Role of nutrition in performance enhancement and postexercise recovery

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Abstract: A number of factors contribute to success in sport, and diet is a key component. An athlete’s dietary requirements depend on several aspects, including the sport, the athlete’s goals, the environment, and practical issues. The importance of individualized dietary advice has been increasingly recognized, including day-to-day dietary advice and specific advice before, during, and after training and/or competition. Athletes use a range of dietary strategies to improve performance, with maximizing glycogen stores a key strategy for many. Carbohydrate intake during exercise maintains high levels of carbohydrate oxidation, prevents hypoglycemia, and has a positive effect on the central nervous system. Recent research has focused on athletes training with low carbohydrate availability to enhance metabolic adaptations, but whether this leads to an improvement in performance is unclear. The benefits of protein intake throughout the day following exercise are now well recognized. Athletes should aim to maintain adequate levels of hydration, and they should minimize fluid losses during exercise to no more than 2% of their body weight. Supplement use is widespread in athletes, with recent interest in the beneficial effects of nitrate, beta-alanine, and vitamin D on performance. However, an unregulated supplement industry and inadvertent contamination of supplements with banned substances increases the risk of a positive doping result. Although the availability of nutrition information for athletes varies, athletes will benefit from the advice of a registered dietician or nutritionist.

Keywords: nutrition, diet, sport, athlete, supplements, hydration

Introduction to the importance and influence of nutrition on exercise

Nutrition is increasingly recognized as a key component of optimal sporting performance, with both the science and practice of sports nutrition developing rapidly. Recent studies have found that a planned scientific nutritional strategy (consisting of fluid, carbohydrate, sodium, and caffeine) compared with a self-chosen nutritional strategy helped nonelite runners complete a marathon run faster and trained cyclists complete a time trial faster. Whereas training has the greatest potential to increase performance, it has been estimated that consumption of a carbohydrate–electrolyte drink or relatively low doses of caffeine may improve a 40 km cycling time trial performance by 32–42 and 55–84 seconds, respectively.

Evidence supports a range of dietary strategies in enhancing sports performance. It is likely that combining several strategies will be of greater benefit than one strategy in isolation. Dietary strategies to enhance performance include optimizing intakes of macronutrients, micronutrients, and fluids, including their composition and spacing throughout the day. The importance of individualized or personalized dietary advice...
is becoming increasingly recognized, with dietary strategies varying according to the individual athlete’s sport, personal goals, and practicalities (eg, food preferences). “Athlete” includes individuals competing in a range of sport types, such as strength and power (eg, weightlifting), team (eg, football), and endurance (eg, marathon running). The use of dietary supplements can enhance performance, provided these are used appropriately. This manuscript provides an overview of dietary strategies used by athletes, the efficacy of these strategies, availability of nutrition information to athletes, and risks associated with dietary supplement intake.

**Review of diet strategies employed by athletes**

**Maximizing muscle glycogen stores prior to exercise**

Carbohydrate loading aims to maximize an athlete’s muscle glycogen stores prior to endurance exercise lasting longer than 90 minutes. Benefits include delayed onset of fatigue (approximately 20%) and improvement in performance of 2%–3%. Initial protocols involved a depletion phase (3 days of intense training and low carbohydrate intake) followed by a loading phase (3 days of reduced training and high carbohydrate intake). Further research showed muscle glycogen concentrations could be enhanced to a similar level without the glycogen-depletion phase, and more recently, that 24 hours may be sufficient to maximize glycogen stores. Current recommendations suggest that for sustained or intermittent exercise longer than 90 minutes, athletes should consume 10–12 g of carbohydrate per kg of body mass (BM) per day in the 36–48 hours prior to exercise. There appears to be no advantage to increasing pre-exercise muscle glycogen content for moderate-intensity cycling or running of 60–90 minutes, as significant levels of glycogen remain in the muscle following exercise. For exercise shorter than 90 minutes, 7–12 g of carbohydrate/kg of BM should be consumed during the 24 hours preceding. Some but not all studies have shown enhanced performance of intermittent high-intensity exercise of 60–90 minutes with carbohydrate loading.

Carbohydrate eaten in the hours prior to exercise (compared with an overnight fast) has been shown to increase muscle glycogen stores and carbohydrate oxidation, extend cycle time to exhaustion, and improve exercise performance. Specific recommendations for exercise of longer than 60 minutes include 1–4 g of carbohydrate/kg of BM in the 1–4 hours prior. Most studies have not found improvements in performance from consuming low glycemic index (GI) foods prior to exercise. Any metabolic or performance effects from low GI foods appear to be attenuated when carbohydrate is consumed during exercise.

**Carbohydrate intake during the event**

Carbohydrate ingestion has been shown to improve performance in events lasting approximately 1 hour. A growing body of evidence also demonstrates beneficial effects of a carbohydrate mouth rinse on performance. It is thought that receptors in the oral cavity signal to the central nervous system to positively modify motor output.

In longer events, carbohydrate improves performance primarily by preventing hypoglycemia and maintaining high levels of carbohydrate oxidation. The rate of exogenous carbohydrate oxidation is limited by the small intestine’s ability to absorb carbohydrate. Glucose is absorbed by the sodium-dependent transporter (SGLT1), which becomes saturated with an intake of approximately 1 g/minute. The simultaneous ingestion of fructose (absorbed via glucose transporter 5 [GLUT5]), enables oxidation rates of approximately 1.3 g/minute, with performance benefits apparent in the third hour of exercise. Recommendations reflect this, with 90 g of carbohydrate from multiple sources recommended for events longer than 2.5 hours, and 60 g of carbohydrate from either single or multiple sources recommended for exercise of 2–3 hours’ duration (Table 1). For slower athletes exercising at a lower intensity, carbohydrate requirements will be less due to lower carbohydrate oxidation. Daily training with high carbohydrate availability has been shown to increase exogenous carbohydrate oxidation rates.

**The “train-low, compete-high” approach**

The “train-low, compete-high” concept is training with low carbohydrate availability to promote adaptations such as

<table>
<thead>
<tr>
<th>Exercise duration</th>
<th>Example</th>
<th>Recommended carbohydrate intake per hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–75 minutes</td>
<td>Sprint triathlon (750 m swim, 20 km cycle, 5 km run)</td>
<td>Small amounts or mouth rinse*</td>
</tr>
<tr>
<td>1–2 hours</td>
<td>Netball (4×15-minute quarters)</td>
<td>30 g*</td>
</tr>
<tr>
<td>2–3 hours</td>
<td>Soccer/football – 2×45-minute halves</td>
<td>60 g*</td>
</tr>
<tr>
<td>&gt;2.5 hours</td>
<td>Marathon run (42.2 km run)</td>
<td>90 g*</td>
</tr>
<tr>
<td></td>
<td>Half ironman triathlon (1.9 km swim, 90 km cycle, 21.1 km run)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Single (eg, sports drinks containing glucose) or multiple (eg, sports drinks containing glucose and fructose) transportable carbohydrates; multiple transportable carbohydrates only. Adapted from Jeukendrup A. A step towards personalized sports nutrition: carbohydrate intake during exercise. Sports Med. 2014;44 Suppl 1:S25–S33.
enhanced activation of cell-signaling pathways, increased mitochondrial enzyme content and activity, enhanced lipid oxidation rates, and hence improved exercise capacity.\textsuperscript{26} However, there is no clear evidence that performance is improved with this approach.\textsuperscript{27} For example, when highly trained cyclists were separated into once-daily (train-high) or twice-daily (train-low) training sessions, increases in resting muscle glycogen content were seen in the low-carbohydrate-availability group, along with other selected training adaptations.\textsuperscript{28} However, performance in a 1-hour time trial after 3 weeks of training was no different between groups. Other research has produced similar results.\textsuperscript{29} Different strategies have been suggested (eg, training after an overnight fast, training twice per day, restricting carbohydrate during recovery),\textsuperscript{26} but further research is needed to establish optimal dietary periodization plans.\textsuperscript{27}

**Fat as a fuel during endurance exercise**

There has been a recent resurgence of interest in fat as a fuel, particularly for ultraendurance exercise. A high-carbohydrate strategy inhibits fat utilization during exercise,\textsuperscript{30} which may not be beneficial due to the abundance of energy stored in the body as fat. Creating an environment that optimizes fat oxidation potentially occurs when dietary carbohydrate is reduced to a level that promotes ketosis.\textsuperscript{31} However, this strategy may impair performance of high-intensity activity, by contributing to a reduction in pyruvate dehydrogenase activity and glycogenolysis.\textsuperscript{32} The lack of performance benefits seen in studies investigating “high-fat” diets may be attributed to inadequate carbohydrate restriction and time for adaptation.\textsuperscript{33} Research into the performance effects of high fat diets continues.

**Protein**

While protein consumption prior to and during endurance and resistance exercise has been shown to enhance rates of muscle protein synthesis (MPS), a recent review found protein ingestion alongside carbohydrate during exercise does not improve time-trial performance when compared with the ingestion of adequate amounts of carbohydrate alone.\textsuperscript{33}

**Fluid and electrolytes**

The purpose of fluid consumption during exercise is primarily to maintain hydration and thermoregulation, thereby benefiting performance. Evidence is emerging on increased risk of oxidative stress with dehydration.\textsuperscript{34} Fluid consumption prior to exercise is recommended to ensure that the athlete is well-hydrated prior to commencing exercise.\textsuperscript{35} In addition, carefully planned hyperhydration (fluid overloading) prior to an event may reset fluid balance and increase fluid retention, and consequently improve heat tolerance.\textsuperscript{36} However, fluid overloading may increase the risk of hyponatremia\textsuperscript{37} and impact negatively on performance due to feelings of fullness and the need to urinate.

Hydration requirements are closely linked to sweat loss, which is highly variable (0.5–2.0 L/hour) and dependent on type and duration of exercise, ambient temperature, and athletes’ individual characteristics.\textsuperscript{38} Sodium losses linked to high temperature can be substantial, and in events of long duration or in hot temperatures, sodium must be replaced along with fluid to reduce risk of hyponatremia.\textsuperscript{35}

It has long been suggested that fluid losses greater than 2% of BM can impair performance,\textsuperscript{35} but there is controversy over the recommendation that athletes maintain BM by fluid ingestion throughout an event.\textsuperscript{37} Well-trained athletes who “drink to thirst” have been found to lose as much as 3.1% of BM with no impairment of performance in ultraendurance events.\textsuperscript{38} Ambient temperature is important, and a review illustrated that exercise performance was preserved if loss was restricted to 1.8% and 3.2% of BM in hot and temperate conditions, respectively.\textsuperscript{39}

**Dietary supplementation: nitrates, beta-alanine, and vitamin D**

Performance supplements shown to enhance performance include caffeine, beetroot juice, beta-alanine (BA), creatine, and bicarbonate.\textsuperscript{40} Comprehensive reviews on other supplements including caffeine, creatine, and bicarbonate can be found elsewhere.\textsuperscript{41} In recent years, research has focused on the role of nitrate, BA, and vitamin D and performance. Nitrate is most commonly provided as sodium nitrate or beetroot juice.\textsuperscript{42} Dietary nitrates are reduced (in mouth and stomach) to nitrites, and then to nitric oxide. During exercise, nitric oxide potentially influences skeletal muscle function through regulation of blood flow and glucose homeostasis, as well as mitochondrial respiration.\textsuperscript{43} During endurance exercise, nitrate supplementation has been shown to increase exercise efficiency (4%–5% reduction in VO\textsubscript{2} at a steady state; 0.9% improvement in time trials), reduce fatigue, and attenuate oxidative stress.\textsuperscript{44} Similarly, a 4.2% improvement in performance was shown in a test designed to simulate a football game.\textsuperscript{44}

BA is a precursor of carnosine, which is thought to have a number of performance-enhancing functions including the reduction of acidosis, regulation of calcium, and antioxidant properties.\textsuperscript{45} Supplementation with BA has been shown to
augment intracellular carnosine concentration.\textsuperscript{45} A systematic review concluded that BA may increase power output and working capacity and decrease feelings of fatigue, but that there are still questions about safety. The authors suggest caution in the use of BA as an ergogenic aid.\textsuperscript{46}

Vitamin D is essential for the maintenance of bone health and control of calcium homeostasis, but is also important for muscle strength,\textsuperscript{47,48} regulation of the immune system,\textsuperscript{49} and cardiovascular health.\textsuperscript{50} Thus inadequate vitamin D status has potential implications for the overall health of athletes and performance. A recent review found that the vitamin D status of most athletes reflects that of the population in their locality, with lower levels in winter, and athletes who train predominantly indoors are at greater risk of deficiency.\textsuperscript{51} There are no dietary vitamin D recommendations for athletes; however, for muscle function, bone health, and avoidance of respiratory infections, current evidence supports maintenance of serum 25-hydroxyvitamin D (circulating form) concentrations of 80–100 nmol/L.\textsuperscript{51}

**Diets specific for postexercise**

Recovery from a bout of exercise is integral to the athlete’s training regimen. Without adequate recovery of carbohydrate, protein, fluids, and electrolytes, beneficial adaptations and performance may be hampered.

**Muscle glycogen synthesis**

Consuming carbohydrates immediately postexercise to coincide with the initial rapid phase of glycogen synthesis has been used as a strategy to maximize rates of muscle glycogen synthesis. An early study found delaying feeding by 2 hours after glycogen-depleting cycling exercise reduced glycogen synthesis rates.\textsuperscript{52} However, the importance of this early enhanced rate of glycogen synthesis has been questioned in the context of extended recovery periods with sufficient carbohydrate consumption. Enhancing the rate of glycogen synthesis with immediate carbohydrate consumption after exercise appears most relevant when the next exercise session is within 8 hours of the first.\textsuperscript{53,54} Feeding frequency is also irrelevant with extended recovery; by 24 hours postexercise, consumption of carbohydrate as four large meals or 16 small snacks had comparable effects on muscle glycogen storage.\textsuperscript{55}

With less than 8 hours between exercise sessions, it is recommended that for maximal glycogen synthesis, 1.0–1.2 g/kg/hour is consumed for the first 4 hours, followed by resumption of daily carbohydrate requirements.\textsuperscript{13} Additional protein has been shown to enhance glycogen synthesis rates when carbohydrate intake is suboptimal.\textsuperscript{56} The consumption of moderate to high GI foods postexercise is recommended;\textsuperscript{13} however, when either a high-GI or low-GI meal was consumed after glycogen-depleting exercise, no performance differences were seen in a 5 km cycling time trial 3 hours later.\textsuperscript{57}

**Muscle protein synthesis**

An acute bout of intense endurance or resistance exercise can induce a transient increase in protein turnover, and, until feeding, protein balance remains negative. Protein consumption after exercise enhances MPS and net protein balance,\textsuperscript{58} predominantly by increasing mitochondrial protein fraction with endurance training, and myofibrillar protein fraction with resistance training.\textsuperscript{59}

Only a few studies have investigated the effect of timing of protein intake postexercise. No significant difference in MPS was observed over 4 hours postexercise when a mixture of essential amino acids and sucrose was fed 1 hour versus 3 hours after resistance exercise.\textsuperscript{60} Conversely, when a protein and carbohydrate supplement was provided immediately versus 3 hours after cycling exercise, leg protein synthesis increased threefold over 3 hours.\textsuperscript{61} A meta-analysis found timed postexercise protein intake becomes less important with longer recovery periods and adequate protein intake,\textsuperscript{62} at least for resistance training.

Dose–response studies suggest approximately 20 g of high-quality protein is sufficient to maximize MPS at rest,\textsuperscript{53} following resistance,\textsuperscript{63,64} and after high-intensity aerobic exercise.\textsuperscript{65} Rate of MPS has been found to approximately triple 45–90 minutes after protein consumption at rest, and then return to baseline levels, even with continued availability of circulating essential amino acids (termed the “muscle full” effect).\textsuperscript{66} Since exercise-induced protein synthesis is elevated for 24–48 hours following resistance exercise\textsuperscript{67} and 24–28 hours following high-intensity aerobic exercise,\textsuperscript{68} and feeding protein postexercise has an additive effect,\textsuperscript{58,64} then multiple feedings over the day postexercise might maximize muscle growth. In fact, feeding 20 g of whey protein every 3 hours was subsequently found to maximally stimulate muscle myofibrillar protein synthesis following resistance exercise.\textsuperscript{69,70}

In resistance training, where postexercise intake of protein was balanced by protein intake later in the day, increased adaptation of muscle hypertrophy resulted in equivocal strength performance effects.\textsuperscript{71,72} Most studies have not found a subsequent benefit to aerobic performance with postexercise protein consumption.\textsuperscript{73,74} However, in two
well-controlled studies in which postexercise protein intake was balanced by protein intake later in the day, improvements were seen in cycling time to exhaustion\(^7\) and in cycling sprint performance.\(^7\)

**Fluids and electrolyte balance**

Fluid and electrolyte replacement after exercise can be achieved through resuming normal hydration practices. However, when euhydration is needed within 24 hours or substantial body weight has been lost (>5% of BM), a more structured response may be warranted to replace fluids and electrolytes.\(^7\)

**Availability of nutritional information to athletes at varying levels**

The availability of nutrition information for athletes varies. Younger or recreational athletes are more likely to receive generalized nutritional information of poorer quality from individuals such as coaches.\(^7\) Elite athletes are more likely to have access to specialized sports-nutrition input from qualified professionals. A range of sports science and medicine support systems are in place in different countries to assist elite athletes,\(^1\) and nutrition is a key component of these services. Some countries have nutrition programs embedded within sports institutes (eg, Australia) or alternatively have National Olympic Committees that support nutrition programs (eg, United States of America).\(^1\) However, not all athletes at the elite level have access to sports-nutrition services. This may be due to financial constraints of the sport, geographical issues, and a lack of recognition of the value of a sports-nutrition service.\(^7\)

Athletes eat several times per day, with snacks contributing to energy requirements.\(^7\) Dietary intake differs across sports, with endurance athletes more likely to achieve energy and carbohydrate requirements compared to athletes in weight-conscious sports.\(^7\) A review found daily intakes of carbohydrate were 7.6 g/kg and 5.7 g/kg of BM for male and female endurance athletes, respectively.\(^8\) Ten elite Kenyan runners met macronutrient recommendations but not guidelines for fluid intake.\(^8\) A review of fluid strategies showed a wide variability of intake across sports, with several factors influencing intake, many outside the athlete’s control.\(^8\)

Nutrition information may be delivered to athletes by a range of people (dietitians, nutritionists, medical practitioners, sports scientists, coaches, trainers) and from a variety of sources (nutrition education programs, sporting magazines, the media and Internet).\(^9\) Of concern is the provision of nutrition advice from outside various professional’s scope of practice. For example, in Australia 88% of registered exercise professionals provided nutrition advice, despite many not having adequate nutrition training.\(^8\) A study of Canadian high-performance athletes from 34 sports found physicians ranked eighth and dietitians, 16th as choice of source of dietary supplement information.\(^9\)

**Risks of contravening the doping regulations**

Supplement use is widespread in athletes.\(^3\) For example, 87.5% of elite athletes in Australia used dietary supplements\(^9\) and 87% of Canadian high-performance athletes took dietary supplements within the past 6 months\(^8\) (Table 2). It is difficult to compare studies due to differences in the criteria used to define dietary supplements, variations in assessing supplement intake, and disparities in the populations studied.\(^5\)

Athletes take supplements for many reasons, including for proposed performance benefits, for prevention or treatment of a nutrient deficiency, for convenience, or due to fear of “missing out” by not taking a particular supplement.\(^4\)

The potential benefits (eg, improved performance) of taking a dietary supplement must outweigh the risks.\(^3\) There are few permitted dietary supplements available that have an ergogenic effect.\(^8\) Dietary supplementation cannot compensate for poor food choices.\(^5\) Other concerns include lack of efficacy, safety issues (toxicity, medical concerns), negative nutrient interactions, unpleasant side effects, ethical issues, financial expense, and lack of quality control.\(^3\) Of major concern, is the consumption of prohibited substances by the World Anti-Doping Agency (WADA).

Inadequate regulation in the supplement industry (compounded by widespread Internet sales) makes it difficult for athletes to choose supplements wisely.\(^3\) In 2000–2001, a study of 634 different supplements from 13 countries found that 94 (14.8%) contained undeclared steroids, banned by WADA.\(^8\) Many contaminated supplements were routinely used by athletes (eg, vitamin and mineral supplements).\(^8\) Several studies have confirmed these findings.\(^3\)

A positive drug test in an athlete can occur with even a minute quantity of a banned substance.\(^3\) WADA maintains a “strict liability” policy, whereby every athlete is responsible for any substance found in their body regardless of how it got there.\(^3\) The World Anti-Doping Code (January 1, 2015) does recognize the issue of contaminated supplements.\(^9\) Whereas the code upholds the principle of strict liability, athletes may receive a lesser ban if they can
show “no significant fault” to demonstrate they did not intend to cheat. The updated code imposes longer bans on those who cheat intentionally, includes athlete support personnel (eg, coaches, medical staff), and has an increased focus on antidoping education.91,99

In an effort to educate athletes about sports-supplement use, the Australian Institute of Sport’s sports-supplement program categorizes supplements according to evidence of efficacy in performance and risk of doping outcome.40 Category A supplements have sound evidence for use and include sports foods, medical supplements, and performance supplements. Category D supplements should not be used by athletes, as they are banned or are at high risk for contamination. These include stimulants, prohormones and hormone boosters, growth hormone releasers, peptides, glycerol, and colostrum.40

Table 2 Dietary supplement use in high-performing athletes from 2010–2015

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Athlete population (sport, level, country)</th>
<th>Use of DSa</th>
<th>Main reasons for DS usea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aljaloud and Ibrahim, 2013</td>
<td>Professional footballers (male, n=105), Saudi Arabia</td>
<td>93.3% currently took DS</td>
<td>Performance – 43.8%; improved health – 32.6%; physical appearance – 11.2%</td>
</tr>
<tr>
<td>Kim et al, 2013</td>
<td>National judo team members (male, n=107 and female, n=65), Korea and Japan</td>
<td>91.1% consumed at least one DS at least once per month</td>
<td>Korean: improve muscle strength – 45%; improve energy – 18%</td>
</tr>
<tr>
<td>Diehl et al, 2012</td>
<td>Elite adolescent athletes from 51 current Olympic sports (male and female, n=1138), Germany</td>
<td>87% declared having taken a DS within past 6 months</td>
<td>Japanese: maintain health – 32%; improve performance – 26%</td>
</tr>
<tr>
<td>Lun et al, 2012</td>
<td>Athletes affiliated with Canadian Sport Centres from 34 sports (male and female, n=440), Canada</td>
<td>46% used DS and 28% used TCM supplements within the past year</td>
<td>Health maintenance/prevent nutritional deficiency – 30.2%; increase energy – 20.5%; exercise recovery – 15.6%</td>
</tr>
<tr>
<td>Rodek et al, 2012</td>
<td>National representative sailors (male, n=39 and female, n=44), Croatia</td>
<td>87% consume DS daily</td>
<td>n/a</td>
</tr>
<tr>
<td>Heikkinen et al, 2011</td>
<td>Olympic athletes from 31 sports (male and female, n=446 in 2002, n=372 in 2008/2009), Finland</td>
<td>2002: 81% reported DS use in the past 12 months</td>
<td>n/a</td>
</tr>
<tr>
<td>Kim et al, 2011</td>
<td>National Sport University athletes from 21 sports (male and female, n=479), Korea</td>
<td>46% used DS and 28% used TCM supplements within the past year</td>
<td>Energy supplement – 33.3%; increase in strength, muscle mass, and muscle power – 17.4%; health maintenance – 14.6%</td>
</tr>
<tr>
<td>Dascombe et al, 2010</td>
<td>State-based sports institute athletes from seven sports (male and female, n=72), Australia</td>
<td>87.5% reported using at least one DS</td>
<td>Maintain health; dietary routine; boost immunity; peer recommendations</td>
</tr>
<tr>
<td>De Silva et al, 2010</td>
<td>National-level athletes (male and female, n=113), Sri Lanka</td>
<td>93.8% reported using DS</td>
<td>Enhance performance – 79.2%; improve general health status – 19.8%</td>
</tr>
</tbody>
</table>

Note: aTop 3 supplements, reasons for use, and sources of information provided where available. Abbreviations: DS, dietary supplement; n/a, not available; TCM, Traditional Chinese Medicine.
Conclusion

Athletes are always looking for an edge to improve their performance, and there are a range of dietary strategies available. Nonetheless, dietary recommendations should be individualized for each athlete and their sport and provided by an appropriately qualified professional to ensure optimal performance. Dietary supplements should be used with caution and as part of an overall nutrition and performance plan.

Disclosure

The authors report no conflicts of interest in this work.

References


