-term adverse consequences of occasional use. Sodium citrate administration, which also results in an alkaline shift in the extracellular fluid, has also been reported to improve peak power and total work output in a 60-s exercise test, but without any adverse gastrointestinal symptoms (McNaughton, 2000).

When an increase in performance after bicarbonate ingestion has been observed, it has been ascribed to an increased rate of hydrogen ion efflux from the exercising muscles, which reduces both the rate of fall of intracellular pH and the pH-mediated inhibition of phosphofructokinase (Sutton et al., 1981). The higher blood lactate concentrations after exercise associated with metabolic alkalosis, even when the exercise duration is the same, may therefore be indicative not only of a higher rate of lactate efflux, but also of an increased contribution of anaerobic glycolysis to energy production. Associated with the development of fatigue during high-intensity exercise is a decline in the muscle adenine nucleotide content. The extent of the fall in muscle ATP concentration that occurs during maximal exercise in humans has been shown to approach 40% of pre-exercise values: even greater losses of ATP (60%) have been reported upon exhaustion in the horse (Snow et al., 1985). There is evidence to suggest that an increase in hydrogen ion efflux during near maximal intensity exercise after bicarbonate administration may decrease the extent of muscle adenine nucleotide loss during exercise (Greenhaff et al., 1990), but whether this is due to a pH-mediated decrease in the activation of AMP deaminase or an increased rate of ADP rephosphorylation via glycolysis is not clear. Whatever the mechanism, it seems reasonable to suggest that bicarbonate administration before high-intensity exercise will only enhance performance when the intensity and duration of the exercise are sufficient to result in significant muscle acidosis and adenine nucleotide loss.

Creatine

Creatine has been used by many successful athletes, particularly in track and field athletics, but in many other sports as well. Some indication of the extent of its use comes from the fact that the estimated sales of creatine to athletes in the USA alone in 1997 amounted to over 300,000 kg. This represents a remarkable growth, as its use first became popular in sport after the 1992 Olympic Games in Barcelona. What distinguishes creatine from most other purported ergogenic aids is that it seems to be effective in improving performance. More significantly, perhaps, its use is not prohibited by the governing bodies of sport and, although long-term safety studies have not been undertaken, there appear to be no harmful side-effects even when very large doses are taken, at least in the quantities that are necessary to produce an ergogenic effect. There are many excellent reviews of the effects of creatine supplementation, but the picture changes rapidly as new information emerges in this topical area. Greenhaff (2000) and Williams et al. (1999) have provided recent overviews.

The highest tissue concentrations of creatine are found in skeletal muscle, and approximately two-thirds of the total is in the form of creatine phosphate. Creatine phosphate is capable of rapid regeneration of ATP within the cell cytoplasm, but a limited amount is available. Increasing muscle creatine phosphate should
increase the available energy supply. Creatine occurs naturally in the diet, being present in meat: 1 kg of fresh steak contains about 5 g of creatine. The normal daily intake is less than 1 g, but the estimated daily requirement for the average individual is about 2 g. The body has a limited capacity to synthesize creatine in the liver, kidney and pancreas and in other tissues, but the primary site of synthesis in humans is the kidney. This supplies the amount required in excess of the dietary intake, and is also the only way in which vegetarians can meet their requirement. Synthesis occurs from amino acid precursors (arginine and glycine), but the synthetic pathway is suppressed when dietary creatine intake is high.

The first study to systematically investigate the effects of supplementation of large amounts of creatine was that of Harris et al. (1992). In a comprehensive study, they showed that ingestion of small amounts of creatine (1 g or less) had a negligible effect on the circulating creatine concentration, whereas feeding higher doses (5 g) resulted in an approximately 15-fold increase. Repeated feeding of 5-g doses every 2 h maintained the plasma concentration at about 1 mmol·l\(^{-1}\) over an 8-h period. Repeated feeding of creatine (5 g four times a day) over 4–5 days resulted in a marked increase in the total creatine content of the quadriceps femoris muscle. An increase in muscle creatine content was apparent within 2 days of starting this regimen, and the increase was greatest in those with a low initial concentration; in some cases, an increase of 50% was observed. Approximately 20% of the increase in total muscle creatine content is accounted for by creatine phosphate. Co-ingestion of creatine and carbohydrate, which results in high circulating insulin, may increase the storage of creatine in muscle (Green et al., 1996a,b).

Most authors who have reviewed the published literature have concluded that the available evidence supports a beneficial effect of creatine on performance in short-term high-intensity exercise (Greenhaff, 2000). Of three recently published meta-analyses, two have concluded that creatine supplementation has positive effects on strength, power and lean body mass (Branch, 2003; Nissen and Sharp, 2003), while the other (Misic and Kelley, 2002) concluded that there was no effect. The reasons for this discrepancy are not entirely clear. Effects are seen in particular in the later stages of multiple short efforts with limited recovery, but improvements are sometimes seen in single sprints lasting less than 30 s. There is little information on the effects of creatine supplementation on the performance of more prolonged exercise, but there is little reason to suspect a positive effect.

The mechanism by which creatine supplementation might improve performance is not entirely clear, although it is clear that this effect is related to increased muscle creatine phosphate. The rate of creatine phosphate resynthesis after intense exercise is enhanced after high-dose creatine supplementation (Greenhaff et al., 1994). This allows faster recovery after sprints as well as allowing more work to be done during each subsequent high-intensity effort. These effects will allow a greater amount of work to be done in training and should therefore result in a greater training response, although it is possible that by maintaining the energy charge better during training, the response will be less. This is especially important in that the muscle creatine content remains high for weeks or even months after only a few days of high-dose dietary creatine supplementation (Hultman et al., 1996).

Many studies and much anecdotal evidence support the suggestion that acute supplementation with creatine is associated with a prompt gain in body mass. This typically amounts to about 1–2 kg over a supplementation period of 4–5 days, but may be more than this. In reviewing those studies where changes in body mass were reported, Branch (2003) reported 43 studies in which body mass increased and 24 where no change was seen; there was a statistically significant effect size for both body mass and lean body mass. Another recent meta-analysis puts the increases in muscle size and strength in perspective. Nissen and Sharp (2003) reported that creatine supplementation increases lean mass and strength by 0.35% and 1.09% per week in excess of the changes observed with resistance training alone, but again effect sizes for the increased lean mass and strength were small (0.26 and 0.36, respectively).

The rapid increases in body mass may be accounted for by water retention. Increasing the creatine content of muscle by 80–100 mmol·kg\(^{-1}\) will increase intracellular osmolality, leading to water retention. Hultman et al. (1996) found a reduction in urinary output during supplementation, which tends to confirm this. The increased intramuscular osmolality due to creatine itself, however, is not likely to be sufficient to account for all of this water retention. It has been suggested that co-ingestion of creatine and carbohydrate, which results in high circulating insulin (Green et al., 1996a,b), may stimulate glycogen synthesis, which will further increase the water content of muscle. There is some preliminary evidence for a stimulation of protein synthesis in response to creatine supplementation (Ziegenfuss et al., 1997), but further experimentation is required. It is unlikely that major effects on muscle protein content can be achieved within 4–5 days, so the reported gains in muscle strength within the same time-scale are difficult to explain.

The effects of the long-term use of large doses of creatine are unknown and its use may pose a health risk. There is concern about possible adverse effects on renal
function, in particular in individuals with impaired renal capacity. Studies on the response to long-term creatine use are in progress but results are not yet available. There have, however, been no reports of adverse effects in any of the studies published in the literature. One study that specifically examined renal function in individuals supplementing with creatine found no reason to believe that renal complications were likely (Poortmans et al., 1997). Anecdotal reports of an increased prevalence of muscle cramps in athletes taking creatine supplements have been circulating for some time, but there is no substance to these stories. It is likely that any injury suffered by an athlete will be ascribed to an easily identifiable change in habit, such as the introduction of a new supplement.

Uninformed comment ascribed the deaths of three American collegiate wrestlers in December 1999 to creatine use, but this was not substantiated at the formal inquiries conducted. Given the increase in body mass that often accompanies supplementation, it is possible that athletes who must reduce body mass acutely to qualify for a particular weight category might face particular problems. It is not unusual in some sports for body mass to be reduced by as much as 10% in the few days before competition: if the mass loss necessary to make the qualifying weight is 1–2 kg more than anticipated, the measures required to achieve the target mass will be unusually severe and may provoke serious and potentially fatal complications related to dehydration and hyperthermia.

It is usually recommended that athletes take 20 g creatine·day$^{-1}$ for 4–5 days (a loading dose) followed by 1–2 g·day$^{-1}$ (maintenance dose). The muscle may be saturated with creatine when a dose as small as 10 g·day$^{-1}$ is consumed for 3–4 days if this is taken together with sufficient carbohydrate to stimulate a marked elevation in circulating insulin. Many athletes, however, work on the principle that more is better and may greatly exceed these amounts. Even with very large doses, however, the possibility of adverse effects is remote. Creatine is a small water-soluble molecule easily cleared by the kidney, and the additional nitrogen load resulting from supplementation is small. The same concerns about renal damage have been raised in the context of protein supplementation among strength athletes and bodybuilders: these athletes may consume up to 3–4 g protein·kg$^{-1}$·BM·day$^{-1}$ over very long periods (Burke and Inge, 1994), but there is no evidence that the theoretical problems of clearance of the extra solute load are real.

Although there is no reason to suppose that there are any risks to health associated with the long-term use of high doses of creatine, the studies quoted above that have used high doses (in the order of 20–30 g·day$^{-1}$) have been of relatively short duration (5–14 days), and long-term safety studies have not been performed. Studies are currently under way to determine some of the effects of long-term creatine supplementation; their results will become available in due course. This leaves the ethical question of whether the use of creatine should be disallowed on the grounds of its ergogenic effect, as is the case with other normal dietary components such as caffeine. As more information emerges, this issue will be resolved and the governing bodies of sport will make a decision.

**Carnitine**

Depletion of intramuscular glycogen stores is one of the main factors involved in the fatigue that accompanies prolonged exercise. A recent review of published work in this area is provided by Coyle (1997). The importance of carbohydrate as a fuel for the working muscles is confirmed by the close relationship between the pre-exercise glycogen concentration and the length of time exercise can be sustained. Further evidence comes from studies which showed that increasing the combustion of fat during prolonged exercise, and thus sparing the limited carbohydrate stores, can improve endurance capacity. Increasing fatty acid mobilization by heparin administration after ingestion of a high fat meal or by caffeine ingestion has been shown to be effective in improving performance. The former method, however, is not acceptable in sport.

The possible effects of carnitine supplementation on fatty acid metabolism are described above. In a review of studies that examined the effects of carnitine supplementation on exercise performance, Spriet (1997) concluded that their findings did not generally support an ergogenic effect of carnitine. It must be concluded that, although there is a theoretical basis for an ergogenic effect of carnitine on performance of both high-intensity and prolonged exercise, this is not supported by the experimental evidence. Supplementation of the diet with carnitine is unlikely to be beneficial for athletes. Spriet also cautioned against the use of racemic mixtures of L- and D-carnitine, as these may result in depletion of L-carnitine.

**Promoting immune function and resistance to illness and infection**

Exercise, nutrition and immune function are covered in detail elsewhere in this issue (Gleeson et al., 2004) and will be discussed only briefly here in relation to supplement use. Modest amounts of regular exercise
are generally associated with an increased sensation of physical well-being and a decreased risk of upper respiratory tract infections (URTI) (Nieman et al., 1993, 1998). The consequences of minor URTI symptoms are usually minimal, but any injury or illness that interrupts training or prevents participation in competition can have a devastating effect on an athlete. Several recent epidemiological surveys have suggested that athletes in intensive training or competing in extreme endurance events are more susceptible to minor opportunistic infections than sedentary individuals (Nieman, 1997; Peters-Futre, 1997; Shephard and Shek, 1997). It has been suggested that severe exercise results in a temporary reduction in the body’s ability to respond to a challenge to its immune system and that an inflammatory response similar to that which occurs with sepsis and trauma is invoked (Nieman, 1997). On this basis, a wide range of nutritional supplements is promoted for use by athletes (Table 1). For most of these supplements, there is little evidence of efficacy from properly controlled trials in humans. For many, there is some evidence of some anti-bacterial or immune stimulating effect in vitro, but this is far removed from evidence to support their use in athletes.

In view of the role of glutamine as a fuel for the cells of the immune system, the fall in circulating glutamine that occurs in response to prolonged exercise has been proposed as a mechanism that compromises the ability to respond to infection (Newsholme, 1994). Other studies have shown that athletes suffering from chronic fatigue symptoms attributed to overtraining also have low circulating glutamine concentrations (Rowbottom et al., 1995). At present, the limited information on glutamine supplementation provides no clear pattern of results. Studies by Newsholme and colleagues suggest a beneficial effect of glutamine supplementation on resistance to infection after endurance exercise (Castell et al., 1996; Castell and Newsholme, 1997), although a positive effect was not always seen (Castell et al., 1997). In the rat, prolonged treadmill running has been shown to reduce the plasma glutamine concentration after exercise and to reduce the proliferative response of leucocytes to a mitogen challenge (Moriguchi et al., 1995); in contrast, animals fed a glutamine-supplemented diet for 3 weeks before exercise maintained their plasma glutamine concentration and showed a higher response to mitogens than the control group. A similar study carried out with humans found no beneficial effect of acute glutamine supplementation on these same parameters (Rohde et al., 1998). Although this hypothesis is undoubtedly attractive, a clear link between hard exercise, compromised immune function and susceptibility to infection has not been established. Nonetheless, glutamine supplementation for athletes is being promoted and supplements are widely available in sports nutrition outlets.

Zinc is commonly believed to be effective in protecting against the common cold and other infectious illnesses. Since 1984, 11 studies of zinc for treatment of the common cold have been published in reputable medical journals. Of these, five found that zinc had beneficial effects and six did not, so the picture is unclear. The study that has drawn the most attention was a 1996 report from the Cleveland Clinic (Mossad et al., 1996). Participants who started taking zinc lozenges within 24 h of the onset of symptoms were free of cold symptoms on average by about 4.5 days. Those who took a placebo had symptoms for 7.5 days. Twenty percent of zinc-takers reported nausea, as opposed to only 4% of those taking the placebo. A subsequent study involving children did not confirm these results (Macknin et al., 1998) and a later review by the same authors concluded that further research is necessary before the use of zinc supplements can be recommended (Macknin, 1999). There is no evidence that taking zinc prevents anyone from catching a cold, although there may be benefits by reducing the severity and duration of symptoms. However, it would appear that supplementary zinc must be taken within 24 h of the onset of symptoms to have any benefit. This effectively means continuous supplementation, and side-effects include nausea and bad taste reactions. Long-term high doses of zinc are probably not a good idea, as they lower high-density lipoprotein cholesterol, suppress immune system function and interfere with the absorption of copper, resulting in microcytic anaemia. It has been suggested

<table>
<thead>
<tr>
<th>Table 1. Supplements sold as immune system stimulants</th>
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<tbody>
<tr>
<td>Antioxidants</td>
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<tr>
<td>Astragalus</td>
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<tr>
<td>Bee pollen</td>
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<tr>
<td>Chlorella</td>
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<tr>
<td>Co-enzyme Q10</td>
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<tr>
<td>Cordyceps</td>
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</table>
that when zinc is taken in lozenge form, it may act locally on the upper respiratory tract.

Preparations made from various plants and plant parts of the genus *Echinacea* constituted the top-selling herbal medicine in health food stores in the USA over the last 5 years and it is also popular in Europe. *Echinacea* is promoted for preventing and treating the common cold, flu and upper respiratory tract infections. It is also claimed to increase general immune system function and is used to treat vaginal candidiasis. The clinical literature tends to provide some support for its use in the treatment for symptoms of colds, flu and URTI. Recent studies do not support its use to prevent URTI. Melchart et al. (2000) reviewed the available literature and identified 16 trials with a total of 3396 participants that investigated the effects of preparations containing *Echinacea* extracts. The methodological quality of the trials was assessed and deemed insufficient to perform a quantitative meta-analysis. However, the authors concluded that existing controlled clinical trials indicated that preparations containing the juice or extracts of *Echinacea* can have a positive effect. In the most recent literature review of clinical trials conducted on various *Echinacea* preparations for prevention or treatment of URTI, Barrett (2003) concluded that ‘while there is a great deal of moderately good-quality scientific data regarding *E. purpurea*, effectiveness in treating illness or in enhancing human health has not yet been proven beyond a reasonable doubt’. In both of these reviews, the authors emphasized that the highest quality trials suggest that early dosing of sufficient doses is important. As with all herbal supplements, there must be concerns about possible adverse effects in some individuals and the use of *Echinacea* is not free from risk.

**Antioxidant nutrients**

It has long been common practice for athletes to take vitamin supplements, usually without any thought as to the vitamin status of the individual concerned. There has been much interest recently among athletes in vitamins C and E, which have been shown to have antioxidant properties, and which may be involved in protecting cells, especially muscle cells, from the harmful effects of the highly reactive free radicals that are produced when the rate of oxygen consumption is increased during exercise (Kanter, 1995). Many studies have shown that unaccustomed exercise, particularly if it involves eccentric exercise in which the muscle is forcibly lengthened as it is activated, results in damage to the muscle structure and post-exercise soreness. Because it normally peaks 1–3 days after exercise, this is often referred to as delayed-onset muscle soreness. It is believed that free radicals, highly reactive chemical species, may be involved in the damage that occurs to muscle membranes. Alleviating or avoiding these symptoms would allow a greater training load to be sustained. An increased generation of free radicals is also associated with damage to cellular DNA and to a variety of lipids and proteins. If the post-exercise damage can be reduced by an increased intake of antioxidants, then recovery after training and competition may be more rapid and more complete. The evidence for this at present suggests a possible role but is not conclusive. Even the suggestion, however, is enough to convince many athletes to take supplements of these vitamins ‘just in case’.

The source of the free radicals generated during exercise seems to be primarily related to the increased oxygen use within the mitochondria (McCord, 1979). This suggests that the extent of free radical generation will be directly proportional to the intensity and duration of exercise. Infiltration of damaged muscle by leucocytes may also account for some of the elevation in free radicals that is observed after exercise as these cells generate free radicals as part of their cytotoxic defence mechanisms (Smith et al., 1989). A variety of other mechanisms that may promote free radical generation has been described (Kanter, 1995).

Free radicals have been implicated in several disease processes, including cardiovascular disease, diabetes and some forms of cancer, as well as in the ageing process. The body has a number of endogenous defence mechanisms that effectively neutralize free radicals before they cause tissue damage: important enzymes are superoxide dismutase, glutathione peroxidase and catalase. Several nutritional antioxidants also play important roles. Nutritional antioxidants include vitamins A, C and E. Other dietary components, including selenium, which has a structural role in glutathione peroxidase, and ubiquinone (or co-enzyme Q10) may also play important roles but are less well researched. Copper, zinc and manganese are structural components of superoxide dismutase and iron is a co-factor for catalase.

Several studies have examined the effects of antioxidant supplementation on indices of free radical-induced muscle damage in exercise, and there is some evidence of a protective effect of supplementation; for reviews of these studies, see Kanter (1995) and Dekkers et al. (1996). The evidence appears to suggest that there may be a reduction in the signs of muscle damage after supplementation, but there is no evidence for any beneficial effect on performance. There are concerns about possible adverse effects of supplementation, as several of these nutrients can also function as pro-oxidants. Toxic effects of megadose supplementation are unlikely, but there are concerns about the possible consequences of the long-term use of megadoses of...
single antioxidants. One study has reported increased exercise muscle damage after supplementation with ubiquinone (Malm et al., 1996), and it is well recognized that many antioxidant nutrients can function as pro-oxidants at high doses.

Regular training increases the effectiveness of the endogenous antioxidant mechanisms so that even extreme exercise (e.g. long-distance triathlon) may not cause any indications of oxidative damage in well-trained athletes (Margaritis et al., 1997). In contrast, short periods of modest exercise (8 weeks of training, 3 sessions of 35 min per week) do not result in any signs of increased capacity to neutralize free radicals (Tiidus et al., 1996). It is not clear from this whether individuals engaged in regular exercise have an increased requirement for exogenous antioxidants.

In conclusion, there is little evidence to support the suggestion that supplementation with antioxidant nutrients can improve exercise performance, but there is a growing body of evidence to suggest that supplementation may reduce the extent of exercise-induced oxidative damage to tissues. If this is indeed the case, it may be that the athlete undertaking a strenuous training programme may benefit in the long term by being able to sustain a higher training load. There is also evidence, however, that prolonged exposure to training increases the effectiveness of the endogenous antioxidant mechanisms, and it may be that supplementation is unnecessary (Margaritis et al., 1997).

### Promoting joint health

Many products are sold with the aim of promoting joint health and reducing the wear and tear caused by overuse, ageing and inflammatory conditions, including arthritis. Some of the products sold are listed in Table 2. An extensive range of herbs, botanicals, and so on are also sold, including turmeric, *Boswellia serrata*, cayenne pepper, ashwagandha, autumn crocus, meadowsweet, stinging nettle, willow bark (*Salix*) and devil’s claw. Animal extracts, including green-lipped mussel and sea cucumber, are also promoted.

The cartilage in joints is made up of proteoglycans (protein molecules to which are bound various complex sugars) and the protein collagen. Chondroitin, one of the main glycosaminoglycans, is a long-chain molecule consisting of many molecules of two components: galactosamine and glucuronic acid. Commercial preparations are extracted from the cartilaginous tissues of animals. Glucosamine is a carbohydrate–amino compound that is produced from the chitin that forms the main structural element of sea shells. Both compounds are reported to stimulate the formation of components of cartilage when given orally to humans.

There is now a considerable amount of information from clinical trials involving patients with osteoarthritis to show that regular (once or twice per day) long-term (about 2–6 months) treatment with glucosamine and chondroitin sulphate can reduce the severity of subjective symptoms and prevent progression of the disease (Fillmore et al., 1999). A meta-analysis of published studies concluded that ‘some degree of efficacy appears probable for these preparations’ but did express caution about the quality of the available data (McAlindon et al., 2000). A recent report (Braham et al., 2003) of the effects of 12 weeks of supplementation in individuals with knee pain showed similar improvements in clinical and functional tests in the treatment and placebo groups, but 88% of the treatment group reported some improvement in knee pain compared with only 17% in the placebo group. At present, there is no evidence of a benefit for athletes with joint pain, but there seem to have been no properly controlled trials in athletes. One study of US military special operations personnel with knee and back pain showed subjective improvements after treatment but no effect on tests of running performance (Leffler et al., 1999). Nonetheless, subjective relief alone has some value and this possible benefit cannot be ignored. There seems to have been little discussion of possible adverse effects of supplementation, but the widespread use of these products means that any problems should have become apparent.

### Central nervous system effects

The list of compounds prohibited for use by athletes includes stimulants, and there is a long history of

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**Table 2. Supplements promoted for joint health and protection against ageing and overuse**

<table>
<thead>
<tr>
<th>Antioxidants</th>
<th>Essential fatty acids</th>
<th>Vitamins: niacin (B3), pantothenate (B5), D</th>
<th>Minerals: boron, calcium</th>
<th>Proteolytic enzymes</th>
<th>Glucosamine</th>
<th>Chondroitin</th>
<th>Methyisulphonylmethane (MSM)</th>
<th>S-Adenosyl methionine (SaME)</th>
<th>Type 2 collagen</th>
<th>Hyaluronic acid</th>
<th>Soy isoflavones</th>
</tr>
</thead>
</table>

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stimulant use in sport. In some cases, fatalities have resulted from the use of amphetamines, sympathomimetics and other stimulant compounds. Some of these agents (including, for example, cocaine) are more commonly used as social drugs rather than for performance enhancement, while others are commonly found in low doses in cough medicines and herbal tonics.

Caffeine

Caffeine occupies a unique place in that it is consumed in a wide range of foods and beverages and is prohibited in competition above a urinary threshold value but its use is not monitored in out-of-competition testing. Caffeine has effects on the central nervous system and on adipose tissue and skeletal muscle that give reason to believe that it may influence exercise performance. Early studies on the effects of caffeine on endurance performance focused on its role in the mobilization of free fatty acids from adipose tissue to increase fat supply to the muscle, which, in turn, can increase fat oxidation, spare glycogen and thus extend exercise time. Caffeine ingestion before exercise to exhaustion at 80% $V\dot{O}_{2\text{max}}$ increased exercise time from 75 min on the placebo trial to 96 min on the caffeine trial (Costill et al., 1978). A positive effect was also observed on the total amount of work achieved in a fixed 2-h exercise test. In this and other studies, caffeine was shown to increase circulating free fatty acids, increase fat oxidation and spare muscle glycogen during prolonged exercise (see Spriet, 1995, for a review of these studies). The consistency and clarity of these findings led to the widespread popularity of caffeine consumption (usually in the form of coffee) before marathon running, although caffeine in much higher doses had long been used, especially in professional cycling. It is also important to note that coffee may not produce an ergogenic effect in circumstances where caffeine is effective, even though the same plasma caffeine concentration results (Graham et al., 1998).

Growing evidence of a positive effect of caffeine on performance in the absence of any glycogen sparing effect, and of effects on high-intensity exercise where glycogen availability is not a limiting factor, has stimulated the search for alternative mechanisms of action. There is evidence for a number of effects of caffeine directly on skeletal muscle. It may affect the activity of Na/K ATPase and the intracellular localization and binding of calcium, it can cause an elevation in intracellular cyclic AMP as a result of inhibition of the action of phosphodiesterase, and it may have direct effects on a number of enzymes, including glycogen phosphorylase (Spriet, 1997; Graham, 2001). Whether all these effects can occur at the tissue concentrations of caffeine that occur after ingestion of moderate doses of caffeine remains unclear. Effects on the central nervous system, either in modifying the perception of effort or affecting the higher motor centres, have been proposed, but in the absence of evidence this remains speculation.

There have been several recent and comprehensive reviews of the effects of caffeine on exercise performance, and a detailed review of the literature will not be attempted here (Spriet, 1997; Graham, 2001). Several studies have reported beneficial effects of caffeine ingestion on a variety of laboratory tests of endurance performance. An increased time to exhaustion has been observed in a number of tests, but performance in simulated race conditions, where a fixed amount of work has to be done in the shortest possible time, is also improved. There appears to be no effect on maximal oxygen uptake. More recent studies have focused on exercise of shorter duration, and a number of studies have shown beneficial effects on performances lasting only a few (about 1–6) minutes; there is less information on performance in sprint tasks or on resistance exercise, but the available evidence does support performance-enhancing effects, although there is no effect on muscle strength (Graham, 2001).

It is clear from the published studies that positive effects of caffeine can be obtained in a variety of exercise conditions with caffeine doses of 3 mg·kg$^{-1}$ or less. The reasons for this variability are not altogether clear, but, perhaps surprisingly, they do not appear to be related to the habitual amount of caffeine consumption.

Caffeine has a number of unwanted side-effects that may limit its use in some sports or by sensitive individuals: these effects include insomnia, headache, gastrointestinal irritation and bleeding, and a stimulation of diuresis. There are also some suggestions that high caffeine intakes may be a risk factor for bladder cancer. This is unlikely to be modified by occasional use of modest doses before competition, but the athlete who may contemplate using high doses of caffeine before training on a daily basis should consider this. With the very high doses sometimes used by athletes, noticeable muscle tremor and impairment of coordination have been noted (Spriet, 1995).

The diuretic action of caffeine is often stressed, especially when dehydration is a major issue. This affects in particular competitions held in hot, humid climates where the risk of dehydration is high, and is more important for endurance athletes for whom dehydration has a greater negative effect on performance. Athletes competing in these conditions are advised to increase their intake of fluid, but are usually also advised to avoid tea and coffee because of their diuretic effect. It would appear, however, that this effect is small for those habituated to caffeine use (Wemple et al., 1997) and the negative effects caused by the
symptoms of caffeine withdrawal may be more damaging.

Until January 2004, an athlete found to have a urine caffeine concentration of more than 12 mg·l⁻¹ was deemed to be guilty of a doping offence and was liable to suspension from competition. It is clear from this that caffeine is considered by the International Olympic Committee to be a drug, but an outright ban on its use is impractical and manifestly unfair to those who normally drink tea and coffee. It is equally clear, however, that the amount of coffee that must be drunk to exceed the permitted limit (about six cups of strong coffee within about 1 h) is such that it is unlikely that this would normally be achieved. In addition, in endurance events, a urine sample taken after the event would probably not register a positive test, even if large amounts had been consumed before the start.

It is also clear that beneficial effects on performance can be achieved with caffeine doses that are less than those that would result in the old IOC urine threshold concentration of 12 mg·l⁻¹ being exceeded, so athletes may feel justified in their view that using these amounts is acceptable. It is difficult, but not impossible, to achieve an effective intake from drinks such as tea or coffee, but there are various products on the market that contain significant amounts of caffeine (Table 3). Caffeine tablets, commonly used by overworked students studying for examinations, are also commonly used, and these can easily lead to an intake that exceeds the permissible limit. These concerns resulted in the decision by the World Anti-Doping Agency to remove caffeine from the list of prohibited substances with effect from January 2004.

Contamination of dietary supplements

The Dietary Supplements Health and Education Act 1994 (DSHEA) passed by US Congress has meant that nutritional supplements that do not claim to diagnose, treat, prevent or cure disease are not subject to regulation by the Food and Drug Administration (FDA). From this it follows that there is no requirement to prove claimed benefits, no requirement to show safety with acute or chronic administration, no quality assurance and liberal labelling requirements. Product recalls by the FDA because of inadequate content include a folic acid product with 34% of the stated dose (FDA, 2003). They have also recently recalled products containing excessive doses of vitamins A, D, B6 and selenium because of potentially toxic effects (FDA, 2003). Some products have been shown to contain impurities (lead, broken glass, animal faeces, etc.) because of poor manufacturing practice (FDA, 2003). Some products do not contain the expensive ingredients listed on the label but only inexpensive materials. There is no way for athletes to know what is in any of these products.

A paper from the IOC laboratory in Cologne reported the results of an analysis carried out on legitimate dietary supplements, none of which declared on the label that they contained steroids, none of which would reasonably be expected to contain prohibited compounds, and none of which gave any warning to athletes that problems might result from their use. Nandrolone, testosterone and other steroids were identified in these supplements: when they were fed to healthy volunteers, they resulted in urinary norandrosterone concentrations of up to 360 ng·ml⁻¹ (the threshold for a positive test is 2 ng·ml⁻¹ for men and 5 ng·ml⁻¹ for women). The supplements tested were chrysin, tribulus terrestris and guarana.

The Cologne laboratory followed this up with a much bigger survey. In total, 634 different product samples were purchased from 13 countries and were analysed for the presence of steroid hormones and their precursors. Altogether, 94 supplements (14.8% of the total) were shown definitely to contain prohibited substances, and for another 10% the analysis was not conclusive but steroids may have been present. That is close to a 1 in 4 risk! Substantial numbers of positive tests were obtained from products bought in The Netherlands (26%), the USA (19%), UK (19%) and elsewhere. The names of the prohibited supplements have not been published, but they included vitamins and minerals, protein and amino acid supplements, creatine and many others. Further details of this study can be found on the website of the Cologne laboratory (www.dopinginfo.de).

The IOC-accredited laboratory in Vienna has repeated the Cologne study, although with a smaller number (n = 57) of supplements. They found that 12 of these (22%) contained prohibited steroids. Unlike the German results, the identities of the companies and the products have been published on the Internet, and can

Table 3. Caffeine content of some commonly used beverages when prepared and consumed in standard amounts

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Caffeine content (mg)</th>
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<tbody>
<tr>
<td>Tea</td>
<td>15–50</td>
</tr>
<tr>
<td>Instant coffee</td>
<td>50–70</td>
</tr>
<tr>
<td>Filter coffee</td>
<td>60–120</td>
</tr>
<tr>
<td>Hot chocolate</td>
<td>8–15</td>
</tr>
<tr>
<td>Cola</td>
<td>20–50</td>
</tr>
</tbody>
</table>

Note: Doses of as little as 2–3 mg·kg⁻¹·BM can result in performance enhancement.

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also be found on the Cologne website at the address above.

The presence of these various anabolic androgenic steroids is commonly assumed to be the result of inadvertent contamination in the manufacturing or distribution process, as the contamination is generally minimal and highly variable between and within batches. Events took a more sinister turn in 2002, however, when the Vienna laboratory found one of the ‘hard’ anabolic steroids (methandienone, commonly known as Dianabol) in three supplements that were bought in England (Gmeiner, 2002). This drug was present in high amounts, enough to have an anabolic effect, but also enough to produce serious side-effects. These results were confirmed by the Cologne laboratory (Geyer et al., 2002) and the presence of this steroid has been described as a ‘deliberate and criminal act’.

More recent results come from the analysis of 110 supplements advertised as having tonic or stimulant properties and bought from different international markets: analysis of these samples showed that a significant proportion of products contained either caffeine (14 samples) or ephedrine (2 samples), even though these were not listed on the label (Parr et al., in press). It is not immediately obvious that this contamination can be accidental. Athletes using these products may be liable to sanctions if a positive doping test results.

The picture has not changed greatly as a result of the availability of this information, although proposed changes in legislation might make the supplement industry more accountable than they are at present. The principle of strict liability still applies, so athletes have to be extremely careful.

**Costs and benefits of supplement use**

Supplements for use in sport with the aim of improving performance should meet certain criteria, although the considerations will not be the same for all athletes. Supplements used by athletes should have demonstrated effectiveness in laboratory and field conditions. They should have a well-identified and plausible mechanism of action based on what is known of metabolism and of the factors that limit performance. They should be free of harmful side-effects and not pose any health risk, and they should be free of any risk of an adverse drug test.

A full analysis of the costs and benefits cannot be completed for most supplements as several parts of the equation are unknown. The risks of falling foul of the drug testing rules cannot be quantified but they are nonetheless very real. The sensible athlete will want to see positive reasons for using any supplement.

**Conclusions**

Supplement use is widespread in sport, even though most supplements used are probably ineffective. Athletes who take supplements should only do so after carrying out a careful cost–benefit analysis. Although these supplements are mostly benign, this is not always the case. Routine iron supplementation, for example, can do more harm than good, and the risk of iron toxicity is very real. Athletes are therefore cautioned against the indiscriminate use of dietary supplements. Supplement use can have a role when food intake or food choice is restricted, or as a short-term remedy where a deficiency syndrome has been shown to exist. Supplement use does not compensate for poor food choices. For a few supplements, the balance of evidence supports a beneficial effect on some types of performance; these supplements include creatine, caffeine and bicarbonate. There is no evidence that androstenedione and similar prohormones are anabolic agents, and these supplements may pose serious health risks. The risk of a positive drugs test resulting from the use of sports supplements contaminated with prohibited compounds is also very real. The evidence for a performance benefit must be very strong to outweigh the well-established risks.

**References**


Dietary supplements


Dietary supplements


MODULE EIGHT

Dietary supplements and ergogenic aids

Module tutor: Professor Ron Maughan

Lectures

1. Uses and abuses of dietary supplements

2. Supplements and sports foods that may be of benefit to athletes: creatine

3. Supplements and sports foods that may be of benefit to athletes: caffeine

4. Supplements and sports foods that may be of benefit to athletes: Buffering agents
Essential Reading for this Module


Note that essential reading that is not found in course texts can either be found via the Internet through PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi)

or will be provided

The lectures in this module are supported by extensive reading lists. This gives you the opportunity to identify relevant articles and access these.

Website resources

There are many websites offering information on dietary supplements, but there is a need for caution. Some of these sites are very good, but some are simply marketing vehicles for supplements companies. The following are among those that can be considered reliable.

Office of Dietary Supplements. This is a US Government Department (part of NIH) and has a vast amount of information. Though not specifically targeted to sports nutrition, there is an enormous amount of relevant information here http://ods.od.nih.gov/

European Food Standards Agency (EFSA) This is the European Commission Agency that reviews scientific information on foods and food ingredients. They regularly publish opinions on the substantiation of claims relating to functional benefits of foods or ingredients. Some of these reports contain a substantial amount of useful background information http://www.efsa.europa.eu/

Australian Institute of Sport (AIS) Sports Supplement Program
www.ais.org.au/nutrition

World Anti Doping Agency
http://www.wada-ama.org/

Assignment

There is one assignment for this module. Information about this assignment is provided at the end of this module overview. Resources to assist in the completion of the assignment can be found from the Registered Students section of the Diploma in Sports Nutrition website www.sportsoracle.com.
Assignments must be submitted as a word document by August 31 2011. They should be uploaded via the password protected section at www.sportsoracle.com. You can find the upload section under the assignments tab.

**Learning outcomes**

After completing this module and associated further reading, students should:

1. Appreciate the reasons that cause athletes to use dietary supplements
2. Be aware of the range of supplements used by athletes and the extent of their use.
3. Understand the need for a cost benefit analysis before using or recommending any dietary supplement and also be aware of the limitations of any such analysis
4. Be aware of those supplements that may be of benefit to some athletes in some situations
5. Appreciate the quality control issues in the manufacture and promotion of dietary supplementations and of the potential consequences of the limited regulation of the market
6. Recognise the potential for positive doping results arising from the use of dietary supplements
Lecture 1  Uses and abuses of dietary supplements

Lecturer: Prof Ron Maughan (UK)

Content: This lecture will look at the broad issues associated with dietary supplement use in sport.

Lecturer biography

**Professor Ron Maughan**

Ron Maughan obtained his BSc (Physiology) and PhD from the University of Aberdeen, and held a lecturing position in Liverpool before returning to Aberdeen where he was based for almost 25 years. He is now Professor of Sport and Exercise Nutrition at Loughborough University, England. His research interests are in the physiology, biochemistry and nutrition of exercise performance, with an interest in both the basic science of exercise and the applied aspects that relate to health and to performance in sport. He has published extensively in the scientific literature, and is on the Editorial Board of several international journals. Professor Maughan is a Fellow of the American College of Sports Medicine and a member of many scientific organisations. He chaired the Human and Exercise Physiology group of the Physiological Society for 10 years and was a member of the Council of that organisation. He is chair of the Sports Nutrition Working Group established by the IOC Medical Commission in 2002.

Essential reading for this lecture


Further Reading

*These papers are cited in the lecture
These papers are available in full, either through PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) or via your online subscription to International Journal of Sport Nutrition and Exercise Metabolism

Review papers/book chapters


Original research


Website resources


Keywords for literature search:

Dietary supplements; ergogenic aids; creatine; caffeine; acid-base
Lecture 2  Supplements and sports foods that may be of benefit to athletes: creatine

Lecturer: Professor Paul Greenhaff (UK)

Content: Metabolic roles of creatine and creatine phosphate; effects of supplementation with creatine on muscle creatine content; performance effects of supplementation; maximising creatine storage; other effects of supplementation

Lecturer Biography

Professor Paul Greenhaff
Professor Paul Greenhaff obtained his Ph. D. in Medical Sciences from the University of Aberdeen in 1988, and conducted post-doctoral research in muscle metabolism through 1991, including research with Professor Eric Hultman in Sweden. In 1991 he was appointed to the position of Lecturer on Research in Muscle Metabolism in the Department of Physiology and Pharmacology of the Faculty of Medicine and Health Sciences at the Medical School of the Queen’s Medical Centre of the University of Nottingham. He was later promoted to a personal Professorship and is now Director of the Centre for Integrated Systems Biology and Medicine at Nottingham University. He has published extensively on diverse areas of muscle metabolism and was one of the first scientists to publish in the area of creatine supplementation.

Essential reading


See the opinion of the European Food Standards agency on creatine at:


A scientific Conference on Creatine in Health, Medicine and Sport was held in July, 2010 at the University of Cambridge, England. A small group of experts presented and debated the available evidence on all aspects of creatine function. Papers from the Conference were published in a special issue of Amino Acids in May, 2011. Unfortunately, copyright issues prevent us from posting copies of this supplement, but anyone interested in creatine should try to obtain a copy.

Further reading

*These papers are cited in the lecture

These papers are available in full, either through PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi ) or via your online subscription to International Journal of Sport Nutrition and Exercise Metabolism
**Review papers**


Rawson ES, Venezia AC (2011) Use of creatine in the elderly and evidence for effects on cognitive function in young and old Amino Acids 40, 1349-1362


**Original research**


**Keywords for literature search:**

Creatine, creatine phosphate
Lecture 3  Caffeine: An Ergogenic Aid That Works

Lecturer:  Dr Lawrence Spriet (Canada)

Content:  Caffeine – a drug that is rapidly absorbed by the body; Caffeine increases endurance performance; Metabolic mechanisms for caffeine’s ergogenic effects?; Caffeine and ion handling?; Evidence that the central nervous system is responsible for caffeine’s ergogenic effects; Mechanistic Conclusions; Practical Issues and Caffeine; Practical Conclusions and Consensus Statement

Lecturer Biography

Professor Lawrence Spriet

Dr. Lawrence L. Spriet is Professor and Chair of the Department of Human Health and Nutritional Sciences at the University of Guelph, Guelph, Ontario, Canada. He earned his Honours BSc degree (1977) in Kinesiology at the University of Waterloo and an MSc degree (1981) in Exercise Physiology from York University. Dr. Spriet completed his PhD (1984) in Medical Sciences at McMaster University and spent two years as a post-doctoral fellow working with Dr. Eric Hultman at the Karolinska Institute in Stockholm, Sweden. Dr. Spriet has been a Professor at the University of Guelph since 1986. Dr. Spriet’s basic research examines how skeletal muscle generates the large amounts of energy needed to exercise and compete in work and sport situations. He studies the regulation of key enzymes in the pathways that metabolize carbohydrate and lipid to produce energy in human skeletal muscle. His practical research examines whether compounds that are purported to be "ergogenic" or “work enhancing” agents actually augment muscle metabolism and /or improve human performance (e.g. blood doping, creatine, carnitine, pyruvate, taurine, and caffeine). Dr Spriet is also Chair of the Gatorade Sports Science Institute (GSSI) of Canada and he conducts hydration/sweat testing and research aimed at counteracting the effects of dehydration in elite ice hockey players (e.g. Canadian Men’s Junior, Women’s National, and Men’s Sledge Hockey Teams). Dr. Spriet is also a member of the Board of Trustees for the American College of Sports Medicine, the IOC Diploma in Sports Nutrition Academic Advisory Board, several physiological and exercise physiology societies and an associate editor of several scientific journals.

Essential reading


Further reading

*These papers are cited in the lecture
These papers are available in full, either through PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi ) or via your online subscription to International Journal of Sport Nutrition and Exercise Metabolism

Review papers


Original research


**Keywords for literature search**

Caffeine, methylxanthines; fatigue, adenosine, exercise performance
Lecture 4  Supplements and sports foods that may be of benefit to athletes: Buffering agents

Lecturer:    Dr Craig Sale (Nottingham Trent University, UK)

Content:    Anaerobic glycolysis; lactate formation, acid base balance; intracellular and extracellular buffering; role of bicarbonate; effects of supplementation on performance, adverse effects; carnosine; effects of supplementation with carnosine and β-alanine

Lecturer biography

Dr Craig Sale MSc, PhD.
Craig is currently a Reader in Applied Physiology at Nottingham Trent University. He was awarded his doctorate from Liverpool John Moores University in 2002 following the completion of his BSc (Hons) and MSc programmes at the same institution. Following his studies, he was a Senior Lecturer in Exercise Physiology at the University of Chichester and then a Senior Scientist at QinetiQ Ltd. Much of Craig’s previous research has been in the areas of muscle biochemistry, function and fatigue, particularly in respect to the effects of various nutritional interventions. More recently he has published in the areas of exercise, nutrition and bone metabolism. Craig is on the editorial board of Amino Acids and was on the Scientific Committee of the recent International Congress on Carnosine in Exercise and Disease, for which he is also the Principal Conference Editor for the forthcoming Special Issue to be published in Amino Acids.

Essential reading for this lecture


Further Reading

*These papers are cited in the lecture
These papers are available in full, either through PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) or via your online subscription to International Journal of Sport Nutrition and Exercise Metabolism

Review papers/book chapters


**Original research**


Keywords for literature search:

Bicarbonate; citrate; acid-case; carnosine; β-alanine,
Module 8 assignment

Assignment type: Research Paper analysis

Instructions


You will find a copy of this paper on the website, and your task is to provide a critique of the paper. This should include a summary of the key elements of the methodology, data analysis and interpretation of results, including any limitations noted by you or by the authors. A take-home message for athletes should be included. The total length of your submission should not exceed 1000 words.

It is important to bear in mind that a critique, or critical analysis, of a paper is NOT the same as a summary. The critique is concerned more with an assessment of the strengths and weaknesses of the paper rather than just summarising what was done and what was found. The key findings should, of course be discussed, but this should be in the context of the rationale for the study, the appropriateness or otherwise of the study design and data analysis and the interpretation of the findings.

Assignments section of www.sportsoracle.com. This will provide you a guide to what is sought in your answer to this assignment.

Deadline for submission

Assignments must be submitted as a word document by August 31 2011. They should be uploaded via the password protected section at www.sportsoracle.com.

Your assignments should be submitted as a file with your surname as the filename. Please title the information line of the email and your attached document with Assignment Mod 1.8 and your surname, as in: Assignment Mod 1.8 Jones
Outline of talk

Supplements in the athlete's diet

Why athletes use supplements

A few supplements that may be useful in specific situations

Potential risks of supplement use
What determines Performance?

**Talent**

Motivation  
Training  
Trainability  
Avoiding injury  
Nutrition

A good diet will not make a mediocre athlete into a champion, but poor food choices can turn a champion into a mediocre athlete.

Why use supplements?

Athletes believe:

Food quality has declined due to intensive farming and modern food production methods

Stress of intense training/competition cannot be met by food alone

Supplements can offer an advantage

Competitors are using supplements

Coach/parent/other recommends supplements

The extent of supplement use

310 athletes at IAAF World Championships

Supplements were used by 86% of the athletes

Males 83%  Females 89%

Reasons for using supplements were:

- to aid recovery from training  71%
- for health  52%
- to improve performance  46%
- to prevent or treat an illness  40%
- to compensate for a poor diet  29%

Depieze et al. Unpublished
**Amount of supplement used**

Most athletes exceed the recommended doses of supplements because:

“If one scoop is good, two scoops must be twice as good. Think how good 10 scoops will be!”

“Opponents are using more than the recommended dose”

### One Athlete’s day

<table>
<thead>
<tr>
<th>Time</th>
<th>Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.10am</td>
<td>3g L-lysine with 30mg Vit B6, 4 phosphate tablets, 2 scoops protein powder, 3 teaspoon acetylglutamine, 3g Vit C, 3 tablets detox, 50 mg zinc</td>
</tr>
<tr>
<td>1.45pm</td>
<td>3g L-lysine with 30mg Vit B6, 3g Vit C, 3 tablets detox, 50 mg zinc</td>
</tr>
<tr>
<td>11.00pm</td>
<td>3g L-lysine with 30mg Vit B6, 3g Vit C, 3 tablets detox, 1 scoop protein powder, 3 teaspoon acetylglutamine</td>
</tr>
</tbody>
</table>
BUT:

“The use of supplements does not compensate for poor food choices and an inadequate diet. Athletes contemplating the use of supplements and sports foods should consider their efficacy, their cost, the risk to health and performance, and the potential for a positive doping test.”

IOC Consensus Statement on Sports Nutrition
Lausanne 18 June 2003

**Issues in Supplementation**

**Efficacy:** does it work? If so, under what conditions?

**Safety:** are there any possible adverse effects of acute or chronic use, even in excessive doses?

(Ethics: is its use in sport legitimate?)

**Why measure efficacy?**

**Consumer benefit**

**Research**

**Claim support**
Types of performance tests

**Strength**
- Isometric
- Dynamic - isokinetic dynamometer, IRM, etc.

**Power**
- Peak power, average power, fatigue index, etc.
- Wind sprints
- Jump tests - vertical jump, etc.

**Endurance**
- Time to exhaustion (constant intensity)
- Power/distance for predetermined duration
- Time trial (predetermined distance or amount of work)
- Intermittent protocol
- Time trial with "built-in sprints"

**Skills**
- Skills alone
- Skills with fatigue

**Cognitive function**

Endurance tests

**Time to exhaustion**

Bad press based on Jeukendrup et al (MSSE 1996)
CV of 27%; 44-112 min for one subject
20 min at 75% Wmax for one subject

CV of 8.3% in an exercise test lasting about 100 min
(Wilson and Maughan, Exp Physiol 1992: 77; 921-924)

CV of 5.9% in a test lasting about 72 min

Variability is high, but sensitivity is also high; ie interventions produce correspondingly large effects

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**How much is important?**

A 1% change in endurance power output produces the following changes:

- 1% in running time-trial speed or time
- ~0.4% in road-cycling time-trial time
- ~0.3% in rowing-ergometer time-trial time
- ~15% in time to exhaustion in a constant-power test

An indeterminable change in any test following a pre-load

Will Hopkins, Sportscience [http://sportsci.org](http://sportsci.org)

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**Statistical significance and biological meaning**

Confidence limits define a range within which the true population or large-sample value is likely to fall

Representation of the limits as a confidence interval:

- probability
- probability distribution of true value, given the observed value
- lower likely limit
- observed value
- upper likely limit

Likely range of true value:

- negative
- positive

Value of effect statistic

Area = 0.95
**Interpreting the results**

For biological significance, confidence limits are interpreted in relation to the smallest clinically beneficial and harmful effects.

Smallest important effect is about half of the athlete’s typical event-to-event variation.

These are usually equal and opposite in sign.

<table>
<thead>
<tr>
<th>Harmful</th>
<th>Trivial</th>
<th>Beneficial</th>
</tr>
</thead>
<tbody>
<tr>
<td>-negative 0 positive-</td>
<td>Value of effect statistic</td>
<td></td>
</tr>
</tbody>
</table>

Put the confidence interval and these regions together to make a decision about clinically significant, clear or decisive effects.

<table>
<thead>
<tr>
<th>Clinically decisive?</th>
<th>Statistically significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes: use it.</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes: use it.</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes: use it.</td>
<td>No</td>
</tr>
<tr>
<td>Yes: depends.</td>
<td>No</td>
</tr>
<tr>
<td>Yes: don’t use it.</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes: don’t use it.</td>
<td>No</td>
</tr>
<tr>
<td>Yes: don’t use it.</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes: don’t use it.</td>
<td>Yes</td>
</tr>
<tr>
<td>No: need more research.</td>
<td></td>
</tr>
</tbody>
</table>

**How strong does the evidence have to be?**

Repeatability (CV as %) of laboratory measurements of endurance performance:

- Time to exhaustion: 5-26%
- Time trial: 1-3%
- Constant load then TT: 1-3%
- Constant duration test: 3-5%
- Intermittent test: 2-5%
LONDON MARATHON 2003

1. G. Abera (ETH) 2:07:56
2. S. Baldini (ITA) 2:07:56 0.00
3. J. Ngolepus (KEN) 2:07:57 0.01
4. P. Tergat (KEN) 2:07:59 0.03
5. S. Ramadhani (TAN) 2:08:01 0.06
6. A. El Mouaziz (MOR) 2:08:03 0.08
7. L. Bong-Ju (KOR) 2:08:10 0.16

We can't measure this difference in the laboratory, so we have to recognise that our information is limited.

Responders and non-responders

<table>
<thead>
<tr>
<th>Treatment X</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>47±3 s</td>
<td>47±3 s</td>
<td></td>
</tr>
</tbody>
</table>

BUT

50% of subjects improve by 2 s
50% of subjects worse by 2 s

Possible examples: Glucosamine?
Echinacea?

Improvement in performance is related to Cr uptake

In studies where measurements of muscle creatine content have been made, a relationship between increases in muscle creatine and performance is seen

Casey et al (1996)
The difficulties in assessing efficacy are magnified many times when there is a less well-defined endpoint. Without a very large financial investment, it is unrealistic to expect clear evidence of efficacy in areas such as:

- Wound healing
- Muscle soreness
- Immune function
- Joint health

From the web
http://www.gaittrial.co.uk/

"the GAIT study (Glucosamine/Chondroitin Arthritis Intervention Trial) has proved that these two supplements in combination are even more effective in treating moderate-to-severe OA knee pain than celecoxib (Celebrex), a COX-2 NSAID (non-steroidal anti-inflammatory drug)."

What the study really found

"Participants taking the positive control, celecoxib, experienced statistically significant pain relief versus placebo—about 70 percent of those taking celecoxib had a 20 percent or greater reduction in pain versus about 60 percent for placebo. Overall, there were no significant differences between the other treatments tested and placebo. For a subset of participants with moderate-to-severe pain, glucosamine combined with chondroitin sulfate provided statistically significant pain relief compared with placebo—about 79 percent had a 20 percent or greater reduction in pain versus about 54 percent for placebo. According to the researchers, because of the small size of this subgroup these findings should be considered preliminary and need to be confirmed in further studies. For participants in the mild pain subset, glucosamine and chondroitin sulfate together or alone did not provide statistically significant pain relief."

What did GAIT cost? The primary GAIT study cost just over $12.5 million.
We need to remember:

Absence of evidence of efficacy is NOT the same as evidence of the absence of efficacy.

Equally, the absence of evidence of harmful effects does not mean that supplements are safe.

BUT we must be cautious.

Supplements that may be useful

Good evidence for performance effects:
- Creatine
- Caffeine
- Buffering agents
  - Bicarbonate
  - Citrate
  - β-alanine
- Nitrate?

Some evidence for performance related or health-related effects:
- Arginine/glutamine
- Echinacea
- Glucosamine
- Antioxidants
- Zinc

Costs and Benefits

It is important to think the process through by a thorough cost-benefit analysis.

A full analysis cannot be completed as several parts of the equation are unknown. The sensible athlete will want to see positive reasons for using supplements in their individual case.
Creatine and Exercise Performance

Adenosine triphosphate (ATP) provides energy for all the body's activities.
The maximum rate of ATP regeneration determines the power output that can be sustained.
Creatine Phosphate (CP) is an essential energy source for high intensity effort.

Maximal ATP resynthesis rates

<table>
<thead>
<tr>
<th>Source of ATP</th>
<th>Rate (μmol/L min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine phosphate</td>
<td>440</td>
</tr>
<tr>
<td>Lactate formation</td>
<td>180</td>
</tr>
<tr>
<td>Carbohydrate oxidation</td>
<td>40</td>
</tr>
<tr>
<td>Fat oxidation</td>
<td>20</td>
</tr>
</tbody>
</table>

Creatine supplements: some effects

Supplementation can:
- increase muscle creatine content
- increase lean tissue mass
- improve strength and power performance
- improve recovery between sprints

10-20 g/d is recommended, but 3-5 g/d is effective.
Meat/fish contains 3-10 g/kg.
Body mass gain (1-4 kg) can occur: may be unwanted.
No adverse health effects likely.

Carbohydrate and Creatine

Adding carbohydrate to creatine supplements can increase creatine storage.

Creatine uptake is enhanced.
All subjects respond.
Total creatine dose is reduced.

Total Creatine muscle levels (mmol/kg dry muscle mass)

- pre
- post
**Creatine and Carbohydrate**

Acute creatine supplementation can:
- Improve recovery?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Exh</th>
<th>24 h</th>
<th>72h</th>
<th>6d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycogen</td>
<td>Placebo</td>
<td>70</td>
<td>512</td>
<td>789</td>
</tr>
<tr>
<td>Creatine</td>
<td>Placebo</td>
<td>77</td>
<td>620</td>
<td>945</td>
</tr>
<tr>
<td>Creatine</td>
<td>Placebo</td>
<td>128</td>
<td>131</td>
<td>129</td>
</tr>
<tr>
<td>Creatine</td>
<td>Placebo</td>
<td>127</td>
<td>145</td>
<td>158</td>
</tr>
</tbody>
</table>

**Creatine Serum**

“No side effects”

**“Creatine Serum”**

(Harris et al., J. Sports Sciences 2004)
Plasma creatine (mmol/l)

[Harris et al., J. Sports Sciences 2004]
Caffeine and Performance

Since 2004 use has not been restricted by WADA
39 published studies met inclusion criteria
Variety of different exercise tasks
Including all data, performance improved by 12.4% relative to the placebo trials
Effect proportional to exercise duration


How does it work?

Old idea: caffeine stimulates fat mobilisation and leads to muscle glycogen sparing. This does not explain effects in exercise where carbohydrate supply is not limiting
New idea: Adenosine exerts inhibitory effects on the brain (neuroexcitability and transmitter release, arousal and spontaneous activity)
Caffeine is antagonistic to adenosine - binds to its receptor

How much caffeine?

Performance effects are seen at low doses
More is not better

Graham & Spriet (1995) JAP 78: 867
Performance effects seen with about 90 mg caffeine

A cup of coffee, a can of Coke, a caffeine tablet, or....

Muscle pH and Fatigue
High rates of anaerobic glycolysis allow fast ATP resynthesis but cause muscle pH to fall.
This has several effects on the muscle:
Calcium binding is affected
Some enzymes are inhibited
Free nerve endings are stimulated
In the same way that antacids buffer excess acidity in the stomach, bicarbonate can buffer the acidity in muscle, delaying the onset of fatigue.
**Muscle pH and Fatigue**

Ingestion of bicarbonate (about 0.3 g per kg body mass, equivalent to about 20 g for a 70 kg athlete) over a period of 2-3 hours prior to exercise can improve performance in events lasting a few minutes.

**Effects of Bicarbonate on 800 m and 1500 m Performance**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Placebo</th>
<th>Bicarbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>800 m</td>
<td>2:05.8</td>
<td>2:05.1</td>
<td>2:02.9</td>
</tr>
<tr>
<td>1500 m</td>
<td>4:18.0</td>
<td>4:15.6</td>
<td>4:13.9</td>
</tr>
</tbody>
</table>

**Adverse effects**

Some individuals experience gastrointestinal effects - sometimes severe. Most people do not experience severe problems, these generally disappear as tolerance develops. Other alkalinising agents may be equally effective, with fewer problems.

Bicarbonate is likely to be most effective where high levels of anaerobic metabolism occur. This probably means events lasting about 30 s to 1 min, but 15 min.

**Muscle buffering: a different approach**

Human muscle contains the dipeptide carnosine (beta-alanyl-histidine).

Carnosine contributes about 7% to pH buffering in normal human skeletal muscle.

The concentration is 1.5 to 2.5 times higher in Type 2 muscle fibres.

The muscle carnosine content is elevated in bodybuilders and accounts for about 20% of muscle buffering.

Tallon et al (2005) JSCA 19, 725-729
**Carnosine and β-alanine**

Muscle carnosine content can be influenced by intake of carnosine and/or β-alanine.

Daily supplementation of the diet with 6.4 g of β-alanine can increase muscle carnosine content by 65-75%.

Ingestion of L-carnosine was not more effective in increasing muscle carnosine content.  

Muscle uptake can be further enhanced by co-ingestion with simple sugars.  
Harris et al (2006) MSSE 38, abstract 1119

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**Beta-alanine supplementation and exercise performance**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dosing Protocol</th>
<th>Performance Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris et al. (2003)</td>
<td>4 x 800mg o.d. 5 for 5 weeks</td>
<td>↑ in knee extensor isometric endurance at 50% MVC (4 min cycle ergometer test)</td>
</tr>
<tr>
<td>Hill et al. (2005)</td>
<td>4 x 800mg o.d. 5 for 4 weeks</td>
<td>Work done at 100% of previously estimated power output on cycle ergometer</td>
</tr>
<tr>
<td>Backus et al. (2005)</td>
<td>1g x 4 per day (16g) + 1g x 2 o per day (22g)</td>
<td>Lactate threshold (Watts)</td>
</tr>
<tr>
<td>Shmack et al. (2005)</td>
<td>1g x 4 per day (16g) + 1g x 2 o per day (22g) + 30g dextrose per dose</td>
<td>↑ in physical working capacity at neuromuscular fatigue threshold (PWCFt)</td>
</tr>
<tr>
<td>Harris et al. (2006a)</td>
<td>3 x 1.8 g (9.6g o.d.) for 1 week</td>
<td>Anaerobic threshold determined via VO2max test</td>
</tr>
<tr>
<td>Harris et al. (2006b)</td>
<td>4 x 1.8g o.d. + 45 - 65 g CHO for 14 days</td>
<td>↑ in isometric endurance performance of knee extensors at 40 - 50% MVC, impulse of the knee extensors</td>
</tr>
</tbody>
</table>
Effects of dietary nitrate on oxygen cost during exercise

P. S. Larsen, E. Wulstberg, J. G. Lundberg and B. Elyson

Department of Physiology and Pharmacology, Department of Sport Medicine, University of Copenhagen, Copenhagen, Denmark.

Methods: In a randomized double-blind placebo-controlled crossover study, we tested the effect of dietary nitrate on physiological and metabolic parameters during exercise. Nine healthy young well-trained men performed submaximal and maximal work tests on a cycle ergometer after two separate 3-day periods of dietary supplementation with sodium nitrate (10.1 mmol kg⁻¹ day⁻¹ or an equivalent amount of sodium chloride placebo).

Results: The oxygen cost at submaximal exercise was reduced after nitrate supplementation compared with placebo. On an average, VO₂ decreased from 2.98 ± 0.87 to 2.82 ± 0.58 L min⁻¹ during NIT (P < 0.02) over the four lowest submaximal work rates. Gross efficiency increased from 19.7 ± 1.6 during CON to 21.1 ± 1.3% during NIT (P < 0.01) over the four lowest workload rates. There was no difference in heart rate, lactate, ventilation (VE), VE/V̇CO₂ or respiratory exchange ratio between nitrate and placebo despite some of the submaximal work rates.

Beetroot Juice

During severe exercise, the time-to-exhaustion was extended (BR: 675±203 vs. PL: 583±145 s; P 0.05).

Safety considerations

Is there a risk of harm to health if the product is taken:

- At the supplier’s recommended dose?
- At the dose commonly used?
- In combination with another supplement or drug?
- By specific population groups?
Drug development

Preceded by:
- Evidence base

Followed by:
- Ongoing safety monitoring

Lapses of GMP and quality assurance do occur in the pharmaceutical industry

Supplements: Adverse effects

Some products contain impurities (lead, broken glass, animal faeces, etc) because of poor manufacturing practice.

Some products do not contain expensive ingredients listed on the label but only inexpensive materials.

Athlete specific problems:
Some products contain doping agents that are not declared on the label.
The IOC Study from Cologne

634 non-hormonal nutritional supplements were obtained in 13 countries from 215 different suppliers.

11 different anabolic androgenic steroids were found.

94 (14.8%) samples contained prohormones not declared on the label ("positive supplements"). No reliable data were obtained for 66 samples (10.4%) because of matrix effects.

23 samples contained prohormones of nandrolone and testosterone, 64 samples contained only prohormones of testosterone, 7 samples contained only prohormones of nandrolone.

For details, see: www.dopinginfo.de

These results have now been confirmed many times.

Other anabolic steroids have also been found in supplements purchased in England, sometimes in very high amounts: deliberate addition!

14 of 110 supplements analysed in Cologne contained caffeine; 2 contained ephedrine.

Strict liability means that the onus is on the athlete to be sure.

HFL Supplement Testing - 2009

FINDINGS:

- Ephedrine (weight management, creatine, mineral, sleep aids, endurance, muscle building products)
- Methylephedrine (endurance products)
- Stanozolol (weight management product)
- Norandrostenedione (pre-workout products, raw materials)
Strict Liability

Strict liability gives no room for error
The offence lies in having a prohibited substance in your sample
Some athletes are undoubtedly victims of contaminated dietary supplements
For others, it is a convenient excuse
How does contamination occur?
1. Manufacturing by-product
2. Cross-contamination during production: the same processing and packaging equipment and storage facilities are used for supplements and for doping agents or other compounds
3. Deliberate adulteration: many products are completely ineffective. Adding an anabolic agent, stimulant or anorectic agent means that the consumer sees a benefit from using the product

Who regulates supplements?
In the US, the FDA is responsible for safety issues relating to dietary supplements, but its remit does not include efficacy

   - Largely responsive mode rather than proactive
   - Limited by funding, so tasks prioritised

Self-regulation by the supplements industry
Is self-regulation working?
### Certification programs

<table>
<thead>
<tr>
<th>Program</th>
<th>Country</th>
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<tr>
<td>Red List</td>
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<td>NSF</td>
<td>USA</td>
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<tr>
<td>IS</td>
<td>UK</td>
</tr>
<tr>
<td>NZVT</td>
<td>The Netherlands</td>
</tr>
</tbody>
</table>

Ostensibly to protect the athlete

Also to provide a service for industry

Red List Germany (Cologne Lab)

NSF USA

IS UK

NZVT The Netherlands

### Manufacturer’s guarantees

A product made from creatine monohydrate should be tested against creatine monohydrate standards. Testing should typically result in a score of 99% pure creatine monohydrate.

### Acceptable levels of impurities

Some websites say that acceptable levels of contaminants are in the range of 50-100 ppm (50-100 µg/g, or 0.005-0.01%)

At a dose of 20 g, this will give an intake of 1000-2000 µg (1-2 mg) of contaminant

Most contaminants at this level will have no effect on health or performance

Some doping agents may cause a failed test at very low levels

How low?
Very low indeed!

Urinary Nandrolone Metabolite Detection after Ingestion of a Nandrolone Precursor.

Very low indeed!

500 mL of water containing 5 g of creatine and 1.0, 2.5, or 5.0 µg of 19M-norandrostenedione

2.5 µg in 5 g is 0.00005%

2.5 µg in 500 g is 0.0000005%
The power of advertising

Athletes generally do not discriminate between scientific evidence and advertising hype.

Supplement sellers have large budgets and can use effective advertising.

Scientists are cautious and often not good at communication.
“Some Hydroxycut products are associated with a number of serious liver injuries. The FAD has received 23 reports of serious health problems ranging from jaundice . . . to liver damage requiring liver transplant. One death due to liver failure has been reported to the FDA.”

**One Athlete’s day**

**JUNE 11TH**

10.10am 3g L-lysine with 30mg Vit B6
4 phosphate tablets
2 scoops protein powder
3 tablets acetylglutamine
3g Vit C
3 tablets detox
50 mg zinc

Drank isotonic drink whilst training

1.45pm 3g L-lysine with 30mg Vit B6
3g Vit C
3 tablets detox

50 mg zinc

11.00pm 3g L-lysine with 30mg Vit B6
3g Vit C
3 tablets detox
1 scoop protein powder
3 teaspoons acetylglutamine

No acetylglutamine

Caffeine

**An unexpected consequence**

Many of the papers in the scientific literature have used commercially available dietary supplements

Where there was an effect, this may have been due to the presence of an undeclared drug

Where there was no effect, this may have been due to the absence of the active ingredient
For most supplements, there is NO evidence of efficacy or safety

- Acetylglutamine
- Antioxidants
- Astrogelatins
- BCAA
- Calcium
- Chondroitin
- Coenzyme Q10
- Creatine
- Energy bars
- Glucosamine
- HMB
- Iron
- Ornithine ketogluutarate
- Pycnogenol
- Selenium
- Taurine
- Vitamin C
- Zinc
- Androstenedione
- L-carnitine
- BCAA
- Carbohydrate
- Choline
- Chrysan
- Cardiox
- Eicosapentaenoic acid (EPA)
- Echinacea
- Tribulus Terrestris
- Zinc
- Etc, Etc

Maughan's Rules of Dietary Supplements for Athletes

1. If it works, it's probably banned
2. If it's not banned, then it probably doesn't work
3. There may be some exceptions

Summary and Key Points

The use of dietary supplements is no substitute for a good diet. Food sources of nutrients are best.

Where energy intake or food choice is restricted, a low-dose, broad-spectrum vitamin-mineral supplement may help.

A few supplements may have role where a specific need is demonstrated.

Athletes are cautioned against indiscriminate use of supplements.
Supplements and sports foods that may be of benefit to athletes: Creatine

1. Limitations to maximal exercise performance in humans
2. Creatine biosynthesis and supplementation studies in humans
3. Effect of insulin on muscle creatine accumulation in humans
4. Biochemical effects of muscle creatine loading in humans
5. Effects of muscle creatine loading on maximal exercise performance in humans
6. Effects of creatine supplementation – other areas of interest to athletes and future research
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Total Cr (mmol/kg dm)

Day 0 Day 7 Day 21 Day 35

Total Creatine (mmol/kg dm)
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Serum Insulin (mIU/l)

Change in muscle TCr (mmol/kg dm)

R1

Muscle Total Creatine

Conclusions

- Insulin: muscle Cr accumulation at high physiological conc
- Insulin probably Na-dependent Cr transport by increasing Na^+/K^-pump activity
- Only ingestion of large quantities of CHO is likely to augment muscle Cr accumulation
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Power output during 30s of maximal isokinetic cycling exercise before and after placebo ingestion.
Power output during 30s of maximal isokinetic cycling exercise before and after creatine ingestion

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Total work (J/kg body mass)

<table>
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</table>

Metabolites involved in muscle contraction

- ATP
- ADP
- AMP
- INOSINE
- HYPOXANTHINE
- XANTHINE
- URIC ACID
- PCr
- FUMARATE
- IMP
- S-ADENYL SUCCINATE
- ASPARATE
- GTP
- HYPOXANTHINE
- XANTHINE
- URIC ACID
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No effect of creatine supplementation on human myofibrillar and sarcoplasmic protein synthesis after resistance exercise


University of Louvain, Brussels, Belgium.

Accepted 18 April 2011, resubmitted 19 June 2011.
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Caffeine: An Ergogenic Aid That Works!

Lawrence L. Spriet, Ph.D.
Professor & Chair, Department of Human Health & Nutritional Sciences
University of Guelph, Guelph, Ontario CANADA

Outline of Presentation

• Caffeine – a drug that is rapidly absorbed by the body
• Caffeine increases endurance performance
• Metabolic mechanisms for caffeine’s ergogenic effects?
• Caffeine and ion handling?
• Evidence that the central nervous system is responsible for caffeine’s ergogenic effects.
• Mechanistic Conclusions
• Practical Issues and Caffeine Ingestion
• Practical Conclusions and Consensus Statement

CAFFEINE

Caffeine is a tri-methylxanthine
Metabolized in the liver to paraxanthine, theobromine and theophylline
Consumed in coffee, teas, soft drinks, energy drinks and chocolate. Also consumed in caffeine gum and “no-doz” tablets.
It gets into your blood quickly!!

Interacts with all body cells - crosses BBB

- 6 mg/kg = ~420 mg CAF
  (~3 cups of coffee)

Graham & Spriet JAP 78:867 '95

Enhancing Sport Performance

Should an Athlete use/try Caffeine?

• Not a nutrient, but a drug
• ↑↑ ↑↑ endurance (and possibly sprint) performance
• Central and peripheral effects on the body
• No serious side effects (hard to abuse)
• Socially acceptable drug - part of society’s fabric
• Impossible to control, used in training
• No longer banned/restricted by the IOC
  I would argue YES

Caffeine Enhances Endurance!

Has stood the test of time!

Long history - Costill et al. (1978)
  – trained cyclists, moderate caffeine doses (5-6 mg/kg bm)
  – 80% VO₂max - 75 (PL) vs. 96 (CAF) min
  – 20% increase in work over 2 hr with CAF

• Proposed a peripheral mechanism
  – CAF increased epinephrine and adipose lipolysis
  – increased plasma FFA & availability to muscle, muscle
    used more fat and less glycogen – spared glycogen
    for later in exhaustive exercise
Caffeine Enhances Endurance - 2

- Several confirmatory studies in 90’s
- Improved performance ~20-50% vs. placebo trial (30-80 min) with 3-13 mg CAF/kg bm [Graham & Spriet, 1991]
- Elite & recreationally trained athletes
  - running and cycling at 80-90% VO\(_2\)max
  - CAF taken ~60 min before exercise
- no need to go higher than 5-6 mg/kg bm
  - no relationship with prior diet or caffeine habituation
  - large variability between subjects

Hypothesis:
"Caffeine (9 mg/kg) at levels just below the IOC legal limit (12 ug/ml in the urine) would NOT increase the performance of well-trained athletes during endurance cycling and running at ~80% VO\(_2\)max".

We were very wrong!

Graham & Spriet, 1991

Possible Caffeine Mechanisms

- Muscle Metabolism
- Muscle Ion Handling
- Central and Peripheral Nervous Systems
Caffeine & Muscle Metabolism

- Increasing fat mobilization and oxidation, sparing muscle glycogen use for later in prolonged exercise

- Direct or indirect (via epinephrine) caffeine inhibition of glycogen phosphorylase (PHOS) and/or stimulation of hormone sensitive lipase (HSL)

- Augmenting muscle glucose uptake/oxidation
  - Increased arterial blood [glucose] – increased liver output
  - Increased glucose intestinal absorption and muscle oxidation?

- Enhancing Glycogen Resynthesis
  - Increased glucose uptake following exercise?

Caffeine and Glycogen Sparing

9 mg CAF/kg bm, ~80-85% VO\textsubscript{2}max

Muscle glycogen sparing – initial 15 min only

Higher muscle glycogen at PL exhaustion point

Increased time to exhaustion

Fig. 5. Muscle glycogen content during cycling to exhaustion after placebo or caffeine injection. *Significantly different from placebo, dm, dry muscle.

Spriest et al. 1992

Role of Caffeine & Glycogen Sparing

HOWEVER - Several additional studies – report no group effect of CAF on muscle glycogenolysis

(i.e. Graham et al. J. Physiol. 2000)

WHY?

- Lower CAF doses, less well-trained Ss
- Lower exercise power outputs
Variable Effect of Caffeine - Muscle Glycogenolysis

Glycogen sparsers and non-sparers!
(defined as > 10% glycogen sparing) !!

15 min at ~80% VO\textsubscript{2max}, (n = 6), 9 mg/kg bm
Chesley et al. 1998

Variable Effect of Caffeine - Muscle Glycogenolysis

Glycogen sparing explained by decreased free ADP (AMP) – leads to decreased PHOS flux and less PCr use.

Theory - greater fat avail. at exercise onset – greater NADH present – as seen when elevate plasma [FFA] before exercise – rely more on fat!
Chesley et al. 1998

Variability - Caffeine & Glycogen Sparing

- Variable effect – “responders and non-responders”?
- Need high doses - 9 mg/kg bm to see sparing – not presently recommended
- Only present early in exercise – under 10 min – use the plasma FFAs quickly
- Only seen at high POs – 80-85% VO\textsubscript{2max}
- Only relevant in exercise where glycogen availability is important - not a mechanism for short-term exercise (<40 min)
Caffeine Inhibits Glycogen PHOS Activity

- In vitro rabbit skeletal muscle
- 250 uM caffeine

Summary - Caffeine & Glycogen Sparing

Conclusion
Role of glycogen sparing as the mechanism to explain increased endurance performance is likely minimal when using low to moderate doses of caffeine and is limited to the initial minutes of intense aerobic exercise.

Could increased glucose absorption/oxidation explain the ability of caffeine to improve 1 hr cycling TT performance?

*significantly different compared with Glu, P<0.001
Caffeine increases intestinal glucose absorption

Van Nieuwenhoven et al, 2000

3-OMG:ramnose ratio

*significantly different compared with Glu, P=0.017

Effects of caffeine on exogenous glucose oxidation

- 8 trained male cyclists
  - age 27
  - Weight 71.2 ± 2.3 kg
  - VO2max 65.7 ± 2.2mL/kg/min
  - 120 min exercise at 55%Wmax
  - 3 conditions

Water, 0.8g/kg Glucose, 0.8g/kg Glucose + U13C glucose tracer, 0.8g/kg Glucose + 5mg/kg/h Caffeine (10 mg/kg total*) with U13C glucose tracer

Effects of caffeine on exogenous glucose oxidation

Yeo et al. 2005

Exogenous CHO oxidation (g/min)

Time (min)
Effects of caffeine on exogenous glucose oxidation

- More recent study did not confirm these findings – Desbrow et al. (2009)
- Higher power output (65 vs. 55%)
- Larger intake of CHO (70 vs 48 g/hr)
- Higher exercise glucose oxid. rate (0.95 vs. 0.57-0.72 g/min)
- Lower dose of CAF (1.5 or 3 vs. 10 mg/kg bm**)
- CAF dose before (-60 min vs. throughout)

Argued that when CHO availability is higher (optimal), CAF effect gone

Effects of caffeine on muscle glycogen resynthesis

- Subjects exercised night before, followed low CHO diet, and exercised again in morning to deplete glycogen - twice
- Consumed 1 g CHO/kg bm/hr for 4 hr during recovery in one trial and the same plus CAF in other
- 4 mg/kg bm CAF right after exercise and at 2 hours = 8 mg/kg bm (plasma caffeine - 32 and 77 uM at 1 & 4 hr)
- Muscle biopsies at 0, 1 and 4 hr of recovery

Pedersen et al. 2008

Caffeine Enhances Muscle Glycogen Resynthesis

Pedersen et al. 2008
Caffeine Enhances Muscle Glycogen Resynthesis

- Blood glucose and insulin higher in recovery (60-90 min on)
- Muscle signalling proteins showed little
- High dose of caffeine – would lower dose work?
- Other study in the pipeline which does not corroborate results
- Seems to contradict acute OGTT + CAF findings, where glucose uptake is slowed!
  
  SO THE JURY IS STILL OUT!

Caffeine Dose Response & Performance

**Performance effect at low dose!!**

3 mg/kg bm or ~200 mg caffeine is ergogenic!

Unlikely that metabolism could account for this!

Graham & Spriet, 1995

Metabolic Conclusions

*Especially if a low dose (~3 mg/kg bm) CAF is used

1. Does caffeine consistently promote fat oxidation and/or decrease muscle glycogen use? **NO** (and limited to initial 10-15 min)

2. Does caffeine augment CHO absorption and oxidation during exercise? **NOT LIKELY**

3. Does caffeine ingestion post exercise alter muscle glycogen resynthesis? **UNKNOWN**
Muscle Ion Handling

• Does caffeine improve Ca\(^{2+}\) handling in muscle?
  – Increases low frequency force (Tarnoplosky & Cupido, 2000)
  – Prolongs time to fatigue – 50% MVC (Meyers & Cafarelli, 2005)
  – “Studies suggest that caffeine can enhance contractile force during submaximal contractions by potentiating calcium release from the ryanodine receptor, not by altering sarcoplasmic excitability” (Tarnopolsky, 2008)
  – In vitro studies use mM caffeine levels!!


Caffeine Dose Response & Performance

Performance effect at low dose!!
3 mg/kg bm or -200 mg caffeine is ergogenic!

Likely to be central nervous system effect

Graham & Spriet, 1995
Can Ingesting Caffeine Late in Endurance Exercise ↑ Performance?

- Australian Institute for Sports (AIS) scientists noticed that endurance cyclists ingest non-carbonated cola late in exercise – why? Could any benefit be due to caffeine, to CHO, caffeine and CHO together, or a placebo effect?
- Without a pre-exercise caffeine dose, cola would produce very low plasma caffeine levels - any benefit would be expected to be central!

Small Amount of Caffeine and Cola Late in Exercise

- 8 well trained cyclists
- 4 trials of 2 hr at 70% VO₂max + time trial ** to exhaustion (**7 kJ/kg ~27 min)
- In all trials, 5 ml/kg sports drink (6.3% CHO, 18 mM sodium) at 20, 40 and 60 min
- At 80, 100 (& 120, if desired) min, cola beverage consumed

Cola Beverage with 4 Combinations:

1. Decaffeinated, 6% CHO - (CONTROL)
2. Caff (90 mg +), 11% CHO - (COLA)
3. Decaff, 11% CHO - (Extra CHO)
4. Caff (90 mg +), 6% CHO - (CAFFEINE)
Time Trial Performance Improved!

- 70% of improvement due to caffeine
- Likely CENTRAL EFFECT!!

Cox et al. 2002

Low caffeine doses taken late in exercise increase performance

- N = 15 well-trained cyclists
- 120 min at ~60% VO2max with hills
- Time trial – 6 kJ/kg bm asap!
- Caffeine at 80 min in CES
- Effective double blinding

Talanian & Spriet, 2007

Caffeine and the Central Nervous System


- Davis JM et al. Central nervous system effects of caffeine and adenosine on fatigue. AJP Reg, 284:R399-R404, 2003 - rat data
Caffeine and Mental Function

- Caffeine has stimulant-like effects on mood and cognitive performance
- Caffeine also can decrease pain perception, force sensation and perceived exertion
- Effects are well documented
  - in rested and sleep-deprived individuals in doses found in single servings of foods (~100 mg)
  - during exercise with higher, but still low doses (150–300 mg)
  - however, there can be large individual differences in optimal doses
- At high doses, side effects can be detrimental to mental performance and health

Most Likely Function of Caffeine

- The ergogenic effects of caffeine ingestion may act by blocking adenosine receptors within the CNS - maintaining stimulatory neurotransmitter levels
  (Caffeine is freely diffusible to the brain)
- Blocking adenosine receptors (x 1)
- Inhibiting PDE (x 20)
- Mobilizing intracellular Ca²⁺ (x 500)

How Does Caffeine Affect the Adenosine Receptors?

- Caffeine crosses the BBB and is a CNS stimulant (increases arousal, wakefulness, alertness, vigilance and mood!)
- Adenosine normally exerts inhibitory effects on the brain (neuroexcitability and transmitter release, arousal and spontaneous activity)
- Caffeine is antagonistic to adenosine - binds to its receptors and reverses its effects!!
Can CNS Adenosine Receptors Blockade Explain How Caffeine Reduces Fatigue?

- Intracerebroventricular injections 30 min before running to fatigue in rats
- 4 groups - vehicle (placebo)
  - NECA (adenosine agonist)
  - caffeine (adenosine antagonist)
  - caffeine & NECA

Davis et al. 2003

CNS Injections

1. Vehicle – control
2. Caffeine - 60% increase
3. NECA - 68% decrease
4. CAF + NECA - balanced out

Davis et al. 2003

Cortical Input & Excitability

Neuromuscular Studies - Humans

Spinal excitability

Supraspinal Drive

A. Self sustain firing

Central Drive

B. Voluntary activation & maximal force

Peripheral Transmission & Contractile Activity

Gliottoni et al. 2009

Kalmar & Cafarelli, 2004
Mechanistic Conclusions

- Metabolic and ion handling mechanisms may contribute to the ergogenic effects of caffeine in specific exercise situations, but the evidence is limited and not very convincing.

- Increasing indirect and direct experimental evidence suggests that the major ergogenic effect of caffeine is manifested at several sites in the central nervous system.

Practical Issues and Caffeine

Short Term Exercise - Caffeine Benefit?

1. Aerobic Exercise Lasting 20 - 35 min
   - Very high aerobic power outputs during exercise/sport
   - Most studies (meta-analyses) say YES - 1500 m swim, ~80-85% VO₂max running and cycling to exhaustion in lab.
   - Likely to be central effect, not peripheral

2. Graded Exercise Tests (8 - 20 min)
   - NO, except two reports at 10-15 mg CAF/kg bm.
3. **Intense Exercise** (4-8 min)

- Near-maximal energy provision from aerobic and anaerobic pathways!!
- YES - 1500 m running, 1-3 cycling bouts at 100% $VO_2$ max to exhaustion, 2000 m rowing (men & women)
- Central effects?

4. **Sprint Exercise - less than 60-90 sec**

- Power output of ~150-300% $VO_2$ max - anaerobic energy provision dominates.
- NO for single sprints but emerging evidence for repeated sprints/bouts of resistance exercise (Woot et al. 2008)

---

**Real-World Issues For Caffeine Ingestion**

1. **Does it work in the field – Mostly yes?**

- Running 21 km in heat - NO; 60-90 min skiing in cold - YES
- Lab or field simulations - YES. 1500 m in pool or on track, 2000 m rowing, time trials (kJ/kg bm) late in exercise, etc

2. **When should the caffeine be taken?**

- Usually ~45-60 min before the event.
- Before and throughout event (Kovacs et al. 1998) and at end of event (Cox et al. 2002) also works!

3. **Can it be taken with a sports drink?**

Ergogenic when given with carbohydrate-electrolyte solution (Kovacs et al. 1998, Conger et al. 2011)
4. Caffeine in tablets or coffee?

- One study - no effect with coffee vs. caffeine
  (Graham et al. 1998 - running at 85% VO\textsubscript{2}max for ~35 min)

- Other studies show effect with coffee
  (Costill et al. 1978 and Wiles et al. 1992 - 1500 m run)

5. Caffeine in energy drinks?

- Caffeine content often not listed
  (~50-150 mg/240 ml or 8 oz serving)
  - presence of guarana extracts (herbal caffeine source – unpredictable amount of caffeine!)

- Many other known & unknown ingredients - nothing to gain and potentially could lose from these supplements

6. Caffeine and Fluid Balance

Evidence suggests that caffeine ingestion

- does not cause dehydration or GI upset when ingested shortly before and/or during exercise
- does not cause water-electrolyte imbalances or hyperthermia
- does not reduce exercise-heat tolerance
- does not have to be avoided in situations where fluid balance may be compromised.
- may slow rehydration after exercise compared to a carbohydrate-electrolyte drink, but not compared to other fluids

Gonzalez-Alonso et al. JSSM 13:399, 1992; Brouns et al. JSSM 19:56, 1998
Maughan & Griffin JHND 16:1, 2003

Side Effects of Caffeine Ingestion

- Some side effects exist at moderate to high doses (6 – 9 mg/kg bm): anxiety, jitters, insomnia, inability to focus, GI unrest, irritability, blabbermouth syndrome, etc.

- There is a dependency to caffeine - anxiety and sleep disorders, withdrawal effects will occur

- Side effects are minimal or non-existent with doses of ~3 mg/kg or ~200 mg.

- There is large individual variation
Practical Conclusions

• Caffeine at low to moderate doses (3-5 mg/kg bm) is ergogenic for lab- and field-based performance tests lasting beyond ~4 min.

• Minimal side effects are experienced at these low to moderate doses.
• No negative interactions with other physiological responses to exercise.
• Can be added to a sports drink – no hydration concerns
• Individual variation exists, so try it in training first!

Practical Conclusions – Cont’d

• The optimal dose for enhancing athletic performance appears to be ~200 mg of caffeine (~3 mg/kg bm)

• This also appears to be the optimal dose for cognitive function

• Even smaller doses are effective at improving performance late in prolonged exercise - (~1-2 mg/kg/bm)
Caffeine Consensus Statement

Caffeine intake has the potential to be ergogenic at low to moderate doses (<3-5 mg/kg bm) in most individuals in most exercise and sports situations, while posing few if any side effects and little health risk.
EXERCISE AND pH

HI Exercise = ↓ IM pH from ~7.1 to <6.5
(6.0; Pan et al., 1991)

H⁺ BUFFERING (β) IN MUSCLE

Lecturer: Dr Craig Sale

IOC Diploma in Sports Nutrition
www.sportsoracle.com
INTRACELLULAR BUFFERS
CREATINE
CARNOSINE (β-ALANINE)

CREATINE SUPPLEMENTATION

- Phosphorylcreatine (PCr) acts as a high energy phosphate donor for the regeneration of ATP during exercise.
- The creatine kinase (CK) reaction results in the breakdown of PCr and the regeneration of ATP.
- Also as part of this process H⁺ is also consumed:
  \[ \text{H}^+ + \text{PCr} + \text{ADP} \xrightarrow{\text{CK}} \text{Cr} + \text{ATP} \]
- So PCr breakdown during high-intensity exercise could contribute to intracellular buffering (Hultman and Sahlin, 1980).
- As such, increasing muscle creatine stores by supplementation might have a small effect on muscle buffering capacity as well as on ATP regeneration.

CARNOSINE MOLECULE

The carnosine molecule consists of histidine and ß-alanine, and it plays a role in intracellular buffering.
### β-ALANINE SUPPLEMENTATION AND mCARN

<table>
<thead>
<tr>
<th>DOSE NUMBER</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<td>2) 8-ala 5.2</td>
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<td>0.8</td>
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<td>0.8</td>
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<td>5.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) Carn 13.0 (isomolar to 8-ala 5.2 g d⁻¹)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**βFALANINE SUPPLEMENTATION AND mCARN**


---

**Correlations with Carnosine (p < 0.05)**

- MPO: \( r = 0.785 \)
- 21-25 s: \( r = 0.694 \)
- 26-30 s: \( r = 0.660 \)
- % Type IIX fibres: \( r = 0.646 \)

βFALANINE SUPPLEMENTATION AND REPEATED WINGATE PERFORMANCE

- 10 Pla: 10 BA
- Average daily dose of 5.2 g·d⁻¹

Week 1
- 5 min w.up
- Sprint 1
- 30 sec
- 2 min active

Week 2
- Sprint 2
- 30 sec
- 2 min active

Week 3
- Sprint 3
- 30 sec

Week 4

βFALANINE AND ISOMETRIC ENDURANCE OF THE KNEE EXTENSOR MUSCLES AT 45% MVIC

- Examined the effects of β-alanine supplementation on a test more likely to be limited H⁺ accumulation
- 13 participants
  - 7 β-alanine and 6 placebo
  - 4 weeks supplementation at 6.4 g·d⁻¹
- Five isometric knee extension tests to fatigue at an intensity of 45% of maximal voluntary isometric contraction force
  - 2 familiarisation tests
  - Baseline test (week 0)
  - Familiarisation (week 3.5)
  - Post-Test (week 4)
βFALANINE AND ISOMETRIC ENDURANCE OF THE KNEE EXTENSOR MUSCLES AT 45% MVIC

<table>
<thead>
<tr>
<th></th>
<th>Pre (s)</th>
<th>Post (s)</th>
<th>Delta (s)</th>
<th>Change (%)</th>
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</thead>
<tbody>
<tr>
<td>β-falanine Mean</td>
<td>76.9</td>
<td>86.6</td>
<td>9.7*</td>
<td>13.2</td>
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<tr>
<td>n = 7</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SD</td>
<td>19.5</td>
<td>21.0</td>
<td>9.4</td>
<td>14.3</td>
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<tr>
<td>Placebo Mean</td>
<td>75.0</td>
<td>72.5</td>
<td>-2.6</td>
<td>-4.0</td>
</tr>
<tr>
<td>n = 6</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>16.7</td>
<td>18.5</td>
<td>4.3</td>
<td>6.6</td>
</tr>
</tbody>
</table>

βFALANINE SUPPLEMENTATION AND CYCLING CAPACITY AT 110% POWERMAX

Muscle carnosine significantly elevated from pre-supplementation:
- 80% after 4 weeks
- 80% after 10 weeks


SUMMARY – ERGONOMIC POTENTIAL?

Exercise Duration (s)

<table>
<thead>
<tr>
<th>0</th>
<th>60</th>
<th>120</th>
<th>240</th>
<th>1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>5RM (Hill &amp; Robinson, 2011)</td>
<td>3RM sprint (van Thienen et al., 2009)</td>
<td>5RM sprint (van Thienen et al., 2009)</td>
<td>3RM cycle (Roach et al., 2011)</td>
<td>5RM (Hill et al., 2008, 2009)</td>
</tr>
<tr>
<td>Wingate (Hill et al., 2006)</td>
<td>Isometric endurance (Hill et al.)</td>
<td>Isometric endurance (Hill et al.)</td>
<td>Wingate test (Roach et al., 2011)</td>
<td>Wingate test (Roach et al., 2011)</td>
</tr>
<tr>
<td>0% OBLA (Jordan et al., 2010)</td>
<td>0% OBLA (Jordan et al., 2010)</td>
<td>0% OBLA (Jordan et al., 2010)</td>
<td>0% OBLA (Jordan et al., 2010)</td>
<td>0% OBLA (Jordan et al., 2010)</td>
</tr>
</tbody>
</table>
**EXTRACELLULAR BUFFERS**

**SODIUM BICARBONATE/CITRATE**

**SODIUM BICARBONATE (NaHCO₃) SUPPLEMENTATION**

- Numerous studies showing efficacy with the following dosing recommendations:
  - 0.2 g·kg⁻¹·BM as a minimal dose
  - 0.3 g·kg⁻¹·BM as a more optimal dose
- These doses sufficient to:
  - Increase blood bicarbonate levels
  - Increase blood pH

**META-ANALYSIS OF PERFORMANCE STUDIES**

- Meta-analysis on 29 studies meeting the inclusion criteria
- Results indicate that:
  - Sodium bicarbonate resulted in a more alkaline extracellular environment
  - Dose was only moderately related to the increase in bicarbonate and pH (r = 0.42)
  - In general, performance was enhanced by sodium bicarbonate supplementation but the range of effect sizes was large
  - 27 ± 20% increase in exercise capacity following sodium bicarbonate supplementation
  - However, the treatment effect was only weakly related to the degree of blood alkalosis

---

INDIVIDUAL RESPONSES IN EXERCISE CAPACITY FOLLOWING SODIUM BICARBONATE

SODIUM BICARBONATE AGAINST OTHER BUFFERS

- Sodium bicarbonate against other buffers (sodium citrate and sodium lactate) and placebo (sodium chloride).
- 15 competitive male endurance runners.
  - Ingested a single oral dose 90 min after exercise.
  - Same osmolar dose relative to body mass (3.6 mosmol x kg).
- Mean run times:
  - Bicarbonate: 82.3 s
  - Lactate: 80.2 s
  - Citrate: 78.2 s
  - Chloride: 77.4 s
- Bicarbonate more beneficial to sprinting than lactate, citrate or chloride.

POSSIBLE PROBLEMS

- Gastrointestinal discomfort
  - Diarrhoea
  - Cramps
  - Bloating
  - Can be prevented by consuming large volumes of water (body mass increase).
  - Can also be reduced by dividing the standard 0.3 g·kg⁻¹·BM dose into parts taken over hours.
  - Some studies have shown sodium citrate ingestion to have similar effects on buffering without GI distress (e.g., McNaughton, 1990).
SUMMARY

- High-intensity exercise results in reduced substrate levels and accumulation of H+ and other metabolites in the skeletal muscle.
- The accumulation of H+ can have deleterious effects on skeletal muscle function and force generation, thus contributing to fatigue.
- Clearly, this is a challenge to sport and exercise performance, so any intervention capable of reducing the negative impact would be useful.
- There are several nutritional supplements that athletes could take to increase buffering capacity and potentially performance during high-intensity exercise.
  - β-Alanine to increase muscle carnosine and possibly creatine monohydrate supplementation offer a means to enhance intracellular buffering.
  - Sodium bicarbonate or citrate supplementation provides a means of enhancing extracellular buffering.
Thank you for listening.
Dietary Nitrate: The New Magic Bullet?

Andrew M. Jones PhD
Professor of Applied Physiology
University of Exeter

Pathways of NO synthesis

New concepts in nitrite biology

- The nitrate – nitrite – NO pathway is an essential ‘back-up’ system for NO generation
- It may be particularly important in hypoxic conditions (such as during exercise?)
- It may compensate for dysfunctional NOS
The Entero-Salivary Circulation of Nitrate

Nitrate (NO$_3^-$)

Nitrite (NO$_2^-$)

Nitric oxide (NO)

- Regulation of blood flow
- Modulation of excitation-contraction coupling
- Regulation of mitochondrial respiration

Nitrite ($\rightarrow$ Nitric oxide)

Bacterial anaerobes

Acidosis

Hypoxia

Oxygen consumption during exercise

3 days supplementation with 0.1 mmol/day NaNO$_3$

Study #1: ‘Beetroot Juice’

NaNO$_3$ not ethically approved for human use in the UK

We wished to investigate whether:

1) Similar effects were manifest following dietary supplementation with nitrate-rich beetroot juice

2) The potential improvement in exercise economy might enhance exercise tolerance

Bailey et al., 2009, J Appl Physiol
**Experimental Design**

- Six day intervention period: supplementation with:
  - Beetroot (NO<sub>3</sub>) = 5.6 mmol-day<sup>-1</sup>) and Placebo (NO<sub>3</sub>) = negligible)
- 10 day washout period
- 8 Male Participants
- Randomized
- Double-Blinded
- Cross-over Design

**Measurements**

- Pulmonary VO<sub>2</sub> Dynamics
  - Breath-by-Breath

  ![Pulmonary VO2 Dynamics](image)

- Tissue Oxygenation
  - Near-infrared Spectroscopy
Measurements

- **Pulmonary VO$_2$ Dynamics**
  - Breath-by-Breath

- **Tissue Oxygenation**
  - Near-infrared Spectroscopy

- **Blood Pressure**
  - Automated Device

- **Plasma [NO$_2$] as biomarker of NO bioavailability**
  - Chemiluminescence

**Influence of Nitrate on Plasma [NO$_2$]**

![Graph showing the influence of nitrate on plasma [NO$_2$]](image)

- Placebo
- Nitrate

Significance levels:
- $*=P < 0.05$
- $##=P < 0.01$
- $###=P < 0.001$
Influence of Nitrate on Systolic BP

![Graph showing the influence of nitrate on systolic BP](image)

**Placebo vs. Nitrate**
- # = P < 0.05
- # = P < 0.01

Influence of nitrate on estimated O\textsubscript{2} extraction and muscle blood volume

![Graph showing O\textsubscript{2} extraction and muscle blood volume](image)

- Reduced [HHb] amplitude with nitrate (indicative of reduced O\textsubscript{2} extraction)
- Increased [Hb\textsub{tot}] with nitrate (indicative of hyperaemia)

Influence of Nitrate on O\textsubscript{2} Cost of Moderate Exercise

![Graph showing O\textsubscript{2} cost of moderate exercise](image)

- # = P < 0.01
Influence of Nitrate on Severe Exercise Tolerance

Summary to Study #1

- Dietary nitrate supplementation increased markers of NO synthesis.
- The O$_2$ cost of moderate exercise was reduced.
- During severe exercise the VO$_2$ slow component was reduced and exercise tolerance was enhanced.

Study #2: Acute and Chronic Supplementation

Previous research:
- Supplementation continued 3-6 days
- Increased vs. restricted NO$_3$ intake

Questions:
- What are the effects of acute and chronic supplementation?
- How might nitrate influence incremental test performance?
- Do the effects persist when NO$_3$ intake is not restricted in the control condition?

Vanhatalo et al., 2010, Am J Physiol
Experimental Design

- 8 subjects, balanced cross-over design
- 0.5 L/day of beetroot juice (5.2 mmol of NO\(_3\)) and placebo
- Plasma [nitrite] measured as an index of NO bioavailability at baseline, 2.5 h post-ingestion on day 1, and after 2, 5, 8, 12 and 15 days
- Exercise testing performed at baseline, 2.5 h post-ingestion on day 1, and after 5 and 15 days

Plasma nitrite concentration

Moderate intensity exercise: VO\(_2\)
Moderate intensity exercise: VO$_2$ gain

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>2.5 h</th>
<th>5 d</th>
<th>15 d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>9.0</td>
<td>9.5</td>
<td>9.0</td>
<td>9.5</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>8.5</td>
<td>8.0</td>
<td>8.5</td>
<td>8.0</td>
</tr>
<tr>
<td><strong>Nitrate</strong></td>
<td>10.0</td>
<td>10.5</td>
<td>11.0</td>
<td>11.0</td>
</tr>
</tbody>
</table>

* Different from baseline; # Different from Placebo; P < 0.05

Ramp incremental exercise: peak work rate and VO$_2$max

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>2.5 h</th>
<th>5 d</th>
<th>15 d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td>3.2</td>
<td>3.4</td>
<td>3.6</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>Nitrate</strong></td>
<td>3.0</td>
<td>3.2</td>
<td>3.4</td>
<td>3.6</td>
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</table>

* Different from baseline; # Different from Placebo; P < 0.05

Effect on [PCr] recovery kinetics

<table>
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<tr>
<th></th>
<th>Control</th>
<th>Nitrate</th>
<th>Placebo</th>
</tr>
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<tr>
<td><strong>Nitrate</strong></td>
<td>33</td>
<td>35</td>
<td>37</td>
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</tbody>
</table>

* Different from Placebo; P < 0.05
Conclusions to Study #2

- Acute reduction in $O_2$ cost of moderate exercise was sustained over 15 days of nitrate supplementation
- The GET and VO$_2$max were not acutely affected but were increased after 15 days
- Positive effects are also seen when habitual NO$_3$ intake is not restricted

Beetroot Juice Constituents: Are There Other Potential ‘Active Ingredients’?

- Beets are a rich source of:
  - Antioxidants
    - Betaine
    - Vitamins
  - Polyphenols
    - Quercetin
    - Resveratrol

- To what extent have these molecules contributed to our findings?

Study #3: Placebo

We developed a process that selectively removes nitrate from beetroot juice

We wished to determine:

1) The effects of nitrate-rich vs. nitrate-depleted beetroot juice
2) The effects upon the oxygen cost of walking and running exercise

Lansley et al., 2011, J Appl Physiol
Nitrate-depleted Beetroot Juice and Moderate-Intensity Running

- Control
- Nitrate-depleted

Nitrate-rich Beetroot Juice and Moderate-Intensity Running

- Nitrate-depleted
- Nitrate-rich

- 4% VO_2 Amplitude (P < 0.05)
- 7% End-exercise VO_2 (P < 0.01)
- 12% Walking VO_2 (P < 0.01)

Nitrate-depleted Beetroot Juice and Severe-Intensity Running

- Control
- Nitrate-depleted
Conclusions to Study #3

- Dietary nitrate reduced the $O_2$ cost of walking and running
  - Possibly important implications for the elderly and clinical populations
- No effect with nitrate-depleted beetroot juice
  - The effects observed following beetroot juice can be attributed to its high nitrate content

Study #4: Performance

A ‘time-to-exhaustion’ test is a measure of ‘exercise capacity’ rather than athletic performance.

The purpose of Study #4:

- Does acute (2.5 h) dietary nitrate supplementation affect cycling time trial performance in trained athletes?
- The test = complete a 4 km (and 16.1 km) distance in the fastest possible time

Lansley et al., 2011, Med Sci Sports Exerc
Influence of Dietary Nitrate on 4 km Time Trial Performance

Conclusions to Study #4

- Dietary nitrate enabled a greater PO for the same VO$_2$
- The improved PO/VO$_2$ resulted in a 2.8% improvement in 4 km (and 16.1 km) TT performance: highly meaningful to an athlete
Nitrate supplementation improves 10 km time trial performance in trained cyclists

Naomi M. Cermak, Martin J. Gibala, and Luc J.C. van Loon

Methods: Using a double-blind, repeated-measures crossover design, 13 male cyclists ingested 140 mL/day of concentrated beetroot (~8 mmol/day nitrate) juice (BEET) or a placebo (nitrate-depleted beetroot juice; PLAC) for 6 d. On the last day of supplementation, subjects performed 60 min of sub-maximal cycling followed by a 10 km time trial.

Results: Sub-maximal VO2 was lower after BEET compared with PLAC (P<0.05). Time trial performance (953±18 vs. 965±18 s; P<0.005) and power output (294±12 vs. 288±12 W; P<0.05) improved following BEET compared with PLAC supplementation.

Conclusion: Six days of nitrate supplementation reduces pulmonary oxygen uptake during sub-maximal exercise and improves 10 km time trial performance in trained cyclists.

A Word of Warning!

• To reduce the O2 cost of exercise at the same WR, dietary nitrate supplementation may have:
  1) Inhibited mitochondrial ATP synthesis- resulting in a compensatory increase in anaerobic energy liberation;
  2) Increased the mitochondrial P/O ratio (i.e., reduced the O2 cost of ATP resynthesis);
  3) Reduced the ATP cost of force production (with similar P/O ratio).

Study #5: Mechanisms (Bailey et al., 2010, J Appl Physiol)
**Experimental Design**

- Six day intervention period - supplementation with:
  - Beetroot (NO\textsubscript{3} = 5.1 mmol-day\textsuperscript{-1}) and Placebo (NO\textsubscript{3} = negligible)
- 7 Male Participants
- Randomized
- Double-Blinded
- Cross-over Design
- 10 Day Washout

### Performance Measures

- **Power Output (W)**
  - Days 4 & 5
    - LOW = 15% MVC
    - HIGH = 35% MVC
  - Day 6
    - HIGH

### Muscle Energetics

- **[Pi]**
  - comparing signal intensities from an external phosphoric acid source and the subjects' quadriceps.
- **[PCr]**
  - ratio of P\textsubscript{i}:PCr
- **pH**
  - chemical shift of the P\textsubscript{i} spectral peak relative to the PCr peak
- **ADP**
  - calculated using the procedures of Kemp et al. (2001).
- **ATP**\textsubscript{p} - rate of change of [PCr] from modeling [PCr] at each time point
- **ATP**\textsubscript{t} - determined by proton flux assuming 1 mol H\textsuperscript{+} yields 1.5 mol ATP
- **ATP**\textsubscript{t} = hyperbolic relationship between ATP production rate and cytosolic [ADP]
- **ATP**\textsubscript{total} = ATP\textsubscript{p} + ATP\textsubscript{t} + ATP\textsubscript{o} (Lanza et al., 2006; Layec et al., 2009).

**Influence of Dietary Nitrate on Indices of NO Production**

- Mean plasma [NO\textsubscript{2}] (nM)
  - Placebo
  - Nitrate
- Mean Systolic BP (mmHg)
  - Placebo
  - Nitrate

* Denotes P<0.05
# Denotes P<0.01
Influence of Dietary Nitrate on VO\textsubscript{2} and Muscle [PCr] Dynamics

\[ \text{VO}_2 \text{(ml min}^{-1}) \]

\[ \text{[PCr] (mM)} \]

\# Denotes P<0.01

---

Low-Intensity Exercise Muscle ATP Turnover Rates

\[ \text{ATP turnover (\mu M.s}^{-1}) \]

\[ \text{ATP}_\text{total}, \text{ ATP}_\text{ox}, \text{ ATP}_\text{PCr}, \text{ ATP}_\text{gly} \]

\* Denotes P<0.05

---

High-Intensity Exercise Muscle ATP Turnover Rates

\[ \text{ATP turnover (\mu M.s}^{-1}) \]

\[ \text{ATP}_\text{total}, \text{ ATP}_\text{ox}, \text{ ATP}_\text{PCr}, \text{ ATP}_\text{gly} \]

\* Denotes P<0.05
Dietary nitrate reduced the $O_2$ cost of low- and high-intensity exercise at the same WR.

**Mechanisms**

1) Inhibit mitochondrial ATP synthesis- resulting in a compensatory increase in anaerobic energy liberation;

2) Increase the mitochondrial P/O ratio (i.e., reduce the $O_2$ cost of ATP resynthesis);
Influence of Dietary Nitrate on P/O Ratio

![Graph showing the influence of dietary nitrate on P/O ratio]

**Summary**
- Dietary nitrate reduced the O₂ cost of low- and high-intensity exercise at the same WR.

**Mechanisms**
- 1) Inhibit mitochondrial ATP synthesis - resulting in a compensatory increase in anaerobic energy liberation;
- 2) Increase the mitochondrial P:O ratio (i.e., reduce the O₂ cost of ATP resynthesis);
- 3) Reduce the ATP cost of force production

**Conclusions to Study #5**
- Dietary nitrate reduced ATP utilisation, PCr hydrolysis and the accumulation of ADP and Pi.
  - effects of NO on actin-myosin interaction or Ca²⁺ transport by SERCA?
  - Implications for control of ox. phosphorylation.
- High-intensity exercise tolerance was enhanced following dietary nitrate supplementation
  - reduced intramuscular metabolic perturbation.
Alternatively: dietary nitrate and mitochondrial function

- 14 healthy subjects
- Randomised, double-blind, crossover, placebo controlled
- 3 days of sodium nitrate (0.1 mmol/kg/day) or placebo, 1 wk washout
- Skeletal muscle biopsies – isolated mitochondria

High resolution respirometry

Substrates
Malate/Pyruvate
ADP
Atractyloside
Larsen et al., Cell Met.

State 3
State 4
State 4 + atractyloside

Respiratory control ratio
(func. integrity)

Nitrate and mitochondrial function
Larsen et al. (2011) Cell Met

Respiratory control ratio
(func. integrity)

P/O ratio
(func. efficiency)

These data indicate an improved mitochondrial efficiency after nitrate supplementation. What is the underlying explanation?
Nitrate and mitochondrial function

LEAK respiration  State 4 respiration  State 4+ atracyloside

State 3 respiration  Uncoupled (FCCP)

Whole body oxygen consumption

$\Delta VO_2$  $\Delta W/VO_2$

$\Delta VO_2$ vs $\Delta P/O$ ratio  $\Delta W/VO_2$ vs $\Delta P/O$ ratio

In vivo  In vitro

$R^2 = 0.64$  $R^2 = 0.76$  $p = 0.02$  $p = 0.005$

Nitrate and mitochondrial function

UCP-3  ATP/ADP translocase

In vivo  In vitro

In vivo  In vitro
Dietary nitrate improves human skeletal muscle mitochondrial efficiency, most likely via reduced proton leakage (reduced expression of the ATP/ADP translocase, involved in proton conductance).

Mechanisms: Summary
Lowering of whole-body VO₂ during exercise following nitrate supplementation:
Muscle contractile efficiency? Mitochondrial efficiency? Both?

New study: dietary nitrate in hypoxia
- 9 subjects (age 28 ± 7 years, body mass 73.4 ± 12.6 kg, height 1.77 ± 0.05 m)
- Blind, randomised, cross-over design

<table>
<thead>
<tr>
<th>Condition</th>
<th>CON</th>
<th>H-PL</th>
<th>H-BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>FV̇O₂(%)</td>
<td>20.9</td>
<td>14.5</td>
<td>14.5</td>
</tr>
<tr>
<td>Supplement</td>
<td>-</td>
<td>NO₃-depleted beetroot juice</td>
<td>Beetroot juice 9.3 mmol of NO₃</td>
</tr>
</tbody>
</table>

- Knee-extension exercise:
  - 24 s bout for the assessment of recovery (PCr)τ
  - High-intensity bout to the limit of tolerance (Tlim)
**NO bioavailability**

![Graph showing NO bioavailability](image)

* Different from CON and H-PL (*P<0.05) * Different from H-PL (*P<0.05)

**Muscle metabolic perturbation**

![Graph showing [P']](image)

[^P]: Different from CON and H-PL (*P<0.05)

![Graph showing [PCO]](image)

[^PCO]: Different from CON and H-PL (*P<0.05)
Muscle metabolic perturbation

**[pH]**

* T<sub>lim</sub> different from CON and H–BR (*P<0.05)*

**Time (s)**

0 120 240 360 480 600

-0.25 -0.20 -0.15 -0.10 -0.05 0.00 0.05 0.10 0.15

[H<sub>2</sub>O] recovery kinetics

**Recovery [PCr] τ (s)**

CON  H–PL  H–BR

* Different from CON and H–BR (*P<0.01)*

**SaO<sub>2</sub>**

~98% ~91% ~91% ~91% ~91%

**Implications**

- A diet that increases NO bioavailability may enhance:
  - Cardiovascular Health ('5 a day')
  - 'Targeted' O<sub>2</sub> Delivery
  - Exercise Economy
  - Exercise Tolerance
Rich in Nitrate!