

Module 4: Supplements

In this module we will discuss a number of supplements that may be important on a match day or in the lead-up to a match day. There are over 55,000 supplements on the market, so it is impossible to discuss all supplements. Here we will focus on 8 supplements that have good rationale and evidence as well as some supplements that are very common (but may not be backed by a lot of evidence).

4.1.1 Caffeine

Caffeine is found in a wide variety of drinks and foods, including tea, coffee, cola, guarana and chocolate. Most of the caffeinated beverages consumed throughout the world are extracted from coffee beans or tea leaves. However, caffeine can also be found in many sports nutrition products, such as gels, chewing gums, energy shots and energy drinks. In Table 1, the caffeine content of a range of products is listed. Caffeine is a drug and a food substance. It is often referred to as the most consumed drug worldwide. It is also the most widely studied of all ergogenic aids. Studies have consistently shown endurance performance is enhanced with caffeine and it is also clear that various cognitive aspects are enhanced.

Table 1: Caffeine content of various foods, beverages and medications

Item	Caffeine content (mg)	Item	Caffeine content (mg)
Coffee		Pain relievers (per tablet)	
Drip method (150 ml [5 oz])	110-150	Anacin	32
Percolated (150 ml [5 oz])	64-124	Excedrin	65
Instant (150 ml [5 oz])	40-108	Midol	32
Decaffeinated (150 ml [5 oz])	2-5	Aspirin	0
Starbucks grande (480 ml [16 oz])	550	Vanquish	33
Starbucks tall (360 ml [12 oz])	375	Diuretics (per tablet)	
Starbucks short (240 ml [8 oz])	250	Aqua Ban	200
Starbucks tall latte (360 ml [12 oz])	70	Pre-Mens Forte	100
Tea		Cold Remedies (per tablet)	
1 min brew (150 ml [5 oz])	9-33	Coryban-D	30
3 min brew (150 ml [5 oz])	20-46	Dristan	0
5 min brew (150 ml [5 oz])	20-50	Triaminicin	30
Instant tea (150 ml [5 oz])	12-28	Weight-control aids (per tablet)	
Iced tea (360 ml [12 oz])	22-36	Dexatrim	200
Chocolate		Prolamine	140
Made from mix	6	Stimulants (per tablet)	
Milk chocolate (30 g [1 oz])	6	Pro Plus	50
Baking chocolate	35	NoDoz	100
Chocolate bar (100 g [4 oz])	12-15	Prescription pain relievers (per tablet)	
Soft drinks		Cafergot	100
Mountain Dew (355 ml [12 fl oz])	55	Davron compound	32
Mello Yello (355 ml [12 fl oz])	52	Florinal	40
Coca-Cola (355 ml [12 fl oz])	46	Migralal	1
Diet Coke (355 ml [12 fl oz])	46		
Pepsi (355 ml [12 fl oz])	38		
Diet Pepsi (355 ml [12 fl oz])	36		
Dr. Pepper (355 ml [12 fl oz])	40		
Red Bull (250 ml [8 oz])	80		

Source: Jeukendrup and Gleeson, 2018, <https://bit.ly/2UEN0q7>.

Caffeine is absorbed with a time to peak plasma concentration of 30 to 90 minutes and its elimination half-life is around five hours. Caffeine is

metabolized by the cytochrome P-450 (CYP) oxidase system to a variety of xanthine metabolites, with about one to three per cent excreted in the urine as free caffeine. The habitual consumption of caffeine also influences metabolism by down-regulating many of the physiological effects (tachyphylaxis). For example, several days of habitual caffeine consumption attenuated acute ingestion-induced rise in heart rate or blood pressure (Robertson, Wade, Workman, Woosley, & Oates, 1981); and the lipolytic effects were attenuated in women during exercise (Fisher, McMurray, Berry, Mar, & Forsythe, 1986). In contrast to the above data, the ergogenic effects of caffeine are similar in both non-habitual and habitual caffeine consumers (Van Soeren, Sathasivam, Spriet, & Graham, 1993).

Early studies in the 1970's showed that caffeine administration (~5 mg/kg) improved endurance cycle performance (Costill, Dalsky, & Fink, 1978; Ivy, Costill, Fink, & Lower, 1979). Subsequently, many laboratory-based studies have shown either a greater power output for a given period of time or a greater time to exhaustion. A large number of studies have also found improvements in endurance sports specific performance, including running, cross country skiing, and cycling. "The vast majority of these studies have used caffeine doses in the range of 3 to 6 mg/kg taken approximately one hour prior to exercise. More recently, studies have reported that much lower doses of caffeine (1.0 - 2.0 mg/kg), especially when taken later during an endurance exercise task, have enhanced performance" (Cox et al. 2002, <https://bit.ly/2RG3P0b>)

"A recent meta-analysis that included forty-six studies concluded that caffeine has a small but evident effect on endurance performance when taken in moderate doses (3–6 mg/kg). As well as an overall improvement following caffeine compared to placebo in mean power output ($3.03 \pm 3.07\%$; effect size = 0.23 ± 0.15) and time-trial completion time ($2.22 \pm 2.59\%$; effect size = 0.41 ± 0.2)" (Southward, Rutherford-Markwick, & Ali, 2018, <https://bit.ly/2sgMSv7>). Another recent meta-analysis also suggested that caffeine may be more effective if the exercise duration is longer (Shen, Brooks, Cincotta, & Manjourides, 2018)

The evidence of an ergogenic effect of caffeine on high-intensity performance is less robust when we analyse the data of endurance tasks. A number of studies have found no improvement in thirty-second all-out sprint cycling performance with caffeine administration, and evidence on single effort strength or power manoeuvres is also mixed. Nevertheless, a recent meta-analysis concluded that "based on the current evidence, it seems that caffeine increases both maximal strength and muscular endurance and power appears to be enhanced with caffeine supplementation" (Grgic, Mikulic, Schoenfeld, Bishop, & Pedisic, 2018, <https://bit.ly/2CbNira>). The authors also noted that this effect might, to a certain extent, be caffeine dose- and external load-dependent.

The mechanisms

The current evidence indicates that caffeine acts through its role as an adenosine receptor antagonist. Adenosine receptors are widely present in human tissue including brain, skeletal muscle and adipose tissue. Adenosine antagonism in adipocytes clearly leads to increased lipolysis and an increase in plasma free fatty acid (FFA) concentration. Consequently, the “classical” studies evaluating the ergogenic potential of caffeine considered that the finding of a lower respiratory exchange ratio during endurance exercise indicated that caffeine was increasing plasma FFA concentration, muscle uptake and fat oxidation and this led to intra-muscular glycogen sparing through the Randle effect (Costill et al., 1978). This hypothesis became well established for over a decade and with a later modification that the sparing occurred primarily in the early rest to exercise transition; however, since then studies showed no evidence for glycogen sparing after long-term endurance exercise (Graham, Battram, Dela, El-Sohemy, & Thong, 2008). The increase in plasma FFA consistently observed at rest is due to adrenergic (epinephrine, norepinephrine) effect on adipocyte lipolysis; however, this effect is overridden by the adrenergic effect of exercise. (Graham, Battram, Dela, El-Sohemy, & Thong, 2008, <https://bit.ly/2Qw4FYV>)

This original explanation about the effects on endurance performance has now been replaced with the view that the performance effects of caffeine reside in the brain.

It is now accepted that most of the performance-enhancing effects of caffeine are accomplished through the antagonism of the adenosine receptors, influencing the dopaminergic and other neurotransmitter systems. Adenosine and dopamine interact in the brain, and this might be one mechanism to explain how the important components of motivation (i.e. vigour, persistence and work output) and higher-order brain processes are involved in motor control (Meeusen, Roelands, & Spriet, 2013). Caffeine maintains a higher dopamine concentration especially in those brain areas linked with 'attention'. Through this neurochemical interaction, caffeine improves sustained attention, vigilance, and reduces symptoms of fatigue (Meeusen et al., 2013). Other aspects that are localized in the central nervous system are a reduction in skeletal muscle pain and force sensation, leading to a reduction in perception of effort during exercise and therefore influencing the motivational factors to sustain effort during exercise. (Meeusen et al. 2013, <https://bit.ly/2HfXapJ>).

At a muscular level, caffeine may have additional effects on muscle contraction. Caffeine may potentiate calcium release from the sarcoplasmic reticulum and can lead to increased muscle excitability.

Enhanced force output in humans during low frequency electrical muscle stimulation with caffeine and we have suggested that this effect was due to enhanced calcium release from the sarcoplasmic reticulum (Tarnopolsky & Cupido, 2000). It was demonstrated that acute caffeine administration (5 mg/kg) increased low-frequency (20 Hz, simulating endurance exercise) electrically stimulated muscle force during a fatiguing protocol (Tarnopolsky & Cupido, 2000).

There are also studies that suggest that caffeine can improve physical, technical and skill-based elements of performance that are typical for football match play. For example, caffeine can enhance repeated sprint and jump performance, reactive agility and passing accuracy during intermittent-type exercise protocols (Duvnjak-Zaknich, Dawson, Wallman, & Henry, 2011; Foskett, Ali, & Gant, 2009; Gant, Stinear, & Byblow, 2010) (Morton, 2014, <https://bit.ly/2Fe2oAc>).

Typically, these measurements of skill performance will have more variability than other measures of performance. This, in combination with relatively small sample sizes, is most likely the reason why the results of various studies seem to be mixed. For example, in some studies, effects are found on agility but not on repeated sprint performance and, in other studies, it may be the opposite. However, overall, it seems that many aspects of football performance can be improved with caffeine. A recent meta-analysis concluded that pre-exercise ingestion of a moderate dose of caffeine (from 3 to 6 mg/kg) resulted in small/trivial, but statistically significant improvements: on jump performance, sprint performance, agility, team sport-specific endurance performance. At the same time, it increased the running distance and sprint running distance during team sport matches (Salinero, Lara, & Del Coso, 2018).

Delivering caffeine

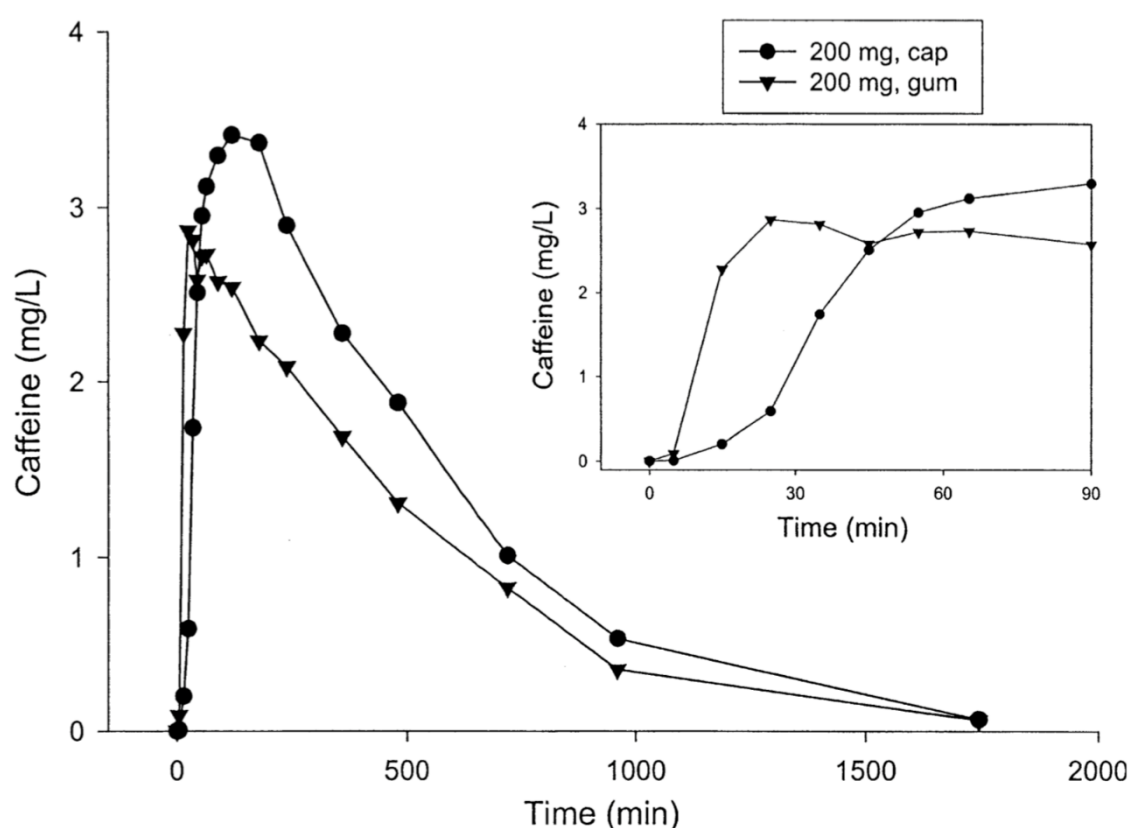
The next section will discuss the practicalities of delivering caffeine. The ergogenic effects of caffeine are typically achieved with ingestion of 2-6 mg/kg body weight. The best or preferred dose will need to be individually determined because efficacy may vary among individuals (this is discussed in a section on personalised nutrition and the role of the genome), but also because side effects may be different (see below).

Traditionally caffeine is administered in pill or capsule form or by drinking coffee, but sports-specific nutrition products are becoming more and more

common. On match days, these caffeine sports products are typically consumed, but on training days caffeine can also be consumed in the form of tea or coffee with breakfast or meal prior to training. Recent evidence has shown that pre-exercise coffee ingestion induces similar performance benefits to that of anhydrous caffeine ingestion in the form of a pill or capsule (Hodgson, Randell, & Jeukendrup, 2013). Given that plasma caffeine levels peak approximately in 45-90 minutes after ingestion, it is recommended to consume caffeinated drinks, capsules or gels (depending on players' preferences) before the warm-up period, i.e. 45-90 minutes before kick-off.

Another form in which caffeine can be delivered is through a gum. This delivery mechanism was developed by the military, who wanted a way to deliver caffeine faster. Caffeine can be absorbed much faster through the buccal mucosa (Figure 1). When absorbed through the gut, there is usually a delay time of 20-30 minutes before significant amounts of caffeine become absorbed. With a gum (or lozenges), the absorption is instant.

Figure 1: Mean caffeine plasma concentration profiles following a 50-, 100- or 200-mg dose of caffeine, delivered as either a capsule or gum formulation to healthy male volunteers (12 subjects in each of the seven treatment groups)



Source: Wickham and Spriet, 2018, <https://goo.gl/VjFaLs>

Studies with caffeine-containing chewing gums show mixed results, but generally, effects are positive in studies that have administered a higher dose, allowed sufficient absorption time and measured performance of longer duration (>30 minutes). For example, Lane et al. (2014) showed that caffeinated chewing gum improved time trial performance 3-4% when a total of 3 mg/kg caffeine was ingested. In another study, 50 mg of caffeine was ingested just before a time trial of approximately 30 minutes (and every 8 minutes thereafter); no effect was observed (Oberlin-Brown, Siegel, Kilding, & Laursen, 2016). Studies have also suggested that simple mouth rinses with a caffeine-containing solution can enhance repeated bout, short-duration, high-intensity exercise performance (Wickham & Spriet, 2018).

Caffeinated aerosol mouth and nasal sprays are gaining popularity. These sprays are suggested to stimulate nerves with direct brain connections and can increase blood caffeine concentrations through mucosal and pulmonary absorption. However, there are few studies and little evidence to support these delivery mechanisms at this point (Wickham & Spriet, 2018).

If the caffeine is given in the form of a capsule, a pill, coffee, a sports nutrition product or other food form, it is generally recommended to take the caffeine dose 45-60 minutes before the activity. If caffeine gum is used, caffeine will reach the blood much faster and this can therefore be used within the 15 minutes prior to the match or during warm-up.

Side effects

Although on average caffeine is clearly ergogenic, not all individuals display performance enhancements after acute caffeine ingestion. Larger doses (> 6 mg/kg BM) may cause negative symptoms in some individuals, including increased heart rate, irritability, tremor, confusion, reduced concentration, shortness of breath, etc. Consuming high doses of caffeine prior to or during night games can also be problematic given that sleep quality can be negatively affected.

Thus, it is highly recommended, that players experiment with caffeine in training sessions to work out the optimal dose for them. Start in training with a low dose and monitor the perception. Then, in the next training session, increase the dose and keep monitoring the perception of effort. Repeat this, till you have found a dose the player feels most comfortable with. Monitor heart rate if possible. On match days, lower the dose slightly as the increased anxiety of match day is likely to alter the physiological responses.

4.1.2 Creatine

Creatine became a popular supplement after the 1992 Olympics in Barcelona. Gold medal winners Linford Christie, in the men's 100 m dash, and Sally Gunnell, in the women's 400 m hurdles, supposedly used creatine supplements. By the time of the Olympic Games in Atlanta in 1996, approximately 80% of all athletes used creatine (Williams et al. 1999). The worldwide creatine consumption by athletes is now estimated to be around 3,000,000 kg/year. This section discusses the efficacy of creatine in different sports and the supposed mechanisms of action. For more detail on the role of creatine in metabolism and performance, see Casey and Greenhaff (Casey et al. 2000), Greenhaff (1998), and Terjung et al. (2000).

In the Body

Creatine (methylguanidine-acetic acid), is a naturally occurring compound present mostly in muscle tissue. It is not an essential nutrient, because it can be synthesized within the human body. In normal, healthy people, diet and oral ingestion together provide approximately 2 g/day of creatine. At the same time and at approximately the same rate (2 g/day), creatine is broken down to creatinine and excreted in the urine. About two-thirds of intramuscular creatine is phosphocreatine (PCr), with the remaining being free creatine. The total creatine pool (PCr + Cr) in the muscle averages about 120 mmol/kg of dry muscle mass for a 70 kg individual and the upper limit of creatine storage appears to be about 160 mmol/kg of dry muscle mass.

The primary dietary sources of creatine are fish and red meat. Strict vegetarians and vegans have negligible creatine intake because plants contain only trace amounts. They are, therefore, dependent on endogenous synthesis of creatine.

In a 70 kg man, the total-body creatine pool is approximately 120 g, 95% of which is in muscle (skeletal, heart, and smooth muscle). The remaining 5% is in the brain, liver, kidneys, and testes. Creatine synthesized in the liver and kidney and absorbed from the diet is transported by blood to the muscle. Muscle takes up creatine against a concentration gradient by a sodium-dependent saturable active transport process. In the muscle cell, creatine is phosphorylated, after which it is trapped within the muscle. Type I and type II muscle fibres have differing creatine content; type II fibres have about 30% more creatine than type I fibres. (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UENOq7>.)

Metabolic Process

PCr serves to regenerate ATP. As muscle contracts, adenosine triphosphate (ATP) is degraded to adenosine diphosphate (ADP) and inorganic phosphate (Pi) to provide energy:



ATP stores are very small and during intense maximal exercise they would be able to provide energy for only 1 to 2 seconds. When the whole-muscle ATP concentration drops and reaches levels around 30%, the muscle fatigues (Hultman, Greenhaff, Ren, & Soderlund, 1991; Karlsson & Saltin, 1970). To prevent fatigue, ATP regeneration must take place at a rate similar to that of ATP hydrolysis to maintain close to normal (resting) ATP concentrations. An important function of PCr in muscle is to provide the high-energy phosphate group for ATP regeneration during the first seconds of high-intensity exercise. This will allow time for glycogen breakdown and glycolysis (the other main process generating cytosolic ATP during high-intensity exercise) to speed up to the required rate. Transfer of the phosphate group from phosphocreatine to adenosine diphosphate (ADP) is catalyzed by the enzyme creatine kinase, resulting in regeneration of ATP and release of free creatine:



PCr is present in resting muscle in a concentration that is three to four times that of ATP. During the 100 m sprint, 22 g of ATP are estimated to be broken down per second, or about 50% of the ATP content per kilogram of active muscle (A. E. Jeukendrup & Gleeson, 2018). Because fatigue occurs in human muscle when the whole-muscle ATP concentration falls by about 30%, the need for rephosphorylation of the ADP formed during contraction is obvious.

Anaerobic degradation of PCr and glycogen is responsible for the extremely high rate of ATP resynthesis during the first seconds of high-intensity exercise (Hultman et al., 1991; Karlsson & Saltin, 1970). But the PCr store in muscle is limited and is depleted within about 5 seconds of supramaximal exercise. In this manner, the concentration of skeletal muscle ATP is maintained to some degree during single bouts or repeated bouts of supramaximal exercise. Anaerobic ATP resynthesis, however, cannot be maintained at the same rate as during the first few seconds of supramaximal exercise. Consequently, over the course of 30 seconds, ATP turnover rates fall by about 20%. High PCr stores possibly reduce the need for anaerobic glycolysis and lactic acid formation during intense exercise, which might be another potential benefit of creatine supplementation.

Another important function of creatine is its potential buffering capacity for hydrogen ions, because those ions are used during ATP regeneration, as

shown in the previous equation. A higher creatine concentration in the muscle also implies increased flux through the creatine kinase reaction, resulting in increased PCr synthesis during recovery from high-intensity exercise. The roles of creatine listed previously suggest that elevating muscle creatine and PCr stores will benefit high-intensity exercise performance.

Supplementation

Harris, Soderlund, & Hultman (1992) were the first to state that ingesting creatine monohydrate could increase total muscle creatine stores (creatine and phosphocreatine). In that study, ingesting 5 g of creatine four to six times a day for several days increased the total creatine concentration by an average of 25 mmol/kg d.w., and 30% of the increase in total creatine content was in the form of phosphocreatine. The first performance study was conducted by Greenhaff et al. (1993). Subjects ingested 20 g/day of creatine for 5 days, and creatine indeed improved performance by about 6% during repeated bouts of maximal knee extensor exercise. After that study, many more studies followed, investigating different modes of exercise, but largely confirming the early results. The results of various studies are summarised in various reviews (Bird, 2003; Kreider, 2003). Here we will focus predominantly on repeated sprint performance, strength training adaptations and cognitive performance, as these are areas highly relevant to football. However, creatine has also been studied in relation to injury, concussion and recovery.

The vast majority of studies assessing the efficacy of creatine supplementation on muscle phosphagen levels, whole body creatine retention, and/or performance have evaluated creatine monohydrate. "Claims that different forms of creatine are degraded to a lesser degree than creatine monohydrate in vivo or result in a greater up- take to muscle are currently unfounded. Clinical evidence has not demonstrated that different forms of creatine such as creatine citrate, creatine serum, creatine ethyl ester, buffered forms of creatine, or creatine nitrate promote greater creatine retention than creatine monohydrate." (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UENOq7>.)

Loading Regimens

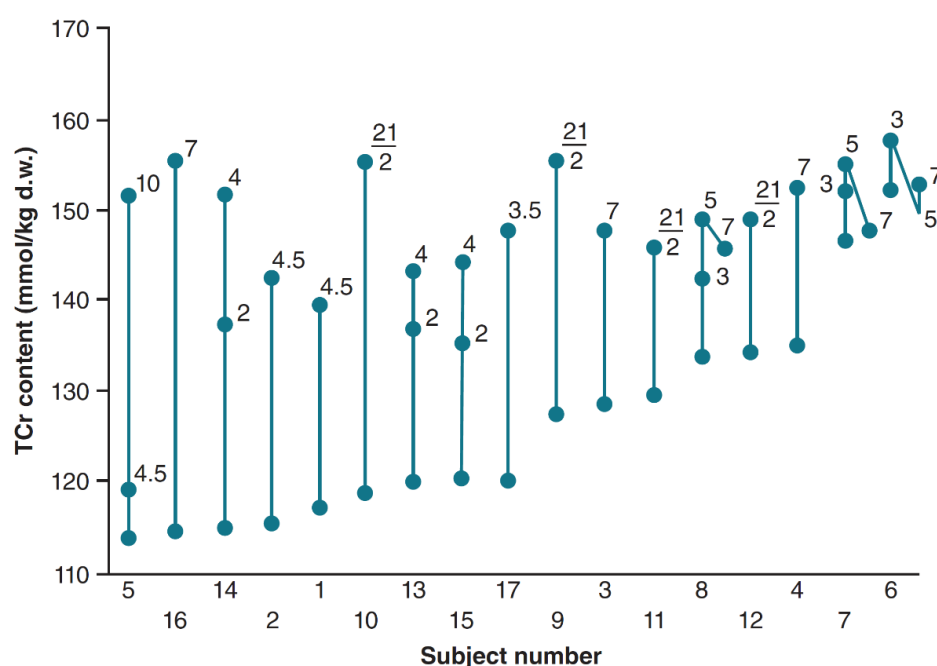
The typical creatine loading regimen is 4 x 5 g/day, each given at different times of the day for a 6-day period. The early studies showed this to be effective and increase muscle creatine concentration by about 25 mmol/kg dry mass. Such an increase corresponds to about 20% of the basal total muscle creatine concentration of about 125 mmol/kg dry mass. Hultman, Soderlund, Timmons, Cederblad, and Greenhaff (1996) observed that, after this initial loading phase of 20 g/day for 6 days, a maintenance dose of 2 g/day was enough to keep the high total creatine concentration for 35 days. Stopping creatine supplementation caused a slow, gradual decline of the creatine concentration in muscle. Research has shown that once creatine

stores in the muscle are elevated, it generally takes 4–6 weeks for creatine stores to return to baseline.

It is not strictly necessary to use a loading phase of 6 days. When creatine was ingested at a lower dose of 3 g/day, the rate of increase in muscle creatine was lower, but after 28 days the same total creatine concentration was reached. Therefore, a loading dose of 20 g/day for 6 days followed by a maintenance dose of 2 to 3 g/day is advised if athletes want to increase muscle creatine to maximal levels quickly, whereas a continuous dose of 3 g/day leads to the same maximal level in about 1 month. The increase in muscle PCr concentration was about 40% of the increase in total creatine concentration with both procedures.

Considerable variation exists among subjects in the initial total muscle creatine concentration (Figure 2). The reasons for variation are largely unknown but may be at least partly related to the habitual diet with vegetarian/vegan athletes usually in the lower ranges. The largest increase in muscle creatine concentration is observed in people with the lowest initial concentration, whereas those who already have high creatine concentrations benefit only marginally from dry mass (Harris et al., 1992). A concentration of 160 mmol/kg dry mass appears to be the maximal creatine concentration achievable by creatine supplementation, but only about 20% of subjects reached this level after creatine supplementation.

Figure 2: Individual responses to creatine loading

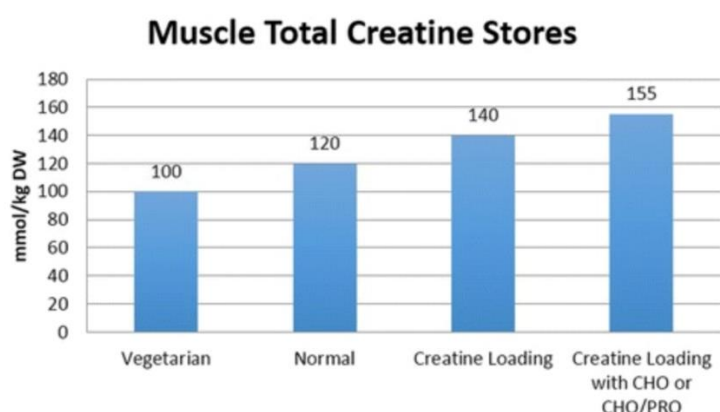


Source: Hultman, Soderlund, Timmons, Cederblad, & Greenhaff, 1996, <https://bit.ly/2FkTb8t>,

People with low creatine stores benefit most, whereas those who already have high creatine stores have minimal increases in muscle creatine. Numbers in the graph are days of supplementation at a rate of 20 to 30 g/day. 21/2 indicates subjects who ingested creatine on alternate days for 21 days. Data from Hultman et al. (1996).

Total muscle creatine can be increased more (mean increase 30 to 40 mmol/kg d.w.) when creatine (20 g/day for 5 days) is ingested in solution with simple carbohydrates (Green, Sewell, Simpson, Hultman, & Greenhaff, 1995; Green, Simpson, Littlewood, MacDonald, & Greenhaff, 1996) (Figure 3). Carbohydrate ingestion may increase insulin concentrations which in turn seems to increase muscle creatine uptake. It is thought that insulin stimulates sodium-potassium pump activity and this increases sodium-dependent muscle creatine transport. (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UEN0q7>.)

Figure 3: Muscle creatine stores varies but can be increased with creatine loading and co-ingestion with carbohydrate



Source: Kreider et al., 2017, <https://bit.ly/2TESomD>.

Casey, Constantin-Teodosiu, Howell, Hultman, & Greenhaff (1996) showed a correlation between the increases in creatine in the muscle and performance. In other words, the individuals who displayed the largest increases in total muscle creatine concentration also exhibited the largest performance benefit. A change in muscle creatine content of about 20 mmol/kg dry mass is believed to be necessary before significant changes in performance are observed. In reality, about 30% of all individuals will not display such large increases in muscle creatine (perhaps because their starting concentrations are already high) and, therefore, do not benefit. Unfortunately, there is no easy way to find out if you are a responder or a non-responder and trial and error is the common method to find out.

Weight gain

Creatine supplementation (20 g/day for 5 to 6 days) is generally accompanied by increases in body weight of around 1 kg. However, considerable inter-individual variation exists and weight gain between 0.5 and 3.5 kg has been reported.

Theoretically, this increase in body mass and possible change in body composition results from increases in intracellular water, stimulation of protein synthesis, or a decrease in protein breakdown. Because the decrease in urine production exactly paralleled the time course of the increase in muscle creatine concentration, creatine likely causes water retention in skeletal muscle cells because of an increase of the intracellular osmolarity of the muscle fibres. Evidence suggests that some of the weight gain may be attributable to the anabolic effect of creatine, although in the short term (5 to 6 days) this effect is not likely to be an important factor. (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UENOq7>.)

High-intensity exercise

Greenhaff et al. (1993) were amongst the first to demonstrate positive effects of creatine on high-intensity intermittent exercise. These findings have been repeated by many other investigators using various experimental models. Most of these studies reported improvements in strength, force production, or torque.

Balsom, Ekblom, Soderlund, Sjodin, and Hultman (1993) randomly assigned 16 trained subjects to a creatine group (25 g/day for 6 days) and a placebo group. "One test that these subjects performed was a repeated sprint test, in which they sprinted 10 times for 6 seconds with 30 seconds of recovery between bouts. Although subjects fatigued with both creatine and placebo, after 7 sprints, fatigue was significantly greater in the placebo group." (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UENOq7>.)

"Mujika et al performed tests with football players and concluded that acute creatine supplementation favourably affected repeated sprint performance and limited the decline in jumping ability with fatigue in highly trained soccer players" (Mujika, Padilla, Ibanez, Izquierdo, & Gorostiaga, 2001).

Resistance training

"Vandenberghe et al. (1997, <https://bit.ly/2FhOSvI>) investigated the "effect of creatine loading on muscle PCr concentration, muscle strength, and body composition after a 10-week resistance-training program. Compared with placebo, maximal strength of the trained muscle groups increased 20% to 25% more, maximal intermittent exercise capacity of the arm

flexors increased 10% to 25% more, and fat-free mass increased by 60% more with creatine supplementation.”

This study and others suggest that the combination of creatine ingestion and strength training is more effective than strength training alone. It has been suggested that creatine supplementation allows more repetitions and, thus, better quality of training and, at the same time, it may have an anabolic effect (Jeukendrup & Gleeson, 2018).

Creatine causes fluid retention, which may result in muscle cell swelling. Cell swelling acts as a universal anabolic signal, causing an increase of protein synthesis and net protein deposition (Jeukendrup & Gleeson, 2018).

It is unlikely that creatine improves the adaptive response to exercise through direct effects on muscle protein synthesis or muscle protein breakdown (Louis, Poortmans, Francaux, Berre, et al., 2003; Louis, Poortmans, Francaux, Hultman, et al., 2003), although Parise, Mihic, MacLennan, Yarasheski, and Tarnopolsky (2001) reported that creatine decreased plasma leucine rate of appearance and leucine oxidation. However, it appears that creatine could enhance the adaptive response by modulating increased expression of growth factors (e.g., myogenin, MRF-4, insulin-like growth factor I and II [IGF-I and IGF-II] (Burke et al., 2008; Deldicque et al., 2005). It has also been reported that creatine supplementation in combination with resistance training increases satellite cell number and myonuclei concentration more than resistance training alone (Olsen et al., 2006). Increasing muscle creatine content through supplementation increases the expression of a number of genes associated with adaptive processes, including: GLUT4 translocation, osmosensing, cytoskeleton remodelling, glycogen synthesis, protein synthesis, satellite cell proliferation and differentiation, DNA replication and repair, mRNA processing and transcription, and cell survival (Safdar, Yardley, Snow, Melov, & Tarnopolsky, 2008). (Rawson et al. 2017, <https://bit.ly/2SQbYg4>).

Although this does not necessarily mean that protein synthesis is affected, these observations would suggest that creatine supports training adaptations.

But the effects are not restricted to muscles. A small amount of creatine is also stored in the brain, where it is used for ATP production. Brain creatine can be increased by about 10% with creatine supplementation, and this has been linked to improvements in cognitive processing (Gualano, Rawson, Candow, & Chilibeck, 2016). Most studies demonstrate an improvement in cognitive processing following creatine supplementation, but few studies have been conducted in a sports setting. Therefore, translation to athletes and athletic performance is still a little premature. “One group compared the effects of acute ingestion of creatine, caffeine, or

placebo on a rugby skill passing test in 10 sleep-deprived professional rugby backs (Cook, Crewther, Kilduff, Drawer, & Gaviglio, 2011). Both creatine and caffeine attenuated the decrease in skill performance caused by the sleep deprivation.”(Rawson et al. 2017, <https://bit.ly/2SQbYg4>) It is possible that there is a role for creatine in improving sport performance through central mechanisms, but more studies are required.

Mechanisms of Action

Several mechanisms through which creatine exerts its effect have been proposed:

- The most obvious explanation is increased PCr availability, particularly, in type II muscle fibres. Evidence indicates that increased PCr stores in the muscle improve contractile function by maintaining ATP turnover.
- Another possible mechanism is the increased rate of PCr resynthesis (Greenhaff et al., 1994), which is particularly important in short recovery periods during repeated bouts of maximal exercise.
- The increased use of PCr as an energy source could reduce anaerobic glycolysis and lactic acid formation. This activity could theoretically reduce hydrogen ion formation in the muscle and delay fatigue caused by increased muscle acidity.
- Creatine could buffer some of the hydrogen ions produced during high-intensity exercise. This process would delay fatigue in high-intensity exercise that is limited by lactic acid formation.
- Creatine also plays an important role in shuttling high-energy phosphates from the mitochondria (site of ATP production) to the myofibrils (site of ATP breakdown). This role of creatine was suggested as a potential mechanism for improved performance in endurance activities. But these types of activities are not affected by creatine supplementation, suggesting that this mechanism may not be important.
- Creatine may have anabolic properties.

Safety

No studies have reported detrimental health effects of creatine. According to numerous anecdotal reports, however, creatine supplementation causes ailments; gastrointestinal, cardiovascular, and muscular problems; nausea, vomiting, and diarrhoea; alterations in kidney and liver function; muscle cramps; and elevated blood pressure. As pointed out in a roundtable discussion by the American College of Sports Medicine, “The evidence is not definitive and/or it is incomplete to indict the practice of creatine supplementation as a health risk; at the same time, our lack of information cannot be taken as an assurance that creatine supplementation is free from health risks. Ignorance provides little comfort of untoward effects yet to be discovered.”

It is probably a good idea to “cycle” creatine and have periods of creatine supplementation followed by periods of no supplementation. This will also allow endogenous synthesis to be maintained. This should be part of a periodized nutrition plan as we will discuss elsewhere.

4.1.3 Beta-Alanine and Carnosine

During intense exercise the increased hydrogen ion (H^+) concentration is buffered by intra- and extra-muscular buffering mechanisms. Sodium bicarbonate ($NaHCO_3$) (which we will discuss below) is an example of extracellular buffering. The dipeptide carnosine or beta-alanyl-L-histidine is one of the most important intracellular buffers. Carnosine is synthesized from its precursors L-histidine and beta-alanine. It is present in relatively high concentrations in the cytoplasm of skeletal muscles (5–10 mM) and is thought to be responsible for approximately 10% of the total buffering capacity of the vastus lateralis. The importance of carnosine also becomes clear if we study different species. Species who are frequently exposed to anaerobic conditions, such as frequent sprints, explosive flight behaviours and prolonged hypoxic dives, have higher initial carnosine concentrations (Derave et al., 2007; Harris, Marlin, Dunnett, Snow, & Hultman, 1990). Carnosine levels are typically higher in fast-twitch muscle fibres compared to slow-twitch fibres. This is in agreement with the observation that animals Human athletes involved in anaerobic sports such as sprinters (Parkhouse, McKenzie, Hochachka, & Ovalle, 1985) and bodybuilders (Tallon, Harris, Boobis, Fallowfield, & Wise, 2005) have also been found to have higher intramuscular concentrations of carnosine.

Carnosine ingestion is ineffective in increasing intramuscular carnosine concentration because it is broken down in the gastrointestinal tract and absorption and bioavailability of carnosine is very poor. Also, carnosine is not taken up by muscle but is synthesized in muscle from its constituent amino acids by the enzyme carnosine synthase. Beta-alanine is a precursor of carnosine and studies have shown that beta-alanine supplementation can lead to an increase in muscle carnosine content of up to about 80%, which in turn can result in enhanced intramuscular H^+ buffering. This has been shown to result in an increase in high-intensity exercise performance in both untrained and trained individuals.

[illegible]

Figure 4: High-intensity exercise increases the energy demand of the muscle, which is met by aerobic and anaerobic energy sources. The primary contributions of ATP degradation and anaerobic glycolysis to the production of H^+ during exercise. Physico-chemical buffers (e.g. carnosine) represent the first line of defence against changes in muscle pH, and are the only defence during exercise when blood flow is occluded. b The carnosine molecule with its imidazole side chain where the accumulating H^+ are buffered. In addition to intracellular buffering, transmembrane H^+ transport is a major controller of pH during dynamic exercise. c The main transporters, including the sodium–hydrogen exchanger (NHE), the sodium bicarbonate co- transporter (NBC) and the monocarboxylate transporter (MCT1, MCT4). The circulating H^+ are subsequently buffered by bicarbonate anions. ADP adenosine diphosphate, ATP adenosine triphosphate. (Lancha Junior, Painelli Vde, Saunders, & Artioli, 2015, <https://bit.ly/2RI1hhW>.)

In order to achieve the desired changes in carnosine content, it is important to take relatively large amounts of beta-alanine. Studies suggest that a single daily dose of 3.2 g beta-alanine, or up to eight daily doses of 0.4 to 1.6 g beta-alanine per single dose (3.2-6.4 g of beta-alanine per day) over a range of 4 to 10 weeks is required to get a 60 to 80% increase in muscle carnosine contents (Harris et al., 2006; Hill et al., 2007). This may not be free of side effects, though. It has been documented that large acute doses of beta-alanine appear to induce mild pseudoallergic skin reactions or paraesthesia (mild flushing and tingling sensations) that seem to disappear within 2 hours approximately. For that reason, the daily dose is usually spread out over four to eight small doses. A slow release version of the supplement was developed to minimise the symptoms. Beta-alanine can now be taken as a slow sustained release tablet formulation (CarnoSyn™). Although the finding that beta-alanine supplementation leads to an increase in muscle carnosine has been very consistent, the effects on performance have been much less clear. One study showed that 4.8 g of beta-alanine per day (4 weeks) in trained 400 m runners improved fatigue resistance in repeated bouts of exhaustive dynamic contractions. But isometric endurance at about 25% of maximal voluntary contraction (MVC) force and 400 m race time were not affected (Derave et al., 2007). In another study sprint performance was enhanced at the end of a simulated cycling race (Derave et al., 2007). More recent studies have demonstrated performance benefits in moderate intensity (45% MVC) isometric exercise (Sale et al., 2009) and several dynamic high-intensity exercise capacity tests lasting 1-4 minutes (Hobson, Saunders, Ball, Harris, & Sale, 2012). Currently, there appears to be some evidence from this review that supplementation with BA may increase athletic performance. Specifically, there appears to be moderate to high quality evidence that BA supplementation may increase time to exhaustion and power output (Quesnele, Laframboise, Wong, Kim, & Wells, 2014). There is also moderate to high quality evidence indicating that beta-alanine supplementation may decrease subjective feelings of fatigue and perceived exhaustion. A number of reviews have been published on beta-alanine and its potential effects:

(Artioli et al., 2010; Christensen, Shirai, Ritz, & Nordsborg, 2017; Lancha Junior et al., 2015; Quesnele et al., 2014; Saunders et al., 2017).

Most studies that have used an exercise protocol lasting more than 1 minute in which acidosis was the primary cause of fatigue have demonstrated significant positive performance effects.

Carnosine may limit acidosis by acting as a hydrogen ion buffer, but improved contractile performance may also be obtained by improved excitation-contraction coupling and defense against reactive oxygen species as carnosine is also an antioxidant. High carnosine concentrations are found in individuals with a high proportion of fast-twitch fibres, because these fibres are enriched with the dipeptide. Muscle carnosine content is lower in women, declines with age and

is lower in vegetarians, whose diets do not contain beta-alanine. Sprint-trained athletes display markedly high muscular carnosine, but the effect of several weeks of high-intensity training on muscle carnosine is rather small. High carnosine levels in elite sprinters are therefore either genetically determined or a result of slow adaptation to years of training. In light of the positive effects on performance, it is not surprising that b-alanine is rapidly developing as a popular ergogenic nutritional supplement for athletes, though potential side effects and the mechanism of action, require additional research.

In summary, the majority of studies that have found significant ergogenic effects to date have been carried out on untrained or recreationally active individuals performing exercise bouts under laboratory conditions. The fewer number of studies on highly trained athletes performing single competition-like exercise tasks indicates that this type of population receives modest but potentially worthwhile performance benefits from beta-alanine supplementation. Some recent studies also provide evidence supporting the use of beta-alanine as a training aid to augment bouts of high-intensity training (Trexler et al., 2015). beta-alanine supplementation has also been shown to increase resistance training performance and training volume in team-sport athletes, which may allow for greater overload and superior adaptations compared with training alone (Trexler et al., 2015). The ergogenic potential of beta-alanine supplementation for elite athletes performing repeated high-intensity exercise bouts, either during training or during competition in sports which require repeated maximal efforts, needs further investigation. (Derave et al. 2010, <https://bit.ly/2FmptQp>)

4.1.4 Sodium bicarbonate and sodium citrate

Sodium bicarbonate is one of the cheapest and most readily available supplements we will discuss. It can be purchased from a supermarket as baking soda and is thus a normal baking ingredient. When maximal exercise is performed for more than 30 seconds, most of the energy is derived from anaerobic glycolysis. Lactic acid is formed at high rates, and the increased acidity of the muscle appears to be an important limiting factor for performance in events lasting 1 to 10 minutes. Where carnosine acts as an intracellular buffer, bicarbonate acts as the extracellular buffer (Figure 4). There are a number of substances that fall in the same category. Here we will discuss sodium bicarbonate and sodium citrate.

Anaerobic Glycolysis

The pH of blood is normally 7.4 and may decrease to 7.1 or slightly lower after high-intensity exercise. The pH of muscle is normally around 7.0 and may decrease to about 6.5. The body has several systems to adjust and regulate the acid–base balance. Chemical buffers provide an effective and rapid way of normalizing the H^+ concentration. Other systems include excretion of CO_2 by pulmonary ventilation and H^+ excretion by the kidneys.

The primary buffers in the muscle are phosphates and tissue proteins. The most important buffers in the blood are proteins, hemoglobin, and bicarbonate. During intense exercise, the intracellular buffers are insufficient to buffer all the hydrogen ions formed. The efflux of H^+ into the circulation increases, and bicarbonate has a role in buffering these H^+ ions.



The mechanism by which bicarbonate supposedly exerts its action is through this buffering of H^+ in the blood (not in the muscle as is often claimed). The buffering of H^+ in the blood, however, increases the H^+ gradient and increases efflux of H^+ from the muscle. Numerous studies on the effects of bicarbonate ingestion and exercise performance have yielded equivocal results. Jeukendrup and Gleeson, 2018, <https://bit.ly/2UENOq7>.

Various studies suggest that a minimal dose of bicarbonate ingestion is needed to improve performance. Meta-analyses from the available literature suggest a dose-response relationship between the amount of bicarbonate ingested and the observed performance effect (Horswill, 1995). A dose of 200 mg/kg, ingested 1 to 2 hours before exercise, seems to improve performance in most studies, whereas 300 mg/kg seems to be the optimum dose (with tolerable side effects for most athletes). Doses of less than 100 mg/kg do not affect performance. These conclusions were more or less supported by a meta-analysis many years later (Carr, Hopkins, & Gore, 2011). Of 38 studies that met all inclusion criteria, sodium bicarbonate produced a possibly moderate performance enhancement of 1.7% (90% CL 2.0%) with a typical dose of 300mg/kg in a single 1-minute sprint. The authors also concluded that the effect was likely greater with repeated sprints.

The dose of 300 mg/kg is quite a large amount but it makes sense because a large amount of bicarbonate is needed to cause a significant increase in the buffering capacity of the

blood. Intakes greater than 300 mg/kg tend to result in gastrointestinal problems (bloating, abdominal discomfort, and diarrhea). No studies show an effect on exercise performance in high-intensity exercise lasting less than 1 minute. Exercises such as squat, bench press, and jumping are unaffected. Also, exercise of long duration is generally unaffected. Therefore, a window for efficacy of bicarbonate has been identified between approximately 1 and 7 minutes. But a study by McNaughton, Dalton, and Palmer (1999) showed improved performance in a 1-hour time trial, which was accompanied by higher blood pH throughout the exercise. (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UENOq7>.)

Side Effects

“The side effects of sodium bicarbonate intake in such large doses can be severe. At doses of 300 mg/kg many athletes experience diarrhea, gastrointestinal discomfort, bloating, and cramps 1 hour after loading. The effects are dose dependent. The main causes of these problems are the large amount of sodium that is ingested with the bicarbonate and the reaction of bicarbonate with the HCl in the stomach, which generates a large volume of CO₂ that distends the stomach wall” (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UENOq7>.)

. Drinking larger amounts of water during loading is likely to alleviate some of the problems. Administration in capsules can reduce the side effects.

“At least in theory extra and intracellular buffers should work in parallel and thus the effects of bicarbonate and beta-alanine should be additive. Indeed, a study in rowers showed that both chronic beta-alanine and acute sodium bicarbonate supplementation alone had positive effects on 2,000-m rowing performance” (Hobson et al., 2012, <https://bit.ly/2FpBMvg>). The combined acute sodium bicarbonate and chronic beta-alanine ingestion further enhanced rowing performance. When the combined ingestion was investigated in intermittent exercise in hypoxic conditions no effect was observed, but in this study, neither bicarbonate nor beta-alanine showed an effect.

A recent investigation showed a significant performance effect in elite soccer players supplemented with sodium and potassium bicarbonate along with calcium phosphate, potassium citrate, and magnesium citrate (Chycki et al., 2018). The players ingested the salts twice a day over a nine-day training period. The improvements in anaerobic performance were most likely caused by increased resting blood pH and bicarbonate levels.

Sodium Citrate

Sodium citrate works similarly to bicarbonate. It increases the buffering capacity of the extracellular space to increase the efflux of hydrogen ions from the intracellular space. Sodium citrate is effective in limiting the decrease in blood pH and improving high-intensity exercise performance of 2- to 4-minute duration (McNaughton & Cedaro, 1992; McNaughton, 1990). The typical doses for sodium citrate is somewhere between 300 to 500 mg/kg. Like sodium bicarbonate, sodium citrate is likely to cause gastrointestinal problems such as diarrhea, cramping, and bloating. Sodium citrate may act as a buffering agent, improving exercise performance in events up to about 10 minutes. It appears that sodium bicarbonate is more effective than sodium citrate. (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UENOq7>.)

4.2.1 Dietary nitrates

There has been a lot of interest in dietary nitrates in the last few years. Perhaps this all started with the work of professor Andy Jones, who used beet root juice to deliver dietary nitrate (NO_3^-) to study metabolism. It was observed that beetroot juice, a good source of dietary nitrate (NO_3^-), reduces the oxygen cost of exercise and may improve endurance performance in some circumstances. Effects have also been observed on blood pressure and muscle function. Studies have examined the effects of ingesting nitrate in the form of either sodium nitrate (NaNO_3) or vegetable sources of nitrate (usually beetroot juice) containing approximately 6 mmol of nitrate, a few hours prior to performing prolonged exhaustive exercise.

Mechanisms

Before dietary nitrate is absorbed in the intestine, it is concentrated into the salivary glands and secreted into the oral cavity where some of it is converted to nitrite by commensal bacteria (Jeukendrup & Gleeson, 2018). When swallowed, it enters the systemic circulation where it is bioactive as nitrite or is further reduced to NO. There are several theoretical mechanisms of action: NO is known to be a factor in the regulation of local blood flow, causing vasodilation when a muscle is receiving less or using more oxygen. This, however, does not explain the reduction in oxygen cost during exercise. Rather, nitrite and NO may act more directly as NO is able to inhibit cytochrome oxidase activity, slowing conversion of oxygen to water.

Also, NO may increase mitochondrial oxidative phosphorylation efficiency by increasing the P/O ratio (i.e. more ATP is formed per amount of oxygen consumed). Skeletal muscle mitochondria harvested from muscle

biopsies after nitrate supplementation display an increased P/O ratio and the improved mitochondrial P/O ratio correlates with the reduction in oxygen cost during exercise (Larsen et al., 2011). Mechanistically, nitrate reduces the expression of ATP/ADP translocase, a protein involved in proton conductance. Thus, it appears that dietary nitrate has profound effects on basal mitochondrial function. There is also the possibility that NO could reduce the ATP cost of exercise by lowering sarcoplasmic reticulum calcium ion (Ca^{2+}) release by protecting channels from Ca^{2+} release induced by reactive oxygen species, since Ca^{2+} is energetically expensive to re-sequester via the Ca^{2+} -ATPase (Bailey et al., 2010; A. E. Jeukendrup & Gleeson, 2018). NO also promotes mitochondrial biogenesis, possibly enhancing adaptation to subsequent exercise. Since these discoveries there has been a great deal of research examining the effects of dietary nitrate supplementation, both acute and chronic, on exercise performance in a variety of activities in subjects ranging from sedentary to elite athletes. The results of these studies suggest that nitrate may be less effective as an ergogenic aid in very highly trained or elite subjects compared with those who are sedentary or recreationally active (Boorsma, Whitfield, & Spriet, 2014). (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UENOq7>.)

Dietary nitrate supplementation is effective in increasing plasma nitrite concentration (NO is difficult to measure) and has been shown to reduce the oxygen cost of submaximal exercise (Bailey et al., 2009; Lansley, Winyard, Fulford, et al., 2011; Larsen, Weitzberg, Lundberg, & Eklom, 2007), improve high-intensity exercise tolerance, improve cycling economy (i.e. a higher power output for the same rate of oxygen uptake) and enhance 4 and 16 km cycling time trial performance (Lansley, Winyard, Bailey, et al., 2011). Furthermore, daily consumption of 0.5 litres of beetroot juice for 6 days can reduce resting blood pressure, lower the oxygen cost of high-intensity treadmill running by about 7% and increase time to exhaustion by 15%. There is also some evidence that intermittent high-intensity exercise performance can be enhanced by nitrate ingestion (Bond, Morton, & Braakhuis, 2012; Wylie et al., 2016).

In most studies, beetroot juice or a beetroot juice concentrate was used to deliver the dietary nitrate. This is because beetroot is one of the richest sources of nitrate. It is, however also possible to deliver the nitrate through high nitrate-containing vegetables other than beetroot include celery, cress, spinach, lettuce, rocket, rhubarb, cabbage and broccoli. But to consume enough nitrate to see meaningful effects (300- 400mg nitrates are needed). This means at least 200g

beetroot, 150g spinach or 100g rocket. Concentrated beetroot juice is therefore a more practical form of consumption. The optimal dose is likely to be 600mg nitrate, equivalent to 2 x 70 ml concentrated beetroot 'shots', although it has also proved to benefit performance in studies using 300-400mg, equivalent to 500ml beetroot juice or a single 70ml shot. Both acute and chronic loads have an effect, but consuming one to two 70ml shots a day for three to five days before competition as well as two to three hours before the match starts is recommended. In addition to that it would be a good idea to increase overall dietary nitrate intake by including more green leafy vegetables. (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UENOq7>.)

Beetroot juice is currently the most popular and convenient means of ingesting sufficient quantities of dietary nitrate to affect exercising oxygen uptake and performance. However, palatability is still one of the biggest challenges. Even with beetroot juice, and even with the beetroot shorts, there are important practical challenges, especially when higher doses are supplied for multiple days. Acceptability and tolerance need to be carefully monitored.

A recent dose response study (Wylie et al. 2013a) found that exercise tolerance was improved with 8 mmol but not 4 mmol of nitrate, but there was no further improvement in performance when 16 mmol of nitrate was ingested. Thus, the effective dose is 6-8 mmoles of nitrate which is contained in about 500 ml of natural beetroot juice or 70 ml of a more concentrated beverage (Beet-It™). This should be ingested 2-3 hours before exercise and chronic ingestion of 6-8 mmoles nitrate per day for several days may be slightly more effective than a single acute pre-exercise dose.

There is one study in football players. In this study, 32 male football players, playing in the first team of a 2nd or 3rd Dutch amateur league club, participated in a randomized, double-blind cross-over study. All subjects participated in two test days in which high-intensity intermittent running performance was assessed using the Yo-Yo IR1 test. The players ingested nitrate-rich (140 mL; ~800 mg nitrate/day; BR) or a nitrate-depleted beetroot juice (PLA) for six subsequent days, with at least eight days of wash-out between trials. The researchers found that 6 days of beetroot juice ingestion increased plasma and salivary nitrate and nitrite concentrations in comparison to PLA and enhanced Yo-Yo IR1 test performance by $3.4 \pm 1.3\%$. Six days of BR ingestion effectively improves high-intensity intermittent

exercise performance in trained soccer players. (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UENOq7>.)

Sodium Nitrate

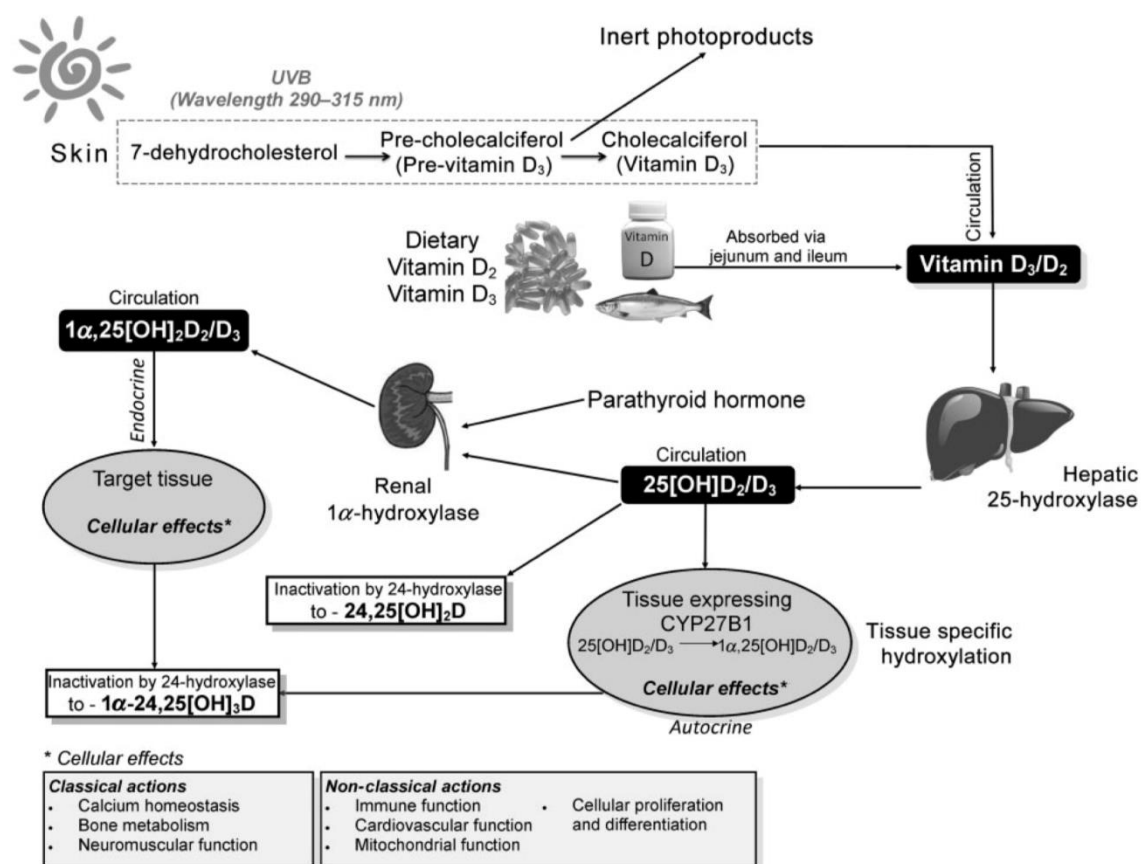
Sodium nitrate is a chemical source of nitrate (NO_3^-) that has been used in some experimental studies to confirm that acute pre-exercise nitrate ingestion can reduce the oxygen cost of exercise and improve endurance performance. However, natural sources of dietary nitrate, such as beetroot juice (see earlier section in this chapter), are preferred as an ergogenic supplement for endurance athletes and game players because there is far less risk of overdosing, which could result in toxic effects that are harmful for health.

4.2.2 Vitamin D

The last decade has seen an exponential increase in the interest in Vitamin D. This is not only visible in vitamin D sales but also in the numbers of publications on Vitamin D. However, there is also a lot of confusion and misinterpretation of the available evidence. This has resulted in unguided supplementation of sometimes very large quantities of vitamin D, especially in sports. It is often believed that the majority of athletes are vitamin D-deficient or at least insufficient. It is also often believed that vitamin D supplementation will help performance. The answer to these questions is “it depends”. It depends on how we define deficiency or insufficiency; it depends on the individual and the time of the year. It is clear, though, that vitamin D should be seen as something that is biologically essential, not as something that is an ergogenic aid. The next section is based on (A. Jeukendrup, 2018c) and (A. Jeukendrup, 2018b)

Vitamin D is mainly obtained through exposure of the skin to UVB through sunlight (80-90%), and a small amount (10-20%) typically comes from the diet. Studies indicate that during the winter months, athletes who live at latitudes above 30°N do not get sufficient sunlight to synthesize vitamin D_3 in their skin and consequently may develop inadequate or deficient vitamin D status. However, there is still discussion, even amongst scientists, what inadequate or deficient is and how it can be measured. (Jeukendrup, 2018, <https://bit.ly/2C9YZOY>)

Figure 5: Schematic representation of the Vitamin D synthetic and metabolic pathways



Source: Owens, Fraser, and Close, 2015, <https://bit.ly/2QzFHYu>.

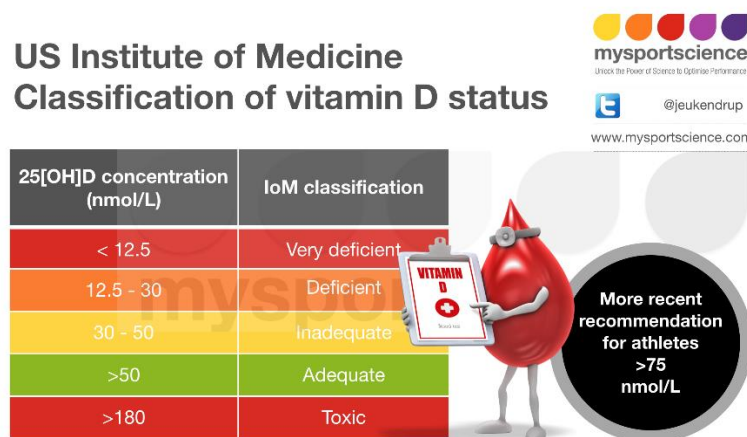
Vitamin D is obtained via dermal synthesis, a self-regulated process that produces vitamin D₃ or inert photoproducts when sufficient production is achieved. Vitamin D is also obtained in both D₂ and D₃ forms from the diet. Both endogenous production and exogenous intake elevate serum concentrations of vitamin D, which undergoes two hydroxylation steps (via hepatic 25-hydroxylase and renal 1α-hydroxylase or target tissues expressing CYP27B1) to activation. The active 1α-25[OH]₂D exerts its effects via the VDR and stimulates rapid non-genomic and genomic effects. Inactivation of the active 1α-25[OH]₂D occurs via hydroxylation at C-24 catalysed by the 24-hydroxylase enzyme. (Owens, Fraser, & Close, 2015, <https://bit.ly/2QzFHYu>).

Exactly what constitutes vitamin D deficiency or insufficiency is subject to continuing debate. Vitamin D status is usually assessed by measuring 25[OH]D, one of its metabolites. There are, however many metabolites that can be measured and a lack of understanding of the key metabolites in the

vitamin D pathway can lead to erroneous recommendations. The most often used guidelines (from the Institute of Medicine or IoM) refer to concentrations of 25[OH]D which is the sum of 25[OH]D₂ and 25[OH]D₃. These metabolites themselves are biologically inactive, but are used as indicators of the concentrations of the active forms.

There are several analytical techniques, and these different techniques are likely to give different concentrations. The gold standard is through LC-MS/MS (Liquid chromatography tandem mass spectrometry), but this is not very often used. It is important to be aware that measurements can vary considerably, and some laboratories may always return low (or high) values. Cheaper methods may not always correlate well with the gold standard. Recommendations by the IoM are relatively old and almost entirely based on the role of vitamin D on bone metabolism.

Figure 6: Classification of vitamin D status according to the United States Institute of Medicine



Source: Jeukendrup, 2018b, <http://www.mysportscience.com/single-post/2018/07/14/Vitamin-D-and-performance>

Especially in sports, the issue is not establishing the minimal amount that needs to be ingested to avoid deficiency. It is about what needs to be ingested for it to be “optimal”. This is a question that is debated a lot by experts, but it is generally believed now that 25[OH]D concentrations should be >75 nmol/L.

For a more comprehensive review of the literature the reader is referred to some excellent recent reviews (Owens, Allison, & Close, 2018; Owens et al., 2015). Here we will focus on the basic questions:

1. What are the effects of vitamin D?
2. Should we supplement with vitamin D?
3. If so, when?
4. And how much?

Effects of Vitamin D

Originally the role of vitamin D was mainly studied in relation to bone health. Vitamin D is required for the normal absorption of dietary calcium, and deficiency of this vitamin is associated with brittle bones. In addition, vitamin D has a role in immune function and many studies show that vitamin D deficiency might be related to reduced immune function. But vitamin D has also been associated with muscle function. There are suggestions that vitamin D supplementation might affect muscle strength, endurance, and athletic performance.

The latter has received considerable attention over the past decade, and the general consensus at present is that vitamin D deficiency could negatively affect athletic performance due to the influence of vitamin D on muscle function. However, there is insufficient evidence from a limited number of cross-sectional vitamin D status studies and longitudinal, randomized, placebo-controlled vitamin D3 supplementation studies in athletes to conclude that vitamin D is a direct performance enhancer (Girgis, Clifton-Bligh, Turner, Lau, & Gunton, 2014). Jeukendrup, 2018b, <http://www.mysportscience.com/single-post/2018/07/14/Vitamin-D-and-performance>

Cross-sectional studies investigating the influence of vitamin D status on performance have produced conflicting findings. In these studies, a cross-section of the population (i.e. a number of athletes) is used, and both performance and vitamin D status are measured to see if there is a correlation. Given the number of factors that influence performance (that were not controlled) and the relatively small subject numbers in these studies, it is perhaps not surprising that these studies did not provide a clear answer.

Therefore, professor Neil Walsh and his team at Bangor University set out to perform 2 studies: In the first one the relationship between vitamin D status and a fairly large (almost 1000) number of men and women was studied. The second study provided safe simulated sunlight or vitamin D3 supplements to see if performance improvements could be achieved.

In the first study all 967 participants completed a 1.5 mile run and maximum dynamic lift as well as explosive power was assessed (Carswell et al., 2018). All participants also gave blood for 25[OH]D analysis and it was found that during winter only 9% of men and 36% of women were vitamin D sufficient. When the researchers then correlated vitamin D status with performance measures, they found that there was a correlation between vitamin D status and endurance

performance. This effect was present in both men and women. Vitamin D status explained about 5% of the variation in performance. Every 1 nmol/L increase in 25[OH]D resulted in a 0.42 sec faster 1.5 mile run. There were no such correlations with maximum dynamic lift or explosive power.

In study 2 (Carswell et al., 2018), 137 men received either placebo, simulated sunlight or vitamin D₃ supplements. Both treatments (sunlight and supplements) are effective in achieving vitamin D sufficiency (in 97% of all participants). However, performance was not affected by the supplementation. The authors discuss that perhaps the duration of supplementation (12 weeks) was not enough to see significant effects.

This new publication adds to the literature and provides some interesting new data. The authors also acknowledge that there are some limitations. For example, in study 1 where correlations were observed it is not possible to determine what is cause and what is effect. It is possible that higher vitamin D levels may improve performance. It is also possible that those with better performance spend more time in the sun and have better vitamin D status.

As a practical message the authors suggest that supplementation should start before the start of the winter season to prevent the decline, rather than trying to repair a deficiency. Jeukendrup, 2018b, <http://www.mysportscience.com/single-post/2018/07/14/Vitamin-D-and-performance>

From the available literature it seems evident that there is great inter-individual variation in basal Vitamin D concentration, even in the same part of the year. There are numerous reports from around the world suggesting that vitamin D deficiency and insufficiency is widespread among athletic communities (Allison et al., 2014; Bescos Garcia & Rodriguez Guisado, 2011; Magee et al., 2013; Wolman et al., 2013). It is possible that this means that normal physiological function and, thus, performance is compromised. It is also clear that supplementation can prevent the decline in vitamin D status that is often observed during the winter months.

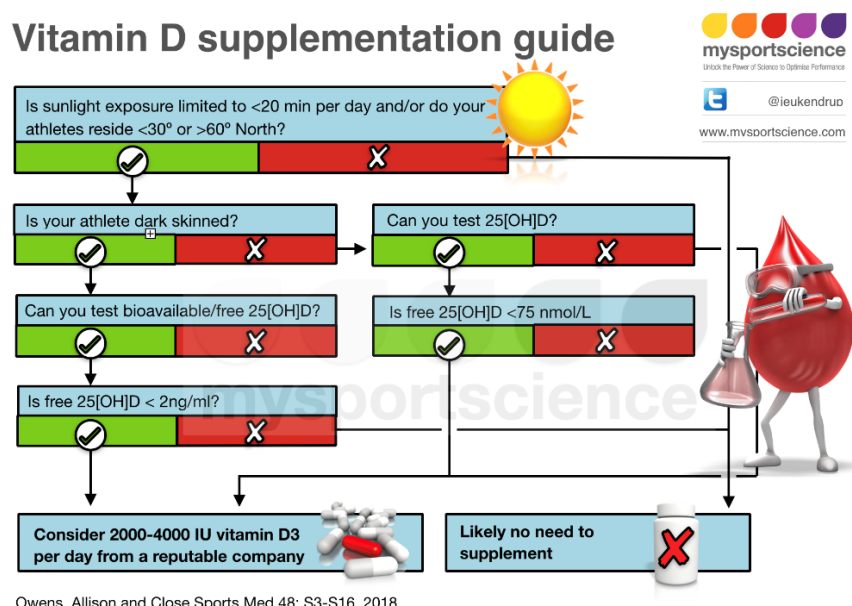
However, it is certainly questionable if vitamin D supplementation has any effects in athletes who do not have a vitamin D deficiency.

On the other hand, it is known that in sports practice at the moment, sometimes very high doses of vitamin D are prescribed or used. Owens et al. reported intakes of 1000 IU per day and up to 100,000 IU per week! High dose vitamin D supplementation may be toxic and, even though few cases of Vitamin D toxicity are known, caution should be exercised, and frequent

high dose supplementation should be avoided (unless there is very clear medical indication).

Owens et al (Owens et al., 2018) developed a decision tree for the use of vitamin D supplements. This will help with making decisions. A decision is best based on measurements of vitamin D status. Thus if possible vitamin D status should be measured. This is where it gets a little tricky. Vitamin D status is often measured by assessing the metabolite 25[OH]D in blood. It has been shown, however, that this “standard” measure may not be a good indication in athletes with a darker skin. In this case bioavailable or free 25[OH]D should be measured. If values indicate deficiency or insufficiency, supplementation should be considered. Jeukendrup, 2018b, <http://www.mysportscience.com/single-post/2018/07/14/Vitamin-D-and-performance>

Figure 7: Vitamin D supplementation decision tree



Owens, Allison and Close Sports Med 48: S3-S16, 2018

Source: Owens, Allison, and Close, 2018, as depicted by mysportscience Jeukendrup, 2018c, <https://goo.gl/kZoja9>

“If it is decided to supplement a dose of at least 2000 IU is recommended up to 4000 IU.

Supplementation should be considered only for the months that exposure of the skin to UVB through sunlight is limited.” Jeukendrup, 2018b, <http://www.mysportscience.com/single-post/2018/07/14/Vitamin-D-and-performance>

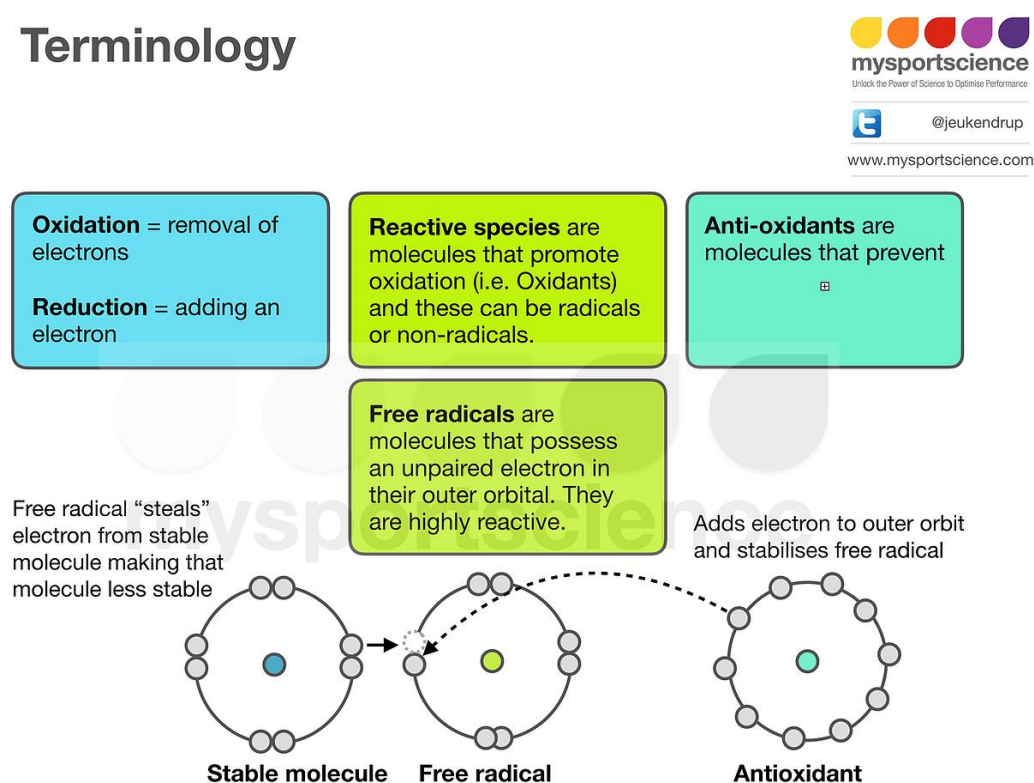
4.2.3 Antioxidants

Antioxidants are a very popular class of supplements, although there seems to be a lot of confusion about their use. "Antioxidants are everywhere: in foods, in supplements, in skincare products, shampoos etc. They are often associated with health. On the other hand, there are reports that antioxidants can impair training adaptation". (Jeukendrup, A, 2018, <https://bit.ly/2K9n7VE>) This section discusses the role of antioxidants and is based on an article in mysportscience (Jeukendrup, 2018a).

First, we need to understand what antioxidants are. Oxidation is the removal of electrons (The opposite of reductions which add electrons). Antioxidants are often thought off as molecules that scavenge free radicals. Free radicals are molecules that possess an unpaired electron in their outer orbital. They are highly reactive. There are also reactive species. These are molecules that promote oxidation (i.e. Oxidants) and these can be radicals or non-radicals. Anti-oxidants are molecules that prevent oxidation. The radicals are a highly reactive chemical species capable of damaging muscle fibre components such as proteins and lipids. (Jeukendrup, A, 2018, <https://bit.ly/2K9n7VE>)

Figure 8: Terminology of a few common terms in the antioxidant literature

Terminology



Source: (Jeukendrup, A, 2018, <https://bit.ly/2K9n7VE>)

Because of the highly reactive nature of free radicals, they are very difficult to measure. They react very quickly, and electrons move from one molecule to the next, making it almost impossible to measure them. We therefore often measure some of the biomarkers of oxidative stress to get an indication. We measure lipids, protein or DNA that has been oxidized. The assumption is that the biomarker we measure is a reflection of oxidative stress, and this is not always the case. (Jeukendrup, A, 2018, <https://bit.ly/2K9n7VE>)

Many studies measure outcomes that have little to do with oxidative stress, so it is important not to base our practical advice on the basis of these measurements.

Physical exercise increases the cellular production of reactive oxygen species (ROS) in muscle, liver, and other organs. In contrast to common belief, there is NO evidence that the source is increased mitochondrial production. Scott was quick to point out that the simplistic reasoning of exercise requires more oxygen, more oxidation at the site where oxidation takes place (mitochondria) cannot be backed by evidence. Originally, ROS were considered detrimental and thus as a likely cause of cell damage associated with exhaustion. (Jeukendrup, A, 2018, <https://bit.ly/2K9n7VE>)

During the 1980s and 1990s, it was widely assumed that muscular activity-induced ROS production was cytotoxic to skeletal muscle fibres. However, growing evidence indicates that increased ROS production plays an important role in the regulation of signalling pathways that are required to promote skeletal muscle adaptation in response to both exercise and muscle inactivity (Powers, Duarte, Kavazis, & Talbert, 2010).

The old view, however, is still portrayed a lot in the popular press. In the past decade, evidence showing that ROS act as signals that are important (amongst other functions) for training adaptation. ROS may thus be seen as positive not negative!

Of course, excessive oxidation needs to be prevented and the body has several mechanisms for this. There are numerous enzymes in the body with an antioxidative capacity. These enzymes are the most important defence system.

Dietary antioxidants, when they get to the site of oxidation can be used as an antioxidant only once. They are used up and thus we need large amounts of exogenous antioxidants for these to be effective and these antioxidants must be at the specific site where oxidation is taking place. It is likely that any supplementation will only deliver small quantities of

exogenous antioxidants and, thus, the impact of these, relative to the endogenous antioxidant system are small. The antioxidant enzymes in our bodies can be used over and over again and these enzymes are upregulated (increase) with training. Many studies have shown that training increases the expression of classical antioxidant enzymes such as superoxide dismutase and glutathione peroxidase. So, the more we exercise, the more enzymes we will make and the more protected we will be, independent of antioxidant intake (S. Powers, Nelson, & Larson-Meyer, 2011). A more detailed discussion about the role of antioxidants can be found in a number of reviews (Konig, Wagner, Elmadfa, & Berg, 2001; Powers & Jackson, 2008; Powers, Ji, Kavazis, & Jackson, 2011).

Several studies have demonstrated now that high dose antioxidants are actually removing the signal for training adaptation and the training adaptations are impaired (Gomez-Cabrera et al., 2008). This negative effect of antioxidant supplementation will be discussed in more detail in a section on periodised nutrition.

Thus, the idea that antioxidant supplementation in exercise should always be recommended is incorrect.

Although the theoretical background may be sound, there is no scientific evidence to recommend increased quantities of antioxidants to physically active people, exceeding the amount provided by healthy balanced nutrition.

1. There is no evidence that physical training requires antioxidant supplementation above the normal antioxidants from a well-balanced diet.
2. Dietary supplementation of antioxidants can play a role when food intake is restricted or where a dietary deficiency of antioxidants is clinically determined (Rare!)
3. There is NO evidence that anti-oxidants have a positive effect on recovery
4. There is little or no evidence that anti-oxidants improve performance
5. There is emerging evidence that antioxidant supplementation in high doses can reduce training adaptation. (Jeukendrup, A, 2018, <https://bit.ly/2K9n7VE>)

Figure 9: Antioxidant for athletes

Antioxidants for athletes

Key messages

-  **1** There is **no evidence** that physical training requires antioxidant supplementation above the normal antioxidants from a well-balanced diet.
-  **2** Dietary antioxidants **can be used** as an antioxidant **only once** whereas the endogenous antioxidant system can be used over and over again.
-  **3** **Exercise is the best antioxidant** Antioxidant enzymes in our bodies can be used over and over again and these enzymes are up-regulated (increase) with training.
-  **4** There is **no evidence** that antioxidants have a positive effect on **recovery**.
-  **5** There is increasing evidence that antioxidant supplementation in **high doses can reduce training adaptation**.
-  **6** **Eat a varied diet** with fruits and vegetables. You will not have to supplement. If you do supplement, be aware that high doses may make training less effective.

Source: (Jeukendrup, A, 2018, <https://bit.ly/2K9n7VE>)

“The practical implications are pretty straight forward

There is no need for antioxidant supplementation if you have a diet with varied fruits and vegetables, this is a sensible means of obtaining a balance of exogenous antioxidants. Studies have shown no advantages of antioxidant supplementation and high doses of antioxidants can be detrimental and should be avoided.” (Jeukendrup, A, 2018, <https://bit.ly/2K9n7VE>)

4.2.4 Omega-3 fatty acids

Fish oil is a natural source of long-chain omega-3 FAs, including both docosahexaenoic acid and eicosapentaenoic acid. An omega-3 fatty acid is a polyunsaturated fatty acid (PUFA), meaning it contains two or more double bonds with one of the double bonds at the third carbon from the methyl end. PUFAs are considered to be essential nutrients because the human body cannot manufacture them in appreciable amounts. Omega-3 fatty acids can be found in mostly in fatty fish (see Table 2).

Table 2: Omega-3 (n-3) polyunsaturated fatty acid content of various commonly consumed food sources

Food Type	g EPA + DHA per 100g serving	Typical Serving Size	Number of servings to equal 1 mackerel fillet
Mackerel	3.2	81g (1 fillet)	-
Sardines	1.9	130g (1 fillet)	1.1
Farmed Salmon	1.4	94g (1 fillet)	2

Wild Salmon	0.7	94g (1 fillet)	3.9
Canned Tuna	0.2	112g (1 can drained)	11.6
Cod Loin	0.2	140g (1 loin)	9.3
Tuna Steak	0.1	120g (1 steak)	21.6
Macroalgae Fed	0.05	125g	41.5
Chicken	0.02	145g (1 breast)	89.4
Lamb	0.01	125g	207.4
Pork	0.01	100g (1 loin)	259.2
Beef	0.01	125g	207.4

DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid.

Source: Adapted from Sprague et al. {Sprague, 2016 #12795}

The Omega-3 fatty acids include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α / γ -linolenic acid (ALA), small amounts of which can be converted to EPA and DHA within the body. Dietary sources of Omega-3 fatty acids include plant base sources, such as flax seeds, flaxseed oil, nuts, nut butters, algae, seeds, soybean oil and rapeseed oil for ALA, whereas both EPA and DHA are found within animal sources such as fish (e.g., cod, mackerel, salmon, tuna), fish oils and krill oil (Table 2). "The Omega-3 fats have been the focus of a great deal of exercise and cognitive performance research since they are known to be incorporated into the membranes of cells, improve muscle protein synthesis, decrease inflammation and improve cognitive function which all have performance and health implications for athletes". (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UEN0q7>.)

Muscle protein synthesis

Some studies have suggested a role of omega-3 fatty acids in muscle protein synthesis. Although most studies have been conducted in older populations (>60 years) or animals, there are also some data in athletes now.

In one study, Omega-3 fatty acid intake appears to result in greater activation of the protein complex known as the molecular/mammalian target of rapamycin complex 1 (mTORC1) during periods of high insulin and amino acid infusions in elderly adults (Smith et al., 2011a). mTORC1 activity is necessary for both resistance exercise, increased amino acid availability and leucine to increase muscle protein synthesis and mTORC1 is also required for muscle to regenerate after injury (Heaton et al., 2017). In a follow-up study, the same authors found that the anabolic response to insulin and amino acid infusion was greater after daily supplementation with 4 g of long chain Omega-3s (including 1.86 g EPA, 1.50 g DHA) for 8 weeks (Smith et al., 2011b). Also a more recent study from the same lab (Smith et al., 2015)

suggests that when insulin and amino acid levels are high, such as following a large carbohydrate and protein containing meal, adequate amounts of omega-3 fatty acids may improve muscle protein synthesis through the activation of mTORC1. Further research is needed to determine if these findings extend to elite athletes.

Several forms of exercise including resistance training and football matches results in significant amounts of damage to muscle and this damage may accumulate as the season progresses. One of the natural responses to damage is an inflammatory response within the muscle that promotes adaptations that strengthen the muscle and make it more resistant to injury. Although some inflammation may be essential for normal training adaptation, too much inflammation can impair/delay the ability of the muscle to recover post-exercise. Omega-3 fatty acids are known to have anti-inflammatory properties. Both DHA and EPA decrease the expression of inflammatory cytokines by leukocytes and also give rise to a family of anti-inflammatory mediators called resolvins (Calder, 2006). DHA also alters the activity of phagocytic cells such as neutrophils and macrophages which are the initiators of inflammation following exercise-induced muscle damage (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UEN0q7>).

Several studies have shown that ingestion of EPA and DHA can decrease delayed onset muscle soreness (DOMS) following eccentric exercise. One such study (Tartibian, Maleki, & Abbasi, 2009) had untrained subjects consume 1.8 g/d of an omega-3 supplement (including 0.32 g of EPA and 0.22 g of DHA) for 30 days before completing a knee extensor eccentric exercise protocol. "Subjects who took the omega-3 supplement reported reductions in perceived muscle soreness and displayed improved knee range of motion 48 h post-exercise, even at this low dose. A similar study using a higher daily dose of omega-3 oils (including 2.0 g EPA and 1.0 g DHA) also showed a decrease in DOMS, 48 h after an eccentric exercise session (Jouris, McDaniel, & Weiss, 2011)." (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UEN0q7>). Further research is required to confirm similar effects in more highly trained individuals, but there appears to be potential for omega-3 supplements to improve recovery of muscle from damaging exercise.

Omega-3 fatty acids that are ingested will be incorporated into various membranes and it is generally thought that this will improve the function of those membranes. For example, when incorporated into the membranes of erythrocytes, it is thought that this will make the erythrocytes more "fluid" and, in theory, this means that flow through capillaries would be easier and delivery of oxygen could be better.

Physical training improves red blood cell deformability and changes the FA composition of membranes toward a higher percentage of unsaturated FAs, so the enhanced fluidity under resting conditions could be masked by physical training (Kamada, Tokuda, Aozaki, & Otsuji, 1993). The enhanced membrane fluidity may be especially important when the uptake of oxygen becomes limiting, as during exercise under hypoxic conditions.

This theory was studied in the late 1980s by Guezennec, Nadaud, Satabin, Léger, and Lafargue (1989), who suggested that increasing the fraction of polyunsaturated FAs (PUFA) in the phospholipids of erythrocyte membranes improves membrane fluidity and increases red blood cell deformability (flexibility), resulting in improved peripheral oxygen supply. They conducted a study in which 14 male subjects were divided into two groups; one group received a normal diet and the other received a diet rich in fish oil for 6 weeks. The fraction of omega-3 fatty acids increased in erythrocyte membranes, but no change in red blood cell deformability was seen under resting conditions. During hypobaric exercise, red blood cell deformability decreased less with consumption of fish oil. Brilla and Landerholm (1990) studied the effects of fish oil intake and exercise training in 32 sedentary males and found that exercise training resulted in an increased VO_2max , whereas fish oil supplementation had no effect. Oostenbrug et al. (1997) also found no effects on membrane characteristics, VO_2max or performance.

Several studies, including a study by Fontani et al. (2005), also suggest that improvements in cognitive function, reaction time and attention span result from supplementation with omega-3 fatty acids which has potential importance for many team games and racquet sports. (Jeukendrup and Gleeson, 2018, <https://bit.ly/2UENOq7>.)

The United States Institute of Medicine recommends that men consume 1.6 g per day of ALA but, although currently there are no established recommendations for EPA and DHA intake, the ingestion of about 1 g daily of both these fatty acids seems appropriate to obtain the benefits described above. One potential disadvantage could be that the anti-inflammatory effects of these fatty acids may add to the anti-inflammatory and immunosuppressive effects of intensive endurance training and so worsen infection risk for athletes, but as yet there is no direct evidence for this.

In conclusion, the evidence on omega-3 fatty acid supplementation for athletes is ambiguous and it is recommended to include good EPA and DHA sources in the diet, making sure that the supply of these fatty acids is

increased through diet rather than supplements.

In this module, we discussed 8 supplements. Some of these supplements could be considered for a match day. Other supplements would need to be ingested throughout a longer term and other supplements could be an important part of preparation throughout the season. Of all the supplements on the market, we discussed seven of them here: caffeine, creatine, bicarbonate, beta-alanine, vitamin D, nitrates and fish oil. We also discussed antioxidants, which are frequently used but could simply be obtained through the diet and ingestion of high doses is discouraged.

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