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Medication and Supplement Use by Athletes

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Athletes are affected in various ways by prescription or over-the-counter medications and by the use of supplements. Physicians caring for athletes need to be aware of the medicines that an athlete is taking and how those medicines may interact with performance, exercise, environment, and other medicines. In addition to treating medical conditions, athletes attempt to gain a performance advantage with the use of a variety of dietary supplements and performance enhancers. It is important to recognize and be knowledgeable of these substances, so that athletes are properly educated with respect to potential benefits and risks, and how each agent may affect them physically.

This article first reviews common medicines that athletes use and their potential efficacy and interactions with exercise and environment, then reviews dietary supplements and the data on their efficacy for performance enhancement. Finally, current and future doping issues are addressed.

COMMON MEDICATIONS

Most athletes are young and healthy, and are therefore thought to ingest few or no medications, but this may not necessarily be true. It is very important to know not only the prescription medicines your athletes are taking but also any over-the-counter (OTC) medicines and supplements. Physicians and their athletic patients seek to avoid any substance that may impair performance or cause physical harm when combined with exercise, to avoid potential side effects, to avoid drug/drug interactions, and to avoid the potential for causing a positive drug test. Although athletes are generally healthy, many may be on multiple medications or supplements. At the Sydney Olympics, 545 athletes took 5 or more medicines, including one who took up to 26 [1]. There also appeared to be a misuse of nonsteroidal anti-inflammatory drugs (NSAIDs) and there were concerns about excessive and inappropriate use of asthma medicines [1]. It is important for physicians to recognize the medicines athletes are taking and to educate them about their proper use, their risks and benefits, and potential interactions that may occur with other medicines or exercise.

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The following material reviews some of the more common medicines used by athletes, reasons for use, and potential problems with exercise. Also discussed are other medications that may affect the active patient. Additionally, because many athletes are involved in outdoor activity, photosensitivity reactions are reviewed.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs are among the most common medicines used by athletes. In a study of high school football players [2], 75% had used NSAIDs in the previous 3 months, and 15% were using NSAIDs daily. A major concern was that the majority of the players did not consult an adult, nor did they recognize the possibility of adverse effects [2]. Among Olympic athletes, NSAID use was second only to vitamin use [1]. NSAIDs, moreover, were often used inappropriately, either at wrong doses or concomitantly with other NSAIDs [1].

NSAIDs are prescribed as analgesics but also for their anti-inflammatory properties. There is an ongoing debate as to whether the inflammation resulting from injury is necessary for adequate tissue regeneration and repair. Following injury to a muscle, ligament, or tendon, there is an influx of inflammatory cells that remove debris and recruit cytokines and other growth factors toward the injury site [3]. This leads to a series of events that allows functional tissue to be laid down [3]. Because each phase is dependent on the prior phase, the blocking of inflammation may theoretically delay healing.

For muscle strains, NSAIDs are associated with a diminished inflammatory response and a delay in degradation of damaged tissue and muscle regeneration [4]. Clinically, however, there has been no demonstrated difference in muscular strength [4]. In ligament injuries, studies in rats who had induced medial collateral ligament injuries of the knee showed that nonselective NSAIDs had no effect on strength at 21 days [5], but use of a cyclooxygenase-2 (COX-2) inhibitor was associated with a 32% lower load to failure at 14 days [6]. In ligament injuries of the ankle, NSAIDs allowed sooner return to activity, but there was increased instability and decreased range of motion as compared with placebo [3]. Another common use for NSAIDs is for tendonitis; NSAIDs may help with pain relief, but long-term effects on the tendon are unknown [3]. This may be due in part to the fact that many tendinopathies that were once thought inflammatory are actually degenerative [3].

NSAIDs are potentially beneficial for short- term recovery of muscle function, and may reduce soreness following exercise [7]. NSAIDs also appear beneficial for arthritis. Both a meta-analysis of hip arthritis and a meta-analysis of knee arthritis demonstrated an increase in efficacy compared with placebo [8]. With deep muscle contusions, NSAIDs may decrease edema and have an analgesic effect allowing for quicker recovery of motion [9]. NSAIDs given for at least 2 weeks for muscle contusions may decrease the rate of heterotopic ossification [9].

NSAIDs are not without side effects. Potential adverse effects include gastric ulcers, renal dysfunction, and less commonly, liver dysfunction [7]. NSAIDs

decrease prostaglandins in the kidney, and thereby decrease renal blood flow [7]. In extreme training situations, NSAID use and dehydration may accentuate the risk for renal dysfunction.

Oral Contraceptives

Oral contraceptive use among female athletes is common for the management of oligomenorrhea, amenorrhea, menstrual cramps, heavy menstrual bleeding, or simply for birth control. Oral contraceptives have been used in the amenorrheic athlete to increase estrogen and decrease the relative risk for stress fractures and osteoporosis, although decreased bone mineral density is a multifactorial problem, with contributions from nutritional inadequacy and low body fat [10]. Data in postmenopausal women show an increase in bone density and a decrease in fracture rates with estrogen replacement, but there is a lack of randomized trial data to support the postulate that estrogen increases bone density and decreases fractures in the young oligomennorheic athlete [10].

Concerns for athletes include side effects such as fluid retention, weight gain, nausea, headaches, and increased risk for deep venous thrombosis (DVT). Another concern is the possibility that performance may be affected. Lebrun et al [11] found a decrease in VO_{2max} among elite female athletes on oral contraceptives (OCPs). Richerlund and associates [12] looked at low-dose oral contraceptive use among oligo/amenorrheic athletes, regularly menstruating athletes, and sedentary controls. There were no changes in performance, except in the oligo/amenorrheic group, which had a 6% decline. Those who had menstrual disturbances also demonstrated an increase in body weight and an increase in bone mineral density.

The primary benefits to athletes using oral contraceptives include resolution of heavy menses and resultant iron deficiency, managing dysmenorrhea, and as part of the multifactorial treatment of amenorrheic athletes or those who have female athlete triad. One must take into account potential effects on exercise, performance, and weight gain, but the benefits often justify the risks.

Antibiotics

Antibiotics are commonly used among athletes to treat respiratory, skin, or urinary tract infections. Common concerns when choosing antibiotics include anticipated side-effect profile as well as the dosing regimen. Side effects such as gastrointestinal upset are common, and may affect an athlete's performance. Because athletes are busy with practice, competition, or other activities, they typically benefit from a medicine that requires a lower dosing frequency.

Among antibiotics, the largest concern with use in athletes has involved the fluoroquinolones. A review of case reports [13] found 98 cases of tendon injury, with the majority occurring with pefloxacin, followed by ciprofloxacin. The majority of injuries involved the Achilles tendon, and one half of the injuries were ruptures. Tendon injury was reported as soon as 2 hours after treatment, with 50% of injuries occurring in the first 6 days, and injuries extending out to 6 months following treatment. Thirty-three percent of these studied patients

had concomitant use of steroids, which may have been a potential contributing factor.

Stimulants for Attention Deficit Disorder

Many student athletes are prescribed amphetamine or amphetamine derivatives for attention deficit disorder. In general, whether amphetamines are performance-enhancing or not is controversial–some studies have shown improvements in exercise performance, whereas others have not [14]. Amphetamines may provide a sense of performance enhancement through their ability to increase aggression, enhance concentration, decrease pain (and thus potentially increase risk for injury), and induce euphoria [14]. Enhanced performance has been demonstrated in activities involving concentration and attentiveness with relatively complex motor activity [14]. Other potential positive effects include increased alertness and wakefulness, decreased fatigue, and an increase in self-confidence [14].

Athletic concerns with the use of amphetamines include vasoconstriction in the skin, increased blood pressure, and decreased thermoregulation, which may contribute to dehydration, heatstroke, and cardiac arrest when the drugs are used in hot conditions [14]. Physicians must also be aware that the athlete may be unknowingly taking other stimulants in supplements or decongestants.

Asthma Medications

Asthma is a chronic inflammatory condition of the airways that is characterized by increased pulmonary responsiveness to various stimuli. Clinical manifestations include cough, dyspnea, and wheezing. Although some athletes have baseline asthma exacerbated by exercise (exercise-induced asthma [EIA]), most athletes have asthmatic symptoms only with exercise (exercise-induced bronchoconstriction, [EIB]). Regardless of the type of asthma, athletes who have controlled asthma have improved performance compared with when their asthma is uncontrolled.

The prevalence of EIA has been increasing in general, but nowhere more than among Olympic athletes [1]. This may be due to better diagnosis and greater awareness of the problem [1]. Athletes may also believe that treatment with beta agonists is performance enhancing; indeed, there is some concern about excessive and inappropriate use of the beta agonists [1]. There is evidence that beta agonists can have an anabolic effect when given orally, but they are not ergogenic when given at the usual inhaled dose [15]. Some beta agonists are banned by sporting organizations, so it is important to be familiar with the organization your athlete falls under. The International Olympic Committee (IOC), for example, permits some inhaled beta agonists, but also requires documentation of a diagnosis of asthma. One concern athletes may have with the use of beta agonists is the possible associated nervousness, shaking, and palpitations, which may hinder performance. At present, inhaled corticosteroids and oral leukotriene antagonists, both commonly prescribed to asthmatic athletes, are not banned or restricted.

Other Medications—Possible Interactions with Exercise or the Environment

There are other medicines that may or may not be commonly used, but should be noted as possibly impairing the performance or health of the athlete. Decongestants are used frequently, either as an OTC or prescription medicine. The most common in the United States is pseudoephedrine. This may be used for upper respiratory infection or by an athlete who perceives it as performance-enhancing. Multiple studies have failed to show conclusive evidence of ergogenic potential [14]. In addition, when used at one to two times the OTC dosage, pseudoephedrine did not improve performance or VO_{2max} in cycling, and caused positive urine tests [16]. One study using higher doses of pseudoephedrine did show an increase in maximum torque produced in an isometric knee extension, and an increase in peak power during maximal cycle performance [17]. Although the side effects of pseudoephedrine at normal doses are less than those associated with the other sympathomimetics discussed in this article, there should be a concern for cardiovascular and central nervous system (CNS) effects when it is used at higher doses or in combination with other sympathomimetics. In addition, although there are many factors involved in the etiology of heat stroke, one should use caution when using any of the sympathomimetic drugs with intense exercise in extreme conditions.

Many athletes suffer from allergic or chronic rhinitis, and may use antihistamines to treat their symptoms. The older antihistamines are available over the counter, and may cause drowsiness and impair reaction time and performance. The newer antihistamines may not demonstrate this effect, but when possible, it may be prudent to attempt allergy control through locally acting steroid nasal sprays. Another group of CNS depressants are the benzodiazepine anxiolytics. These medications may cause drowsiness and affect coordination. For anxiety sufferers, an attempt should be made to switch to a maintenance medication such as a selective serotonin reuptake inhibitor (SSRI). These medications also need to be used with caution, because they can provoke nausea and drowsiness, particularly when initiating the medicine. If possible, attempt to start at a noncritical time in the competitive or training season, and use an SSRI that is more activating rather than sedating, such as fluoxetine or venlafaxine.

Among cardiovascular medicines, practitioners need to be aware of the antihypertensives and lipid lowering agents. Athletes who have hypertension should be screened for blood pressure-elevating supplement use such as sympathomimetics, anabolic steroids, alcohol, or recreational drugs. If determined to have essential hypertension, some of the typical first-line medications for the general population should be avoided in athletes. Beta-adrenergic blockers may limit exercise capacity [18], and the nonselective agents (such as propranolol) reduce performance to a greater extent than the cardioselective agents (such as atenolol or metoprolol) [19]. Diuretics may exacerbate conditions that lead to dehydration and electrolyte disturbances. In addition, diuretics are used as a masking agent for drug tests, and are therefore banned by many organizations. Among lipid-lowering agents, the statin drugs can cause muscle complaints. In a

study looking at 22 athletes who have familial hypercholesterolemia who were treated with statin drugs, 16 could not tolerate their use secondary to muscle symptoms such as weakness, cramping, or aching [20].

Photosensitivity Reaction

Many athletes are participating in activities outdoors and have prolonged exposure to the sun. Therefore, when prescribing a medicine, one should take into account the potential for a photosensitivity reaction. Photosensitivity occurs most commonly as a phototoxic response and less frequently as a photoallergic response [21].

A phototoxic reaction resembles exaggerated sunburn and occurs on exposed areas. There are three general types of phototoxic responses: (1) erythema and edema occurring 8 to 24 hours after sun exposure and lasting 2 to 4 days; (2) rapid, transient erythema starting in 30 minutes, lasting 1 to 2 days, and associated with burning and itching; and (3) a rapid transient wheel and flare reaction associated with a burning sensation. In contrast, a photoallergic response presents 1 to 14 days after exposure and is associated with a papulovesicular eruption, pruritis, and eczematous dermatitis [21].

There are many drugs with potential for causing a photosensitivity reaction. These include diuretics, antipsychotics, older generation antidepressants, hypoglycemics, cardiovascular drugs, and antimalarials. Some of the more common drugs used in athletes that can cause photosensitivity include NSAIDs, antimicrobials, antihistamines (diphenhydramine, loratidine), and estrogen/progesterone. Among the NSAIDs, the most photoactive are the 2-arylpropionic acid derivatives (ibuprofen, naproxen, ketoprofen). Other NSAIDs also may potentially cause a photosensitivity reaction, and include diclofenac, piroxicam, indomethacin, sulindac, and the COX-2 specific inhibitors. Antibiotics include the tetracyclines (lower incidence with doxycycline and minocycline), the fluoroquinolones, and sulfamethoxazole. In female athletes, photosensitivity may arise from combined oral contraceptive use, and topical medicines such as the retinoid creams for acne are prime offenders as well [21].

When prescribing medicines to outdoor athletes, it is important to consider photosensitivity when discussing the risks and benefits. At times it may be prudent to avoid the use of a drug with potential to cause photosensitivity or to substitute a similar drug that has less photoactive potential. Other measures include using protective clothing and the application of sun block with a high sun protection factor (SPF) rating.

SUPPLEMENTS

The use of supplements is increasing widely in an attempt to improve performance at all sports levels. Supplements may or may not work, and may have potentially serious side effects. It is important to understand what these substances are, how they work, whether they provide benefit, and the potential short- and long-term effects. This provides the ability to converse openly with athletes, and to directly address their beliefs and the often skewed information they may get from marketing or anecdotal evidence.

Steroids and Prohormones

Anabolic steroids have been shown to be ergogenic, but at a physical and ethical cost. Steroids have received recent publicity with use among Olympic athletes and professional baseball players. One of the earliest and largest uses was among the athletes of the German Democratic Republic (GDR). With the fall of the GDR in 1990, not all of the documentation of steroid use was destroyed, and over 150 documents were discovered [22]. Details of use began in 1966. Oral-turinabol was most frequently used in strength and speed events, and improvements were noted in the shot put, discus, hammer, javelin, running events, and swimming [22]. The use of steroids over this prolonged period showed a variety of devastating side effects.

Although athletes believed in the ergogenic effects of anabolic steroids, there remained controversy in the scientific community, because most studies were either inconclusive or did not replicate the actual use pattern among athletes. Bhasin and coauthors [23] subsequently studied 43 men divided into four groups: (1) placebo with no exercise, (2) testosterone with no exercise, (3) placebo plus exercise, and (4) testosterone plus exercise. The testosterone groups received supraphysiologic doses of testosterone (600 mg weekly) for 10 weeks, and the results clearly showed that muscle size and strength were increased most prominently in the testosterone plus exercise group.

The mechanism of action of anabolic steroids is through their anticatabolic action and provision of a positive nitrogen balance [24], which leads to muscle-fiber hypertrophy. Muscle size is also likely increased through the formation of new muscle fibers [25]. The side effect profile is extensive. Cardiac effects include muscle hypertrophy, an increase in low-density lipoprotein (LDL) cholesterol and a decrease in high-density lipoprotein (HDL) cholesterol, and an increased risk of thrombosis [26]. In addition, elevations in heart rate and blood pressure can occur [24], and there are reports of sudden cardiac death [27], myocardial infarction [28], and atrial fibrillation [29] occurring with steroid use.

Anabolic steroids have also been associated with abnormal liver function tests, although this may be partially attributed to muscle enzyme release [30]. This increase appears reversible [31], although there has been a report of toxic hepatitis associated with steroid use [32]. Psychologic effects include aggression, hostility, paranoia, hypomania, mania, and depression [26]. Cancers that have been associated include hepatocellular carcinoma, hepatic adenoma, clear-cell renal adenocarcinoma, and intratesticular leiomyosarcoma [26,33]. Endocrine effects include testicular atrophy; detrimental effects on sperm count, mobility, and morphology; gynecomastia in males due to aromatization; and virilization in females, which may be irreversible [26]. Common skin changes include acne and striae.

With the lure of ergogenic effects of steroids, athletes have become interested in prohormones or precursors of testosterone. After the passage of the 1994 Dietary Supplement and Health Education Act, prohormones were introduced into the US market, providing easy access for users. This act has unintentionally allowed "natural substances" to be sold without FDA approval, and has allowed substances that may be unproven as well as potentially harmful to

freely enter the marketplace [34]. There are multiple concerns about prohormone use. There is the potential for contamination of other supplements with prohormones. Various OTC supplements have been analyzed and found to contain prohormones not included in the listed ingredients; this raises both safety and drug testing issues.

Two popular prohormones include androstenedione and dehydroepiandrosterone (DHEA). Androstenedione is purported to reduce fat, increase muscle mass, and improve sexual performance, but studies do not support this. Androstenedione does not increase serum testosterone at the 100 mg dose, but may at the 300 mg dose [35–39]. This may be due in part to the aromatization of testosterone to estradiol, because increased levels of estradiol are seen in multiple studies [35–40]. There also has been an increase in testosterone glucoronide, which is biologically inactive. Most androstenedione undergoes first-pass hepatic metabolism before release into the systemic circulation, which may limit oral androstenedione's ability to increase serum testosterone [41]. Androstenedione has not had an effect on body composition or exercise performance [35,37,39], or on the ability to stimulate protein synthesis [38].

DHEA is another unproven testosterone precursor. Studies have shown no change in free or total testosterone with doses up to 150 mg/day [39,42]. In addition there is no significant change in body composition or strength versus placebo [39,42].

Human Growth Hormone

Human growth hormone (HGH) is secreted by the pituitary in a pulsatile manner, increasing throughout childhood and adolescence and then decreasing thereafter [43]. Growth hormone is anabolic in its behavior and may increase bone and muscle mass, primarily through the increased production of insulin-like growth factor-1 (IGF-1) [44]. Growth hormone also stimulates lipolysis [44]. Beginning in the 1980s, this has led to the abuse of growth hormone in an attempt to achieve the gains associated with steroids, with the added benefit of being difficult to detect through testing.

In adults who have closed physes, an excess of growth hormone causes acromegaly. A feature of acromegaly is an increase in muscle volume and lean body mass, but no increase in strength [43]. Additionally there are no studies that clearly show that growth hormone in healthy adults has an effect on protein synthesis, body composition, or strength [44].

Chronic growth hormone use is associated with multiple adverse effects. Growth hormone activates the renin angiotensin system and can cause fluid accumulation, which can lead to arthralgias, carpal tunnel syndrome, and pseudotumor cerebri [44]. Other effects include increased rates of cardiovascular disease, abnormal lipid metabolism, breast and colorectal cancer, and insulin resistance [44]. The method of administration of growth hormone is via injection. Pharmaceutical-grade growth hormone is produced through recombinant technology, but if obtained on the black market, it may be cadaveric pituitary growth hormone, which carries the risk of Creutzfeldt-Jacob disease [44].

HGH and supplements that may potentially cause secretion of growth hormone are marketed to middle-aged and elderly patients as rejuvenating agents [44]. Growth hormone, however, is not well-absorbed orally because of its molecular size. In addition, the secretagogues of growth hormone have not been shown to be effective as an ergogenic or antiaging agent [45].

Protein

Protein is one of the most popular supplements that athletes ingest. It is used in an attempt to increase body mass and strength. Following resistance exercise, the rate of muscle protein resynthesis is elevated above resting levels for up to 48 hours [46]. As long as there is a positive nitrogen balance, there will be increases in lean body mass and muscle hypertrophy [46]. To support these synthetic gains, athletes are thought to require an increase in protein. Recommended intake for sedentary individuals is 0.8 to 1.0 g/kg/day [47], whereas recommendations for endurance athletes are 1.2 to 1.4 g/kg/day, and strength-trained individuals require 1.6 to 1.7 g/kg/day [48]. The actual recommended levels are not clear, because exercise results in a more economic use of protein and therefore may reduce requirements [46]. Nevertheless, athletes in general ingest much more protein than the required levels, and there is no evidence that consuming additional protein promotes muscle growth [47]. Protein supplementation may benefit those taking in inadequate amounts, such as vegetarians. Also, those who may restrict energy intake, such as wrestlers, may spare muscle mass by increasing protein intake [46]. Ingestion of protein immediately following exercise appears to be optimal for anabolism [46].

Branched chain amino acids (BCAA) have been shown to decrease exercise-induced muscle damage [47], and supplementation during intense exercise may help minimize protein degradation and increase lean body mass [47]. BCAA have not been shown to effect body composition with resistance exercise, nor have they been shown to enhance performance. Pitkanen and coworkers [49] studied the branched-chain amino acid leucine. In male athletes, leucine did not increase performance in a strength exercise session or a maximal-running training session.

The amino acids arginine, lysine, and ornithine are used as possible stimulants to growth hormone secretion. These are taken before a workout to accentuate the increases in growth hormone that exercise causes, in an attempt to promote greater gains in muscle mass and strength [50]. In response to exercise, there appears to be a greater increase in females versus males, in younger athletes versus older athletes, and in those not already on a high-protein diet [50]. Even though growth hormone release may be increased, it may require doses of amino acids high enough to cause gastrointestinal discomfort. There have been no well-designed studies to show increases in muscle mass and strength to a greater degree with BCAA use than with resistance training alone [50].

One amino acid that may be beneficial is glutamine. There is some evidence that glutamine supplementation may prevent upper respiratory infections in athletes performing exercise of prolonged duration [47]. Glutamine is also

thought to increase muscle mass by increasing intramuscular glycogen concentration. Although this could potentially attenuate amino acid release from skeletal muscle and reduce muscle protein degradation [51], a 6-week study of glutamine supplementation with resistance training [51] showed no difference as compared with placebo in strength, torque, or lean body mass.

Other common supplements with a relationship to amino acids are the nitric oxide products. These usually contain arginine alpha-ketoglutarate, which is thought to increase the body's nitric oxide production. Nitric oxide increases vasodilation and is touted to increase blood flow to muscle, potentially allowing improved workouts, increased muscle growth, and decreased recovery times. There are no studies to substantiate these claims.

Creatine

Creatine was discovered in the 1830s, and creatine supplementation studies began in the early 1900s [52]. More recently, creatine use among athletes as an ergogenic agent has become widespread. In a study of high school football players [53], up to one half of senior players reported use of creatine, and a survey of Division I college athletes [54] found that one half of male athletes were using creatine, and that up to 71% of football players used creatine. Creatine use has even spread to younger athletes, with reports of creatine use in sixth to eighth graders [55].

Creatine is a nitrogenous amino acid compound produced by the liver at a rate of 1 to 2 gm/day [52]. Creatine is involved in the formation of phosphocreatine, which is a high-energy compound and an important energy store for ATP resynthesis in muscle [52]. Supplementation with creatine at 20 gm/day increases muscle creatine and phosphocreatine concentration by an average of 15% to 20%, with a majority of the increase occurring in the first 2 days [56]. This allows for an increased availability of ATP.

Creatine contributes to ATP requirements mainly for short, high-intensity exercise. For this activity, the hydrolysis of phosphocreatine contributes to approximately 50% of the total ATP requirement. As exercise becomes longer (such as a 30-second sprint), phosphocreatine hydrolysis contributes to about 25% of the total ATP requirement as oxidative phosphorylation and glycolysis become more important contributors [52]. In addition, phosphocreatine hydrolysis is partially responsible for ATP restoration after physical exercise [52]. Therefore, creatine supplementation is thought to improve performance of brief, intense exercise and repetitive bursts of intense exercise with short recovery periods. This has been confirmed in the literature. There is some belief that creatine may also be ergogenic for longer-duration exercise involving aerobic metabolism. The proposed mechanisms include buffering the pH drop associated with intense exertion, enhancement of oxidative phosporylation, an increase in glycogen loading capacity, and a possible improvement of muscle efficiency when there is a requirement for a greater percentage of Type II fibers [52].

Many studies have been performed on creatine supplementation, and more than 90% of the studies show that short-term creatine supplementation increases total creatine and phosphocreatine content. In addition, approximately 70% of

the studies on creatine supplementation report some ergogenic benefit, which includes increases in strength, power, sprint performance, or work performed during multiple sets of maximal-effort contractions [57]. Creatine is also associated with an increase in body mass, which may be due to increases in fat-free mass or muscle-fiber diameter rather than fluid retention as previously thought [57].

A recent meta-analysis [58] on creatine supplementation has confirmed increases in body composition, and supports the ergogenic effect of creatine for exercise of high intensity and short duration (<30 seconds). There was also an improvement seen in exercise of longer duration (30–150 seconds), but to a lesser degree. As exercise continues beyond 150 seconds and relies more heavily on oxidative phosphorylation, an improvement was only seen in bicycle ergometry. Further study of creatine supplementation for exercise of longer duration is warranted.

Although there have been no consistent detrimental effects of creatine supplementation, long-term studies are lacking. There are anecdotal reports of gastrointestinal distress, but these have not been confirmed in studies and may be related to the timing of creatine ingestion or to coingestion with other substances [52]. Potential complications include renal function, given the large creatine load, but a study looking at up to 5 years of supplementation did not reveal a decrease in glomerular filtration rate (GFR) [59]. There has been one report of interstitial nephritis and one patient who had focal segmental glomerulosclerosis and who had a decrease in GFR while on creatine [56]. There has also been a concern about creatine causing liver dysfunction, but studies have not shown significant changes in liver enzymes [60]. Other anecdotal reports include muscle cramping, stiffness, or strains, which also have not been confirmed in controlled studies. Muscle symptoms may be due to the intensity of exercise, or supplementation may create a psychological stimulation to exercise over optimal intensity [60]. One concerning side effect may be the potential for increase in compartment pressure. A study looking at creatine supplementation over a 34 day period and anterior compartment pressures in the lower leg [61] did find pressures to be increased at rest and after 20 minutes of running at day 6 and day 34.

Beta-Hydroxy Beta-Methylbutyrate

Beta-hydroxy beta-methylbutyrate (HMB), a metabolite of leucine, is a supplement that claims to build muscle and strength. HMB is thought to be anticatabolic, and may minimize protein breakdown and the damage to cells that can occur with intense exercise [62]. This is inferred from the reduction in levels of muscle enzymes, creatine kinase (CK) and lactate dehydrogenase (LDH), with HMB supplementation during weight training [63]. HMB may also provide structural precursors for membrane cholesterol synthesis. Because HMB is metabolized to Beta-hydroxy-betamethylglutaryl coenzyme-A (HMG-CoA), HMB may provide increased amounts of HMG-CoA and allow for cholesterol synthesis and membrane production. This may allow for quicker recovery during periods of high muscular stress [62].

In one of the initial studies of HMB supplementation in humans [64], 1.5 to 3 gm/day of HMB was shown to improve strength and increase muscle mass. In a study of untrained individuals who initiated a resistance training program [65], a combination of both HMB and creatine showed strength gains, and their effects were additive.

HMB supplementation in trained individuals has had more conflicting results. If HMB works by decreasing protein breakdown, its effects in trained athletes may not be as significant as in untrained individuals. This is due to training-induced suppression of protein breakdown and a reduction of muscle protein turnover after repeated resistance exercise [62]. Nissen and colleagues [64] showed an increase in bench press lift, but the study was limited because a carbohydrate/protein powder was also given. Thomson [66] showed an increase in leg extension strength with HMB supplementation. In contrast, there have been multiple studies that did not show a change in body composition or strength with HMB use in trained individuals [67–69].

In limited studies on safety, there have been no reported adverse effects. In an 8-week study, there were essentially no changes in hepatic enzyme function, lipid profile, renal function, or hematological parameters [70]. A 6-week study showed no significant effect on glucose, urea, triglycerides, lipids, hematological parameters, or electrolytes, except for a decrease in bicarbonate level in the HMB-supplemented group [71]. There were also no changes in testosterone, cortisol, or male fertility [71].

HMB supplementation in untrained individuals who undertake a resistance program may produce increases in body mass and strength. In addition, HMB appears safe for short-term use. Results for trained individuals are not as impressive, and further study is needed to determine if it is beneficial.

Caffeine

Caffeine is an alkaloid widely available in coffee, tea, soda, and nutritional supplements. Caffeine has been shown to be ergogenic in aerobic activity, and has increased times to exhaustion in cycling and running, decreased times to finish a fixed period of cycling, increased times to exhaustion in intense repeated cycling, improved tennis performance, decreased recovery times, and decreased 1500 meter swim times [14]. Caffeine has shown little benefit for short-burst activity [14].

The exact mechanism for caffeine's ergogenic effect is unclear. Possibilities include adenosine receptor antagonism, glycogen sparing by increasing lipolysis, elevating epinephrine levels, increasing cortisol, or antioxidant effects [14].

The level of caffeine needed to produce an ergogenic effect is in the range of 250 to 700 mg; such levels would not cause disqualification by the National Collegiate Athletic Association (NCAA) and the IOC [45]. Estimating caffeine intake is difficult, however, because caffeine is in multiple products at varying levels, and urinary measurements of caffeine may be inaccurate [45].

Caffeine at lower doses may improve hand steadiness and reduce fatigue, but as doses become higher, hand steadiness decreases and there is an increase in

jitteriness [14]. Too much caffeine can have negative effects on mood, concentration, and alertness, all of which can affect exercise performance. Other potential effects include an increase in heart rate and blood pressure.

Ephedrine

Ephedrine is a sympathomimetic amine that has been promoted for weight loss and enhancement of athletic performance. These products were readily available in supplements until a recent ban by the Food and Drug Administration (FDA). The mechanism for possible ergogenic effect is not clear, but may be related to increasing dopamine and noradrenaline release, or an increase in CNS stimulation, causing a delay or masking of the perception of fatigue [72].

Shekelle and coauthors [73] performed a meta-analysis and found that ephedrine can promote weight loss in the short term (6 months). Seven trials were evaluated for effects on exercise performance, but variations in exercise type and outcome measures made them inappropriate for pooled analysis. These trials individually did not find significant effects on the common parameters of exercise performance. Studies that combined caffeine with ephedrine demonstrated a 20% to 30% increase in performance. Bell and associates [74], however, found that ephedrine decreased 10 km run times, but there was no additive effect with caffeine. Jacobs and coworkers [72] found a significant increase in the number of repetitions that could be performed during the first set of leg press and bench press exercises 90 minutes after ingesting either ephedrine or ephedrine plus caffeine. There was no evidence of an additive effect of ephedrine and caffeine.

There are many safety concerns with ephedrine. In the meta-analysis [73], ephedrine was associated with a two-to-three fold risk of psychiatric symptoms, autonomic symptoms, upper gastrointestinal symptoms, and heart palpitations. Serious adverse events that have been associated with ephedrine include stroke, seizures, and death [75].

Sodium Bicarbonate

Sodium bicarbonate has been used as an alkaline solution to buffer the acidosis associated with anaerobic glycolysis. Because acidosis contributes to fatigue, buffering the acidosis may delay onset of fatigue. Theoretically, the usefulness of sodium bicarbonate should occur with exercise of high intensity and short duration, and several studies have shown sodium bicarbonate to be performance enhancing in this setting [76–80].

Sodium bicarbonate has also been shown to be effective in repeated, short-duration, high-intensity exercise interspersed with short recoveries [81]. This type of activity attempts to simulate the repetitive bursts of exercise associated with team sports. Data on whether sodium bicarbonate improves exercise performance in prolonged (30–60 minutes) endurance exercise are conflicting [82], but it has not shown benefit in repetitive resistance exercise [83,84]. Use of sodium bicarbonate has a potential for gastrointestinal distress, which may impair performance.

Erythropoietin

Erythropoietin is a glycoprotein hormone produced primarily by the kidney to stimulate the proliferation and differentiation of erythroid progenitor cells in the bone marrow [85]. Recombinant erythropoietin became available in the late 1980s, and was used to treat patients who had anemia [86]. By the 1990s, it was being used by athletes to improve endurance performance [86]. More recently the use of darbepoietin, a similar hormone to erythropoietin but with a longer half life, was discovered in three athletes, who were subsequently disqualified from the Salt Lake City Olympics [85].

Before erythopoietin, it is believed that the practice of "blood doping" began in the 1960s with a Tour de France cyclist. Widespread use started after the 1968 Mexico City Olympics, and came to the public's attention by the early 1970s [87]. Blood doping involves either autologous or homologous infusion of blood to increase red blood cell mass and oxygen carrying capacity. Typically one to four units are withdrawn 8 to 12 weeks before an event, stored, and then reinfused 1 to 4 days before competition [87]. By the early 1970s, it became well-established that increasing total body hemoglobin increased VO_{2max} and therefore performance. When erythropoietin became available, it became the preferred method to increase an athlete's oxygen carrying capacity.

Erythropoietin use is associated with hyperviscosity, thrombosis, and hypertension. Erythropoietin may have played a role in the deaths of 18 Dutch and Belgian cyclists from 1987 to 1990 [87].

Vitamins

Vitamins are compounds that cannot be synthesized by the body, catalyze numerous biochemical reactions, and facilitate energy metabolism [88]. The B vitamins modulate the synthesis and degradation of carbohydrate, fat, protein, and bioactive compounds [88]. Vitamins A, C, and E act as antioxidants; they reduce muscle damage and enhance recovery from exercise [88]. Individuals who are deficient in a vitamin will benefit from supplementation, but those who consume an adequate diet and are vitamin replete will not enhance performance through supplementation.

Studies of vitamins on exercise performance have been limited because of study designs [88]. Based on their mechanism of action, the type of vitamins that have been studied as potential performance enhancers are the antioxidants. Because physical activity may cause oxidative stress and increase the generation of free radicals, antioxidants are marketed as having utility in counteracting this stress [89]. Studies showing an increase in exercise performance with vitamin A, C, or E are lacking [88]. Additionally, there is a need for protein degradation to stimulate postexercise muscle protein synthesis [88]. Therefore, it is at present unclear what level of oxidative stress is beneficial and what level becomes harmful.

In general, athletes who may be vitamin deficient or who are restricting their diets may benefit from vitamin supplementation at the recommended daily

allowance. Athletes who eat a diet that maximizes vitamin and mineral intake do not require supplementation.

Iron

Iron is an element contained in proteins, including hemoglobin, and is required for the delivery of oxygen to tissues [88]. A deficiency in iron leads to anemia, which in turn decreases work capacity. Iron supplementation is beneficial when there is frank anemia, but is more controversial in athletes who are iron-deficient but not anemic. Multiple studies have shown no effect of iron supplementation on performance in athletes who have a low serum ferritin (the most useful marker of iron storage) [90,91]; however, some of these studies included athletes who have a ferritin above 20, and most studies did not meet the minimum therapeutic requirement for iron [92]. In studies that have shown a benefit, hemoglobin was in the low normal range and increased with iron supplementation [91]. Friedmann and colleagues [92] required ferritin levels below 20 and supplemented 100 mg of iron twice per day for 12 weeks. Their results did show significant increases in VO_{2max} and oxygen consumption.

Some authorities recommend screening for iron deficiency and anemia, whereas others recommend supplementation in high-risk individuals without testing. Although still controversial, supplementation alone carries a risk for potentiating hemochromatosis or delaying the clinical presentation of other underlying diseases, such as celiac disease, occult gastrointestinal bleeding, or uterine abnormalities [91].

Chromium

Chromium is an essential trace element involved in the regulation of carbohydrate, lipid, and protein metabolism [93]. Chromium supplementation has been used for weight loss and muscle development in the form of chromium picolinate. Chromium picolinate is more efficiently absorbed and may provide 100 times more chromium than dietary chromium [93]. Many studies have looked at supplementation, with the majority showing no significant effect on body composition [93]. In addition, chromium picolinate has been associated with anemia, thrombocytopenia, liver dysfunction, renal failure, rhabdomyolysis, cognitive, perceptual, and motor changes, exanthematous pustulosis, and hypoglycemia. It is also potentially mutagenic [93].

FUTURE DOPING ISSUES

Sports participation is often associated with the potential for personal and financial glory. This will continually drive athletes to try to gain an edge in performance, prompting some to attempt doping. To provide fair competition and to protect the health of athletes, organizations have developed testing programs to combat doping. This testing is not foolproof, and problems may include difficulty detecting a substance (erythropoietin or HGH) or developing a reliable method to detect a substance, quick clearance of some substances, manipulation of substances to avoid testing positive, and the use of masking agents to avoid a positive test.

Testing for substances can be modified to stay ahead of the cheaters. This may involve developing new or more sensitive methods of detecting substances, changing the pattern of testing, or adding other tests to assist in detection. An example of the latter is hair testing. This provides information on long-term use and eliminates false-negative results obtained through use of masking agents or manipulation of drug use around the testing time [94]. Another use is confirmation of the exact substance causing a positive test when a positive test is the metabolite of more than one substance [94]. Problems with hair testing include uncertainty of the minimal amount of drug detectable in hair after administration, uncertainty of the relationship between amount of drug used and the concentration in the hair, and the concentration of drugs potentially being affected by hair color or hair washing, discoloring, and tinting of hair [94].

A foreshadowing of future difficulties for sports regulating agencies became apparent with the discovery of tetrahydrogestrinone (THG). This steroid was synthesized in an effort to provide anabolic effects while eluding drug tests, and has been the center of a major doping scandal [95]. The practice of synthesizing new substances will no doubt continue; testing labs will have to be proactive in predicting new substances and developing new methods of detection.

Doping through gene therapy is a significant concern for the future. The Human Genome Project has provided the medicine field with potential treatments for diseases, but has also become a potential source for enhancement of athletic performance in healthy individuals. Artificial genes may be introduced into the body by direct injection of DNA into muscle, insertion of genetically modified cells, or through viral vectors [96]. Potential sources of abuse include the gene for erythropoietin, IGF-1, myostatin, and vascular endothelial growth factor. The gene for IGF-1 has been shown to cause muscle hypertrophy and increase power in patients who have degenerative muscle diseases [96]. In addition, mice injected with a viral vector carrying the IGF-1 gene showed a significant increase in muscle size and power [96]. The vascular endothelial growth factor gene increases the production of new blood vessels in peripheral arterial disease [96]. In healthy subjects, use may increase blood flow to muscles and vital organs, thereby delaying exhaustion [96]. In contrast to adding beneficial genes, detrimental genes may be extracted. When the myostatin gene is removed in mice, there is an increase in muscle hypertrophy and power [96]. Gene therapy poses problems because there are no current methods to detect this method of doping.

References

[1] Corrigan B, Kazlauskas R. Medication use in athletes selected for doping control at the Sydney Olympics (2000). Clin J Sport Med 2003;13(1):33–40.

[2] Warner DC, Schnepf G, Barrett MS, et al. Prevalance, attitudes and behaviors related to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in student athletes. J Adolesc Health 2002;30:150–3.

[3] Stovitz SD, Johnson RJ. NSAIDs and muskuloskelatal treatment. Phys Sportsmed 2003; 31(1):35–42.

[4] Almekinders LC. Anti-inflammatory treatment of muscular injuries in sport an update of recent studies. Sports Med 1999;28(6):383–8.

[5] Dahners LE, Gilbert JA, Lester GE, et al. The effect of a nonsteroidal anti-inflammatory drug on the healing of ligaments. Am J Sports Med 1988;16(6):641–6.
[6] Elder CL, Dahners LE, Weinhold PS. A cyclooxygenase-2 inhibitor impairs ligament healing in the rat. Am J Sports Med 2001;29(6):801–5.
[7] Lanier AB. Use of nonsteroidal anti-inflammatory drugs following exercise-induced muscle injury. Sports Med 2003;33(3):177–86.
[8] Gorsline RT, Kaeding CC. The use of NSAIDs and nutritional supplements in athletes with osteoarthritis: prevalence, benefits and consequences. Clin Sports Med 2005;24(1):71–82.
[9] Larson CM, Almekinders LC, Karas SG, et al. Evaluating and managing muscle contusions and myositis ossificans. Phys Sportsmed 2002;30(2):41–6.
[10] Cumming DC, Cumming CE. Estrogen replacement therapy and female athletes. Sports Med 2001;31(15):1025–31.
[11] Lebrun CM, Petit MA, McKenzie DC, et al. Decreased maximal aerobic capacity with use of a triphasic oral contraceptive in highly active women: a randomized control trial. Br J Sports Med 2003;37:315–20.
[12] Rickenlund A, Carlstrom K, Ekblom B, et al. Effects of oral contraceptives on body composition and physical performance in female athletes. J Clin Endocrinol Metab 2004; 89(9):4364–70.
[13] Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. Clin Infect Dis 2003;36:1404–10.
[14] Bouchard R, Weber AR, Geiger JD. Informed decision-making on sympathomimetic use in sport and health. Clin J Sport Med 2002;12:209–24.
[15] McKenzie DC, Stewart IB, Fitch KD. The asthmatic athlete, inhaled beta agonists, and performance. Clin J Sport Med 2002;12:225–8.
[16] Swain RA, Harsha DM, Baenziger J, et al. Do pseudoephedrine or phenylproponolamine improve maximum oxygen uptake and time to exhaustion? Clin J Sport Med 1997;7(3): 168–73.
[17] Gill ND, Shield A, Blazevich AJ, et al. Muscular and cardiorespiratory effects of pseudoephedrine in human athletes. Br J Clin Pharmacol 2000;50(3):205–13.
[18] Kaplan NM, Deveraux RB, Miller Jr HS. 26th Bethesda Conference recommendations for determing eligibility for competition in athletes with cardiovascular abnormalities Jan 6–7, 1994: task force 4: systemic hypertension. J Am Coll Cardiol 1994;24(4):885–8.
[19] Anderson RL, Wilmore JH, Joyner MJ, et al. Effects of cardioselective and nonselective beta-adrenergic blockade on the performance of highly trained runners. Am J Cardiol 1985;55(10):149D–54D.
[20] Sinzinger H, O'Grady J. Professional athletes suffering from familial hypercholesterolemia rarely tolerate statin treatment because of muscular problems. Br J Clin Pharmacol 2004; 57(4):525–8.
[21] Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management. Drug Saf 2002;25(5):345–72.
[22] Franke WW, Berendonk B. Hormonal doping and androgenization of athletes: a secret program of the German Democratic Republic government. Clin Chem 1997;3(7):1262–79.
[23] Bhasin S, Storer TW, Berman N, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996;335(1):1–7.
[24] Kutscher EC, Lund BC, Perry PJ. Anabolic steroid: a review for the clinician. Sports Med 2002;32(5):285–96.
[25] Kadi F, Eriksson A, Holmner S, et al. Effects of anabolic steroids on the muscle cells of strength trained athletes. Med Sci Sports Exerc 1999;31(11):1528–34.
[26] Parrsinen M, Seppala T. Steroid use and long-term health risks in former athletes. Sports Med 2002;32(2):83–94.
[27] Huie MJ. An acute myocardial infarction occurring in an anabolic steroid. Med Sci Sports Exerc 1994;26(4):408–13.
[28] Dickerman RD, Schaller F, Prather I, et al. Sudden cardiac death in a 20-year-old bodybuilder using anabolic steroids. Cardiology 1995;86(2):172–3.

[29] Sullivan ML, Martinez CM, Gallagher EJ. Atrial fibrillation and anabolic steroids. J Emerg Med 1999;17(5):851–7.
[30] Dickerman RD, Pertusi RM, Zachariah NY, et al. Anabolic steroid-induced hepatotoxicity: is it overstated? Clin J Sport Med 1999;9(1):34–9.
[31] Urhausen A, Torsten A, Wilfried K. Reversibility of the effects on blood cells, lipids, liver function and hormones in former anabolic-androgenic steroid abusers. J Steroid Biochem Mol Biol 2003;84:369–75.
[32] Stimac D, Milic S, Dintinjana RD, et al. Androgenic/anabolic steroid-induced toxic hepatitis. J Clin Gastroenterol 2002;35(4):350–2.
[33] Froehner M, Fischer R, Leike S, et al. Intratesticular leiomyosarcoma in a young man after high dose doping with oral-turinabol. Cancer 1999;86:1571–5.
[34] Delbeke FT, Van Eenoo P, Van Thuyne W, et al. Prohormones and sport. J Steroid Biochem Mol Biol 2003;83:245–51.
[35] Broeder CE, Quindry J, Brittingham K, et al. The andro prject. Arch Intern Med 2000; 160(13):3093–104.
[36] Brown GA, Vukovich MD, Martin ER, et al. Endocrine responses to chronic androstenedione intake in 30- to 50-year-old men. J Clin Endocrinol Metab 2000;85(11):4074–80.
[37] King DS, Sharp RL, Vukovich MD, et al. Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men. JAMA 1999;281(21):2020–8.
[38] Rasmussen BB, Volpi E, Gore DC, et al. Androstenedione does not stimulate muscle protein anabolism in young healthy men. J Clin Endocrinol Metab 2000;85(1):55–9.
[39] Wallace BM, Lim J, Cutler A, et al. Effects of dehydroepiandrosterone vs androstenedione supplementation in men. Med Sci Sports Exerc 1999;31(12):1788–92.
[40] Leder BX, Longcope C, Catlin DH, et al. Oral androstenedione administration and serum testosterone concentrations in young men. JAMA 2000;283(6):779–82.
[41] Leder BZ, Catlin DH, Longcope C, et al. Metabolism of orally administered androstenedione in young men. J Clin Endocrinol Metab 2001;86(8):3654–8.
[42] Brown GA, Vukovich MD, Sharp RL, et al. Effect of oral DHEA on serum testosterone and adaptations to resistance training in young men. J Appl Physiol 1999;87(6):2274–83.
[43] Dean H. Does exogenous growth hormone improve athletic performance? Clin J Sport Med 2002;12(4):250–3.
[44] Rennie MJ. Claims for the anabolic effects of growth hormone: a case of the emperor's new clothes? Br J Sports Med 2003;37:100–5.
[45] Juhn MS. Popular sports supplements and ergogenic aids. Sports Med 2003;33(12):921–39.
[46] Phillips SM. Protein requirements and supplementation in strength sports. Nutrition 2004; 20:689–95.
[47] Kreider RB. Dietary supplements and the promotion of muscle growth with resistance exercise. Sports Med 1999;27(2):97–110.
[48] American College of Sports Medicine. American Dietetic Association and Dieticians of Canada. Joint position statement. Nutrition and athletic performance. Med Sci Sports Exerc 2000;32(12):2130–45.
[49] Pitkanen HT, Oja SS, Rusko H, et al. Leucine supplementation does not enhance acute strength or running performance but affects serum amino acid concentration. Amino Acids 2003;25:85–94.
[50] Chromiak JA, Antonio J. Use of amino acids as growth hormone-releasing agents by athletes. Nutrition 2002;18:657–61.
[51] Candow DG, Chilibeck PD, Burke DG, et al. Effects of glutamine supplementation combined with resistance training in young adults. Eur J Appl Physiol 2001;86:142–9.
[52] Mesa JLM, Ruiz JR, Gonzalez-Gross MM, et al. Oral creatine supplementation and skeletal muscle metabolism in physical exercise. Sports Med 2002;32(14):903–44.
[53] McGuine TA, Sullivan JC, Bernhardt DT. Creatine supplementation in high school football players. Clin J Sport Med 2001;11(4):247–53.
[54] Labotz M, Smith BW. Creatine supplement use in a division I athletic program. Clin J Sport Med 1999;9(3):167–9.

[55] Metzl JD, Small E, Levine SR, et al. Creatine use among young athletes. Pediatrics 2001; 108(2):421–5.
[56] American College of Sports Medicine. The physiological and health effects of oral creatine supplementation. Med Sci Sports Exerc 2000;32(3):706–17.
[57] Kreider RB. Effects of creatine supplementation on performance and training adaptations. Mol Cell Biochem 2003;244:89–94.
[58] Branch JD. Effect of creatine supplementation on body composition and performance: a meta-analysis. Int J Sport Nutr Exerc Metab 2003;13:198–226.
[59] Poortmans J, Francaux M. Long term oral creatine supplementation does not impair renal function in healthy athletes. Med Sci Sports Exerc 1999;31(8):1108–10.
[60] Poortmans JR, Francaux M. Adverse effects of creatine supplementation: fact or fiction. Sports Med 2000;30(3):155–70.
[61] Schroeder C, Potteiger J, Randall J. The effects of creatine dietary supplementation on anterior compartment pressure in the lower leg during rest and following exercise. Clin J Sport Med 2001;11(2):87–95.
[62] Slater GJ, Jenkins D. B-hydroxy-B-methylbutyrate (HMB) supplementation and the promotion of muscle growth and strength. Sports Med 2000;30(2):105–16.
[63] Gallagher PM, Carrithers JA, Godard MP, et al. B-hydroxy-B-methylbutyrate ingestion, Part I: effects on strength and fat free mass. Med Sci Sports Exerc 2000;32(12):2109–15.
[64] Nissen S, Sharp R, Ray M, et al. Effect of leucine metabolite B-hydroxy-B-methylbutyrate on muscle metabolism during restance-exercise training. J Appl Physiol 1996;81(5): 2095–104.
[65] Jowko E, Ostaszewski P, Jank M, et al. Creatine and B-hydroxy-B-methylbutyrate (HMB) additively increase body mass and muscle strength during a weight-training program. Nutrition 2001;17:558–66.
[66] Thomson JS. Beta-hydroxy-beta-methylbutyrate (HMB) supplementation of resistance trained men. Asia Pac J Clin Nutr 2004;13(Suppl):S59.
[67] Slater G, Jenkins D, Logan P, et al. Beta-hydroxy-beta-methylbutyrate (HMB) supplementation does not affect changes in strength or body composition during resistance training in trained men. Int J Sport Nutr Exerc Metab 2001;11(3):384–96.
[68] Hoffman JR, Cooper J, Wendell M, et al. Effects of beta-hydroxy-beta-methylbutyrate on power performance and indices of muscle damage and stress during high-intensity training. J Strength Cond Res 2004;18(4):747–52.
[69] Ransone J, Neighbors K, Lefavi R, et al. The effect of beta-hydroxy-beta-methylbutyrate on muscular strength and body composition in collegiate football players. J Strength Cond Res 2003;17(1):34–9.
[70] Gallagher PM, Carrithers JA, Godard MP, et al. B-hydroxy-B-methylbutyrate ingestion, Part II: effects on hematology, hepatic and renal function. Med Sci Sports Exerc 2000; 32(12):2116–9.
[71] Crowe MJ, O'Connor DM, Larkins JE. The effects of B-hydroxy-B-methylbutyrate (HMB) and HMB/creatine supplementation on indices of health in highly trained athletes. Int J Sport Nutr Exerc Metab 2003;13:184–97.
[72] Jacobs I, Pasternak H, Bell DG. Effects of ephedrine, caffeine, and their combination on muscular endurance. Med Sci Sports Exerc 2003;35(6):987–94.
[73] Shekelle PG, Hardy ML, Morton SC, et al. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance. JAMA 2003;289(12):1537–45.
[74] Bell DG, McLellan TM, Sabiston CM. Effect of ingesting caffeine and ephedrine on 10-km run performance. Med Sci Sports Exerc 2002;34(2):344–9.
[75] Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. N Engl J Med 2000; 343(25):1833–8.
[76] Van Montfoort MCE, Van Dieren L, Hopkins WG, et al. Effects of the ingestion of bicarbonate, citrate, lactate, and chloride on sprint running. Med Sci Sport Exerc 2004; 36(7):1239–43.

[77] McNaughton LR. Bicarbonate ingestion: effects of dosage on 60s cycle ergometry. J Sports Sci 1992;10(5):415–23.
[78] Bird SR, Wiles J, Robbins J. The effect of sodium bicarbonate ingestion on 1500-m racing time. J Sports Sci 1995;13(5):399–403.
[79] Goldfinch J, McNaughton L, Davies P. Induced metabolic alkalosis and its effects on 400-m racing time. Eur J Appl Physiol Occup Physiol 1988;57(1):45–8.
[80] Gao JP, Costill DC, Horswill CA, et al. Sodium bicarbonate ingestion improves performance in interval swimming. Eur J Appl Physiol Occup Physiol 1988;58:171–4.
[81] Bishop D, Edge J, Davis C, et al. Induced metabolic alkalosis affects muscle metabolism and repeated-sprint ability. Med Sci Sports Exerc 2004;36(5):807–13.
[82] Stephens TJ, McKenna MJ, Canny BJ, et al. Effect of sodium bicarbonate on muscle metabolism during intense endurance cycling. Med Sci Sports Exerc 2002;34(4):614–21.
[83] Portington KJ, Pascoe DD, Webster MJ, et al. Effect of induced alkalosis on exhaustive leg press performance. Med Sci Sports Exerc 1998;30(4):523–8.
[84] Webster MJ, Webster MN, Crawford RE, et al. Effect of sodium bicarbonate ingestion on exhaustive resistance exercise performance. Med Sci Sports Exerc 1993;25(8):960–5.
[85] Guadard A, Varlet-Marie E, Bressolle F, et al. Drugs for increasing oxygen transport and their potential use in doping. Sports Med 2003;33(3):187–212.
[86] Joyner MJ. VO_{2max}, blood doping and erythropoietin. Br J Sports Med 2003;37:190–1.
[87] Leigh-Smith S. Blood boosting. Br J Sports Med 2004;38:99–101.
[88] Lukaski HC. Vitamin and mineral status: effects on physical performance. Nutrition 2004; 20:632–44.
[89] Urso ML, Clarkson PM. Oxidative stress, exercise, and antioxidant supplementation. Toxicology 2003;189:41–54.
[90] Zoller H, Vogel W. Iron supplementation in athletes—first do no harm. Nutrition 2004; 20:615–9.
[91] Garza D, Shrier I, Kohl 3rd HW, et al. The clinical value of serum ferritin tests in endurance athletes. Clin J Sports Med 1997;7(1):46–53.
[92] Friedmann B, Weller E, Mairbaurl H, et al. Effects of iron repletion on blood volume and performance capacity in young athletes. Med Sci Sports Exerc 2001;33(5):741–6.
[93] Vincent JB. The potential value and toxicity of chromium picolinate as a nutritional supplement, weight loss agent and muscle development agent. Sports Med 2003;33(3): 213–30.
[94] Kintz P, Samyn N. Use of alternative specimens: drugs of abuse in saliva and doping agents in hair. Ther Drug Monit 2002;24(2):239–46.
[95] Vogel G. A race to the starting line. Science 2004;305:632–5.
[96] Unal M, Unal OU. Gene doping in sports. Sports Med 2004;34(6):357–62.