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Popular Sports Supplements and Ergogenic Aids

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Abstract

This article reviews the evidence-based ergogenic potential and adverse effects of 14 of the most common products in use by recreational and elite athletes today. Both legal and prohibited products are discussed. This is an aggressively marketed and controversial area of sports medicine worldwide. It is therefore prudent for the clinician to be well versed in the more popular supplements and drugs reputed to be ergogenic in order to distinguish fact from fiction.

Antioxidants, proteins and amino acids are essential components of diet, but additional oral supplementation does not increase endurance or strength. Caffeine is ergogenic in certain aerobic activities. Creatine is ergogenic in repetitive anaerobic cycling sprints but not running or swimming. Ephedrine and pseudoephedrine may be ergogenic but have detrimental cardiovascular effects. Erythropoietin is ergogenic but increases the risk of thromboembolic events. β-Hydroxy-β-methylbutyrate has ergogenic potential in untrained individuals, but studies are needed on trained individuals. Human growth hormone and insulin growth factor-I decrease body fat and may increase lean muscle mass when given subcutaneously. Pyruvate is not ergogenic. The androgenic precursors androstenedione and dehydroepiandrosterone have not been shown to increase any parameters of strength and have potentially significant adverse effects. Anabolic

steroids increase protein synthesis and muscle mass but with many adverse effects, some irreversible. Supplement claims on labels of product content and efficacy can be inaccurate and misleading.

Products that claim to be performance enhancing are popular with recreational and elite athletes. Some are classified as drugs, others as supplements. Drugs that are used for medical purposes but have ergogenic properties are prohibited by most major sport governing bodies, since it is the elite athlete that is most likely to be tempted by such products. Supplements, however, are marketed aggressively to all types of athletes, which has generated its own controversy in this very profitable industry.[1]

Often, performance-enhancing products are purchased based on popular magazine advertisements, peer or coach recommendation rather than professional medical advice.[2,3] Furthermore, some products are popular and marketed as ergogenic despite a lack of objective evidence to support claims of an ergogenic effect. In the US for example, ergogenic claims of supplements can be made without verification by the Food and Drug Administration (FDA), ever since the controversial passage of the Dietary Supplement Health and Education Act in 1994.[4]

For this review, the Medline database was utilised to research the products listed (table I). Few studies had sample sizes of greater than 20 per group. Therefore, whenever possible, crossover designs were given high priority. Reviews of particular supplements or drugs were also analysed. Only reviews that provided a critique of studies rather than a rehashing of Medline abstracts were utilised. Many studies on over-the-counter (OTC) supplements were funded by supplement companies. While this did not necessarily exclude the study from consideration, conclusions from such studies were carefully assessed since supplements do not undergo the rigorous multiple-phase scrutiny of FDA approval. Surveys and case reports were judiciously utilised as some products have a paucity of controlled studies.

1. Antioxidants

An antioxidant is a product that can detoxify free radicals back into water and oxygen. Some antioxidants are endogenous to the human body, including glutathione and superoxide dismutase. The most popular antioxidants obtained by diet are ascorbic acid (vitamin C), tocopherol (vitamin E), coenzyme Q10, and β-carotene (precursor to vitamin A).[5]

A discussion of antioxidants must begin with defining a free radical, also known as a reactive oxygen species. A free radical is a molecule with an unpaired electron, and a normal by-product of life. Hydrogen peroxide (H_2O_2), superoxide (O_2^-) and hydroxyl radical (OH) are examples of free radicals. Free radicals are unstable, and produce cellular damage such as damage of lipid membranes and changes in membrane protein structure via lipid peroxidation.[6,7] The basis for antioxidants as a potential ergogenic aid lies in the fact that physical exercise increases oxygen uptake by body tissues resulting in oxidative stress, which leads to enhanced production of free radicals.[7] Free radicals can be a factor in prolonging recovery from exercise-induced fatigue.[5,7]

Antioxidant supplementation is popular among some endurance athletes, but the research does not support them as an effective ergogenic aid. In a double-blind, cross-over study, Nielsen and colleagues evaluated seven male triathletes taking the commonly marketed strategy of multiple antioxidants.[8] The athletes were supplemented for 6 weeks with 600mg ascorbic acid (reference daily intake [RDI] = 60mg), 270mg tocopherol (RDI = 20mg), and 100mg coenzyme Q10 (no RDI exists). No change was noted in maximal oxygen uptake ($\dot{V}O_{2max}$), muscle energy metabolism and muscle fatigue.

In another study of 25 blinded study participants (15 placebo and ten experimental), 2 weeks of 667mg (1000 IU)/day tocopherol supplementation

Table I. Popular sports supplements and ergogenic aids

Product	Ergogenic potential	Adverse effects/safety	Banned by	Typical dosage	Comments
Antioxidants	No	None known	None	Megadoses of ascorbic acid (vitamin C), tocopherol (vitamin E), β-carotene, etc.	Although not ergogenic, a diet high in antioxidants is recommended by most dietitians
Caffeine	Events >30 min = yes; 30 sec–30 min = probably; repetitive sprints = no	Dependency; withdrawal; CNS stimulant effects; mild diuretic (but exercise diminishes this effect)	IOC, FIFA: max. urine conc. of 12 μg/mL. NCAA: max. 15 μg/mL	2–9 g/kg (~150–700mg) PO 1h prior to event (8oz cup of coffee = 100–250mg, but coffee not ideal method)	Mechanism is adenosine receptor antagonism, and possibly enhanced fat metabolism which spares glycogen stores
Creatine	Repetitive max. cycling bouts = yes; running = no; swimming = no; repetitive bouts weight lifting = probably; isometric strength = no; endurance activity = no	Weight gain due to water retention; ↑ intra-compartment pressure in lower extremities – the likely cause of cramps; case reports regarding renal and muscle dysfunction	None	20 g/day PO for 5d; 2–5 g/day for maintenance; *or* starting with maintenance dose ok, although takes 28d to achieve what 5d of loading does	Ergogenic effect related to increased PCr stores that are converted to ATP; has not been shown to directly enhance protein/muscle synthesis; studies are difficult to do because individuals can often detect weight gain and know they are on creatine; weight gain may be detrimental to runners and swimmers; high individual variability
Ephedrine (ephedra, Ma Huang) and pseudoephedrine	Anaerobic activity = yes; endurance events = possibly	Hypertension; tachycardia; stroke; CNS over-stimulation	IOC, NCAA, NFL	Ephedrine: 1 mg/kg 1h prior to event. Pseudoephedrine: 60–180mg 1h prior to event	Mechanism due to CNS arousal as opposed to muscle metabolism. Pseudoephedrine is a drug. Ephedrine is marketed as an herbal supplement
r-HuEPO	Yes	Hypertension; thromboembolic events	IOC, FIFA, NCAA, NFL	50 IU/kg r-HuEPO IV or SC, typically for 15–30d	r-HuEPO extremely expensive, injectable only
HMB	Untrained individuals = possibly; trained individuals = no	Safe in studies of 8 wks or less, but few studies done	None	3 g/day PO	HMB is a metabolite of the essential amino acid leucine
HGH and IGF-1	Prescription injectable HGH can ↓ adipose tissue and ↑ lean body mass in the elderly. Performance studies lacking	Hypoglycaemia; ↓ endogenous HGH secretion; ↑ risk lung, colon cancer; TMJ discomfort; weight gain; dyspnoea; sinus tachycardia	IOC, FIFA, NCAA, NFL	For medical conditions, 6–12 μg/kg SC daily. Anecdotal reports that abusers use much higher doses	Beware the OTC products that are 'precursors', or homoeopathic amounts (600ng) of HGH, given sublingually or nasally (unproven methods of delivery). Real HGH is only available by Rx SC injection
Proteins, amino acids, branched-chain amino acids	No	Excess protein stored as fat, not utilised; theoretical concerns about renal load	None	Variable doses, PO	A proper diet is all that is needed, even for strength athletes, to get the protein they need. Protein and amino acid supplements have not been shown to enhance protein/muscle synthesis
Pyruvate	No	Unstudied	None	5 g/day	Never caught on – lack of ability to reproduce studies and lack of interest

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Table I. Contd

Product	Ergogenic potential	Adverse effects/safety	Banned by	Typical dosage	Comments
Steroid precursor: androstenedione	No	↓ HDL; ↑ estradiol/estrogen; virilism	IOC, FIFA, NCAA, NFL, NBA[a]	Studies done on 100–300 mg/day PO. Product labels often instruct to take more	Although a testosterone/androgen precursor, does not promote protein/ muscle synthesis. Can create positive drug test for testosterone
Steroid precursor: DHEA	No	↓ HDL; ↑ estradiol/estrogen	IOC, FIFA, NCAA, NFL, NBA[a]	25 mg/day PO, although studies up to 150 mg/day show no ergogenic effect	Although a testosterone/androgen precursor, does not promote protein/ muscle synthesis. Can create positive drug test for testosterone
Anabolic steroids	Yes	Hirsutism; menstrual irregularities; aggression; ↓ spermatozoa; ↑ cardiovascular risk; liver dysfunction	IOC, FIFA, NCAA, NFL, NBA, MLB	250–3200 mg/week, PO or injectable. Many alternate dosage strategies exist.	Enhances protein/muscle synthesis

a The NBA Players Association has filed a grievance challenging the banning of androstenedione and DHEA. The National Hockey League does not keep a list of banned substances and only ban substances in accordance with local laws; however, this is under constant scrutiny for potential change.

ATP = adenosine triphosphate; **conc.** = concentration; **DHEA** = dehydro-epiandrosterone; **FIFA** = Fédération Internationale de Football Association (Soccer); **HDL** = high-density lipoprotein; **HGH** = human growth hormone; **HMB** = β-hydroxy-β-methylbutyrate; **IGF-1** = insulin growth factor-1; **IOC** = International Olympic Committee; **IV** = intravenously; **max.** = maximum; **MLB** = Major League Baseball; **NBA** = National Basketball Association; **NCAA** = National Collegiate Athletic Association (USA); **NFL** = National Football League (American Football); **OTC** = over-the-counter; **PCr** = phosphocreatine; **PO** = orally; **r-HuEPO** = recombinant erythropoietin; **Rx** = prescription; **SC** = subcutaneously; **TMJ** = temporomandibular joint; ↑ = increase; ↓ = decrease.

did not enhance performance in a marathon run.[9] Coenzyme Q10 for 28 days did not affect $\dot{V}O_{2max}$, heart rate, blood pressure, or anaerobic respiratory threshold in a study of male cyclists and triathletes (eight experimental, ten placebo).[10] A large dose of ascorbic acid (400 mg/day) for 2 weeks did not improve muscle soreness, muscle damage (measured by creatine kinase), or lipid peroxidation (measured by malondialdehyde) in active male runners.[11] It must be noted that most of these studies involved short-term supplementation, and the results may be different with long-term supplementation. Additionally, small sample sizes not performed with a crossover design increases the likelihood of a Type II statistical error, meaning an ergogenic effect may exist, but the sample size is too small to see it. Further research into antioxidants with larger sample sizes or crossover designs would help clarify the ergogenic potential of antioxidants.

It is important to distinguish an ergogenic effect from an objective measurement of cellular damage. Several studies have shown that supplementation with antioxidants can improve measurements of oxidative stress in humans.[6,12] Such measurements are very complex, but generally involve by-products of lipid peroxidation (conjugated dienes, thiobarbituric acid-reactive substances, malondialdehyde, or lipid peroxides). While such results have potential clinical implication in preventive healthcare, they should not be interpreted as proving ergogenic potential.

Regardless of ergogenic potential, it is well accepted that antioxidants are a key dietary component for athletes and non-athletes alike. In those athletes who restrict dietary intake, particularly if they lack in fruits and vegetables, supplementation with antioxidants is advisable. The potential for antioxidants to prevent muscle damage and lipid peroxidation resulting from high level repetitive training warrants further study, as such prevention may have long-term health benefits.[6,13] Antioxidants may not be truly ergogenic and supplementation is not necessary in most cases; however, athletes are still advised to ingest a diet rich in antioxidants.[5-7]

2. Caffeine

Caffeine is an adenosine-receptor antagonist and a stimulant of the dimethylxanthine class. Caffeine can be considered a drug as it is an ingredient in some pharmaceutical products, but since it is so ubiquitous OTC, it is often classified as a supplement. The mechanism for the ergogenic effect of caffeine remains somewhat inconclusive in humans, although rat studies clearly show that caffeine inhibits adenosine receptors,[14] and such receptors are located throughout the human body. On the cellular level, a recent rat study found that the phosphorylation and dephosphorylation of dopamine- and cyclic adenosine monophosphate (cAMP)-regulated phosphoprotein of relative molecular mass 32 000 (DARPP-32) plays a role in the stimulant action of caffeine.[15] Another theory put forward is stimulation of adrenaline secretion, resulting in the mobilisation of free fatty acids – an important fuel for muscle. This increase in fat utilisation decreases carbohydrate utilisation, thus delaying glycogen depletion.[16] While there have been studies to support this latter theory,[17] recent studies have failed to support it.[18,19]

The strength of evidence of caffeine's ergogenic potential is strong, particularly in aerobic activity.[16,20] In a double-blind, crossover study, Kovacs et al. studied 15 well-trained male triathletes and cyclists in a 1-hour cycling time trial at 75% of work maximum.[18] Three different dosages of caffeine were consumed: 154mg (2.1 mg/kg), 230mg (3.2 mg/kg) and 328mg (4.5 mg/kg). Even in the lowest dosage, there was improvement in time trial performance. Interestingly, the highest dosage was no more efficacious than the middle dosage, indicating a possible saturation effect of caffeine as an ergogenic aid. Urinary concentrations of caffeine were also measured (samples collected 5 minutes post-exercise), and did not reach any higher than 2.5 μg/mL. This is well below the disqualification limits imposed by the International Olympic Committee (IOC) [12 μg/mL] and the US-based National Collegiate Athletic Association (NCAA) [15 μg/mL].

In a double-blind, crossover study involving physical activity of a shorter duration, Bruce et al. found enhancement of 2000m rowing performance after caffeine consumption of either 6 or 9 mg/kg.[21] The improvement in time averaged 1%, with a 3% improvement in power output when comparing both caffeine groups to placebo. Similar to Kovacs study,[18] the higher dose of caffeine was no more efficacious than the lower dose. However, urinary concentration at the higher dose did reach as high as 14 μg/mL, a disqualifying number based on IOC standards. One strength of Bruce's study is that all eight study participants were well trained.

Even for sprint activity, caffeine has shown ergogenic promise in a single cycling[22] or swimming[23] sprint. However, Paton et al.[24] demonstrated in a double-blind, crossover study that caffeine is not ergogenic for repetitive bouts of sprinting, which is commonly used in team sport workouts.

Generally speaking, the doses of caffeine used in studies range from 2–9 mg/kg (about 250–700mg caffeine), taken 1 hour or less prior to the event. Clearly, an ergogenic effect of caffeine in aerobic activity is demonstrated in doses that would not reach the disqualifying levels of NCAA and IOC sport, as it takes approximately 9 mg/kg consumed to achieve a urinary concentration of 12 μg/mL.[18]

Adverse effects of caffeine are minimal; however, its central nervous system effects can cause anxiety, dependency and withdrawal. The diuretic effect of caffeine, although theoretically a concern in endurance events, appears to be attenuated or eliminated by exercise.[18,25]

The use of caffeine by athletes is not surprisingly common. Caffeine does not have the stigma branded to it that some supplements do, and is quite safe. It is likely that many Olympians use caffeine since the cut-off for disqualification is considered high enough to warrant taking the risk. Athlete beware, however, that urinary measurements of caffeine concentration are notoriously inaccurate.[18]

Finally, although coffee is not considered the ideal method of consumption of caffeine (tablets are the usual recommendation), it should be emphasised that coffee can vary greatly in its caffeine content. For example, an 8oz cup of brewed Maxwell

House®[1] coffee contains 110mg, and an 8oz Starbucks® cup of coffee has 250mg.[26] Caffeine content in common foods and drink are summarised by Harland.[26]

3. Creatine

Creatine is a nitrogenous compound that exists naturally in skeletal muscle in an equilibrium with phosphocreatine (PCr). PCr is the primary source of adensosine triphosphate (ATP) in skeletal muscle during intense, burst-type (anaerobic) exercise.[27] Creatine supplementation allegedly exerts its ergogenic effect by increasing resting concentrations of creatine in skeletal muscle, which subsequently increases PCr concentration by 12–18%.[28] This allows for more ATP availability, which is rapidly used during intense exercise.[29] Additionally, creatine causes a rapid weight gain due to water retention,[27,28,30] and it has been hypothesised that intracellular water retention may stimulate protein/muscle synthesis.[31] However, despite manufacturer claims, creatine itself has not been shown to be anabolic (i.e. it does not enhance protein synthesis and therefore does not increase muscle mass).[29,32,33]

The typical regimen involves oral intake of 20 g/day for 5 days as a loading dose, followed by 5 g/day as a maintenance dose. However, athletes often take more than is needed,[3,34,35] and even the 5g maintenance dose is more than necessary, as 2 g/day is enough to maintain the maximum elevated creatine concentration in skeletal muscle.[30] A study by Green et al.[36] found that carbohydrate ingestion enhanced performance over creatine alone, allegedly by enhancing the insulin-dependent creatine transporter to increase muscle uptake of creatine. However, such doses of carbohydrate are known to cause their own kinds of problems such as diminished gastric motility which can adversely affect performance.

No sports supplement has been studied more than creatine, but there remains substantial controversy over its alleged ergogenic effect due to the numerous 'ergogenic' studies with questionable methodology and biased conclusions.[28,29,37,38] For example, authors sometimes conclude an ergogenic effect in the highly visible abstract that appears on the Medline database, but a detailed analysis of the body of the paper raises questions as to the validity of such conclusions.

A recent double-blind, crossover study with excellent methodology did find an ergogenic effect of creatine in repetitive bouts of high-intensity cycling and a maximal voluntary dorsiflexion of the ankle.[39] However, creatine has not been shown to enhance all strength parameters. It has not been shown to enhance isometric strength[40] or overhead motion strength.[41,42] There are seemingly countless ways to evaluate muscle strength, including peak torque, maximal voluntary contraction, peak power, and one repetition maximum. Since many athletic endeavours involve various muscle activities, the average clinician can find such strength measurements confusing and difficult to clinically correlate.

There is considerable scepticism as to the ergogenic potential of creatine in mass-dependent sports such as running and swimming. This is because consumption of creatine results in a rapid weight gain due to intra- and extra-cellular water retention,[27-30] which can be detrimental to running or swimming performance. The great majority of 'sprinting' studies are on stationary cycles in laboratories, which is not the same as a running or swimming sprint. In an endurance run of 6km, creatine-supplemented individuals actually ran 26 seconds slower than the placebo-supplemented individuals.[43] There have also been several studies reviewed[28] that demonstrated no benefit in running sprints and swimming sprints. A recent study, however, did conclude an ergogenic effect of creatine in repetitive 5m and 15m running sprints.[44] The study participants were well-trained soccer players and the study was designed to be more akin to a true field test than the many previous laboratory studies; however, the experimental group was small (n = 8).

A more recent running study by Cox et al.[45] demonstrates how difficult it is to interpret many of

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

the creatine studies that exist today. In one of the few on-field studies on creatine, Cox et al.[45] studied 12 female soccer players (six experimental, six placebo) in 20m running sprints and agility runs. A total of 55 running sprints and ten agility runs were studied. In nine of the 55 sprints, and three of the ten agility runs, the creatine group achieved faster post-supplementation times. However, this means that most individuals taking creatine did not improve their times (46 out of 55 sprints, seven out of ten agility runs). Additionally, in all study participants, there was no change in overall sprint time nor overall agility run time. Through no fault of the authors, such a study is often interpreted by the athletic community in a very 'ergogenic' light.

The simplest conclusion regarding creatine is that it is ergogenic for repetitive bouts of high intensity anaerobic exercise which are not mass-dependent (such as cycling), and for certain parameters of strength including one-repetition maximal voluntary contraction. However, its effect is highly variable between individuals. The weight gain associated with creatine is likely the reason why an ergogenic effect in running and swimming is questionable, probably more so with swimmers due to an increased drag effect.[46] It should be noted that the rapid weight gain from creatine supplementation also makes it very difficult to blind individuals in such studies.

There are two proven adverse effects of creatine. One is weight gain, which has been well documented,[27,47] and the other is increased muscle compartment pressure.[48] This increase is likely the reason for the numerous reports of muscle cramping in athletes who take creatine.[3,27,34,49] Recently, Robinson reported a case of rhabdomyolysis in an individual taking creatine.[50] While a cause and effect relationship cannot be firmly established, the data of Schroeder et al.[48] and the numerous reports of muscle dysfunction should make the clinician wary that creatine is not entirely innocuous, and any athlete taking creatine should report muscle pain or cramping to a physician.

Renal parameters such as glomerular filtration rate and serum creatinine levels can be affected by creatine, but in studies of 10 weeks or less such effects were reversible.[47] An animal study found progression of renal disease as a result of creatine supplementation,[51] and there have been two published reports of renal dysfunction in humans taking creatine.[52,53] However, both individuals were taking more than the recommended dose, and one[53] had previous renal disease. Nonetheless, since skeletal muscle has a threshold of how much creatine it can store, patients should be informed that the 'more is better' philosophy does not apply with creatine, and only increases chances of adverse effects.

Finally, it should be noted that creatine is naturally found in almost all tissues, including testes, liver, kidneys, heart and brain. Creatine supplementation increases brain creatine levels in humans,[54] and animal studies demonstrate increased creatine levels in kidneys, lungs and liver after oral supplementation.[55] The significance of these findings is unknown.

Patients who insist on taking creatine should be told to dose appropriately, be aware that creatine may or may not work for them, and that creatine is taken at their own risk.

4. Ephedrine (Ephedra) and Pseudoephedrine

Ephedrine and pseudoephedrine are sympathomimetic amines known for their stimulant properties. For this reason, many athletes use them in the hope of increasing energy and delaying fatigue. Ephedrine, also classified as ephedra alkaloids, is classified as an herb, and therefore a dietary supplement. Pseudoephedrine is classified as a drug, and is the world's most commonly used decongestant sold OTC. Both are also marketed as appetite suppressants used for weight loss, leading to indiscriminate use by wrestlers wishing to reduce body mass prior to competition.

It has been proposed that sympathomimetic agents such as ephedrine and pseudoephedrine are ergogenic by a glycogen-sparing mechanism, but this has not been supported in recent work.[56] Ephedrine increases the release of monoamines such as dopamine both centrally and peripherally.[57] This

may explain its ergogenic effect in some studies but again remains only a theory.

In a study of 16 male participants, Bell et al.[58] found that 1 mg/kg ephedrine improved anaerobic performance in a 30-second Wingate test, although the study participants were untrained. The authors hypothesised the ergogenic effect to be due to increased arousal as opposed to enhanced muscle metabolism. Bell et al.[56] also studied 12 individuals (ten men and two women, all recreational runners) in a 10km run, and found that 0.8 mg/kg ephedrine improved running time from 46.8 ± 3.2 minutes to 45.5 ± 2.9 minutes, suggesting that ephedrine is ergogenic in prolonged exercise. Thus far, no published studies have evaluated ephedrine in burst-type activity.

Most studies on pseudoephedrine have not demonstrated an ergogenic effect.[59-62] Two randomised, double-blind, crossover studies involving ten individuals each demonstrated no ergogenic effect of 120mg pseudoephedrine.[59,60] One study involved a 1-hour bout of high-intensity cycling,[59] the other involved maximal anaerobic output and fatigue.[60] Even high-dose pseudoephedrine (240 mg/day for 3 days) did not enhance performance of eight trained male runners in a 5000m timed treadmill run at 70% $\dot{V}O_{2max}$.[63] However, Gill et al.[61] did a double-blind, crossover study of 22 male athletes who took 180mg of pseudoephedrine. There was an increase in maximum torque in an isometric knee extension, increase peak power in cycling, and improved forced expiratory volume in 1 second. Taken together, the above studies suggest that pseudoephedrine is not ergogenic in aerobic or endurance activity, but at a high enough dose, may be ergogenic in maximal anaerobic burst-type activity.

Adverse effects of pseudoephedrine and ephedrine are of great concern, primarily because of the high incidence of cardiovascular events reported. Since pseudoephedrine is a drug, adverse effects are well documented as with other sympathomimetic drugs. Label precautions centre on cardiovascular and central nervous system effects.[64]

Recent high-profile deaths of athletes taking ephedrine supplements have led to an FDA consumer warning in the US.[65] A detailed review by Bent et al.[66] found that ephedra-containing products accounted for 64% of all adverse reactions to herbs in the US, despite representing only 0.82% of sales. Higher doses of ephedra also increases the risk of haemorrhagic stroke.[67] A detailed 22-month review[68] found 140 adverse events related to the use of supplements containing ephedra alkaloids, primarily involving cardiovascular events and stroke. Ten involved death, and 13 resulted in permanent disability. Dosages of ephedra alkaloids in most of these cases ranged from 20–60 mg/day, clearly within range of many OTC products.

In summary, sympathomimetics such as ephedrine and pseudoephedrine may differ in their ergogenic potential. Pseudoephedrine may have ergogenic potential in burst type activity but not prolonged activity. Ephedrine has potential in activity of longer duration, but the mechanisms are unclear. Intuitively, sympathomimetics may be ergogenic due to a stimulant effect, but safety reasons alone should place them on the not-recommended list, and they are banned by most sport governing bodies.

5. Erythropoietin

Erythropoietin (EPO) is produced naturally by the kidneys to regulate red blood cell production,[69] and is approved for medical use in chronic renal failure and certain types of anaemia. It remains, unfortunately, a widely abused drug in the sporting world, particularly with the advent of recombinant human EPO (r-HuEPO), which allowed for convenient subcutaneous injection as opposed to autologous blood doping in the older days.[70] Darbepoetin (Aranesp®), a newer product approved for chronic renal failure, is the newest agent. Its detection resulted in the disqualification of three cross-country skiers, including a gold and silver medal winner, in the 2002 Salt Lake City Winter Olympic Games. Darbepoetin has a 3-fold longer terminal half-life than r-HuEPO (21 hours intravenously, 49 hours subcutaneously), and therefore does not have to be administered as often as r-HuEPO.[71] For example, in chronic renal failure, if a patient uses r-HuEPO 2–3

times weekly, the frequency of darbepoetin is only once weekly.

There is no argument that EPO is ergogenic due to its ability to improve the oxygen carrying capacity of blood.[72-74] Audran et al.[72] studied the effects of subcutaneous injection of 50 IU/kg of r-HuEPO for 26 days in nine athletes (seven men and two women). Haemoglobin and haematocrit values were significantly elevated by the end of treatment. Each athlete performed an incremental exercise cycle test to exhaustion. $\dot{V}O_{2max}$ improved by 9%, power output by 7%, and maximum heart rate decreased by 5%.

EPO is an unquestionably dangerous substance for athletes to use. Potential adverse effects centre on thromboembolic events due to the increased packed red blood cell count and viscosity after administration. The most common adverse effects seen with medical use of EPO are hypertension, seizures and thromboembolic events.[75,76] There is little doubt in the minds of many in the medical community that several untimely deaths of elite cyclists and other athletes were related to blood doping or the use of exogenous EPO.

Advances have been made in the detection of autologous or recombinant EPO administration, as it is banned by most major sporting organisations. A 50% haematocrit rule was imposed by the Union Cycliste Internationale, and an 18.5 g/dL haemoglobin limit by the Federation Internationale de Ski. However, these numbers have been subject to criticism because of the effects on such parameters due to posture, dehydration and exercise.[77,78] Additionally, a small percentage of athletes have such values as baseline,[77] and high altitude living elevates baseline values.[79]

Detection of EPO abuse has been implemented at major sporting events such as the Tour de France and the Olympic Games.[1] Detection tests centre on the fact that r-HuEPO administration causes a predictable haematological response involving haematocrit, serum erythropoietin, reticulocyte count, macrocyte count, and soluble transferrin receptor. Parisotto and colleagues have revealed some promising and reproducible results in two consecutive studies,[77,80] which are much more sophisticated than the crude measurement of one haemoglobin/haematocrit value. They concluded that r-HuEPO administration not only causes such predictable and reproducible haematological responses, but they exist even several weeks following r-HuEPO administration. Furthermore, results did not vary with ethnicity. Continued research into detection methods will undoubtedly yield testing that is superior to an arbitrary limit of haemoglobin or haematocrit.

Nonetheless, the administration of sophisticated tests faces a major hurdle, as their cost can be prohibitive. Recently, the 'GH2000' project, which was an international effort to detect abuse of growth hormone, was dropped due to lack of IOC funding, even though it was acknowledged that better detection is needed.[1] It is easy to see why the perpetrators are often one step ahead of the detectors.

6. β-Hydroxy-β-Methylbutyrate

β-hydroxy-β-methylbutyrate (HMB) is a metabolite of the essential amino acid leucine. It is promoted as a supplement to increase strength and lean body mass not by being truly anabolic, but rather anti-catabolic (preventing muscle breakdown).

HMB is metabolised to hydroxymethylglutaryl-coenzyme A, which has been hypothesised to be the rate-limiting enzyme when cholesterol synthesis is in demand.[81] Because cholesterol synthesis is needed in membrane repair, it is thought that HMB supplementation can decrease muscle damage and enhance recovery. Despite the popularity and heavy marketing of this hypothesis, it has yet to be proven, and studies on the ergogenic effect of HMB have been equivocal.[82]

Knitter et al.[83] studied 13 untrained individuals supplemented with 3 g/day of HMB for 6 weeks, and found that the HMB group had a lower increase in creatine phosphokinase and lactate dehydrogenase after a 20km run, supporting the hypothesis that HMB may prevent muscle damage. However, the study does not address performance, and does not support, or refute, the cholesterol synthesis theory.

In a study funded by two sports supplement companies, Gallagher and colleagues[84] studied un-

trained college men during 8 weeks of resistance training, supplementing one experimental group (n = 12) with 3 g/day of HMB, the other group (n = 11) with 6 g/day HMB. The results were mixed and therefore difficult to draw conclusions from. One repetition maximum strength did not improve in either group. The 3 g/day group did show a greater increase in peak isometric torque than placebo, but interestingly, greater than the 6 g/day group also. No differences were observed in body fat between the three groups, but the 3 g/day group showed a greater increase in fat-free mass than placebo. Strangely, the 6 g/day group did not show a greater increase in fat-free mass than placebo. The authors conclude that HMB appears to increase peak isometric and isokinetic torque values, and increase fat free mass. Such a conclusion seems a bit tenuous since the two experimental groups varied in their results.

Equivocal results were also obtained in a supplement company-sponsored study by Panton et al., where 21 individuals supplemented with 3 g/day HMB for 4 weeks demonstrated an increase in upper body strength compared with placebo.[85] However, lower body strength did not improve. In another study on untrained individuals, Jowko et al. studied 3 g/day HMB supplementation with resistance training in nine men, and found beneficial results in six of seven strength tests compared with placebo, but no significant changes in body fat or lean body mass.[86]

The results of HMB on trained individuals are less promising. A recent study by Slater and colleagues found that HMB supplementation for 6 weeks did not affect strength or body competition in trained men.[87] It is thought that this may be due to the training-induced suppression of protein breakdown.[88]

On a positive note, Gallagher and colleagues found that HMB did not adversely affect lipid profiles, hepatic enzyme levels or renal function in their study participants.[89] The safety of HMB was further addressed by Nissen and colleagues at Iowa State University and no untoward effects were seen, although the longest study was 8 weeks in duration.[90]

HMB, while probably safe for 8 weeks or less, may have a role as an ergogenic aid in untrained individuals; however, its data on trained individuals is less convincing. Further research, not only on performance but also the cholesterol synthesis hypothesis, would be of value in understanding the role of HMB in exercise and muscle breakdown.

7. Human Growth Hormone and Insulin-Like Growth Factor-1

Human growth hormone (HGH) is synthesised by the anterior pituitary gland, and its metabolic effects are mediated by the hormone insulin-like growth factor-1 (IGF-1).[91] HGH is a prescription drug that has been shown in men over 60 years of age to increase lean body mass, decrease adipose tissue, and slow the thinning of the skin.[92] It is therefore classified as 'anti-aging' by some, a rather dubious terminology. Not surprisingly then, there has been recent interest in the use of HGH (also abbreviated GH) as a sports supplement[93,94] even though it remains essentially unstudied in younger populations. The postulated mechanism behind HGH in athletes includes enhanced amino acid and glucose uptake in skeletal muscle, thus stimulating protein synthesis, possibly combined with increase of free fatty acid mobilisation as an energy source.[93] HGH also stimulates IGF-1 synthesis, which is discussed later in this section. The strong endorsement bestowed upon HGH in the notorious publication '*The Underground Steroid Handbook*' helped solidify the place of HGH in the elite athlete's mind, despite no evidence to support the aforementioned theories.

What is often misunderstood, however, is that HGH is a drug only available by injection, and is not available OTC or on the Internet. The HGH molecule is too big to be absorbed in the gastrointestinal tract, and is broken up into its constituent amino acids when taken orally.[95] OTC products are labelled precursors, secretagogues or releasers of HGH. There is no evidence to suggest that such precursors of HGH are effective as an ergogenic, weight-loss or anti-aging agent. Advertisers of these products often cite Rudman et al.'s study,[92] without

mentioning that the study used real, injectable, prescription HGH. Furthermore, the participants in the study were men over 60 years of age, who naturally would have lower GH levels to begin with. No legitimate published studies on OTC products have been done, and therefore their safety and efficacy is in question.

Recently, some advertisers claim to have real HGH in their product. The concentration of HGH within these products (usually 600ng) are not only minute and unverified by the FDA, but are also derived from different sources than prescription HGH. Furthermore, the claimed superior method of delivery (nasal or sublingual) is speculative at best. Again, safety is not established, and there is legitimate concern about black market HGH that is pituitary (not recombinant) derived, which runs the risk of Creutzfeld-Jacob disease or other contamination.[95]

Certainly, prescription HGH has legitimate medical uses, including Turner syndrome in children, and Adult Growth Hormone Deficiency syndrome. Recent studies have yet to convincingly demonstrate HGH to be ergogenic.[94,96] Adverse effects of injectable HGH must also be considered, and include insulin resistance, glucose intolerance, oedema, and decreased endogenous HGH secretion.[97] Because of growth hormone's role in the regulation of lipoprotein (a), there are also cardiovascular concerns particularly with long-term use.[97]

IGF-1 is produced primarily by the liver and is thought to have a protein anabolic effect by enhancing amino acid uptake and accelerating transcription and translation.[98] IGF-1 is often mentioned together with HGH, as HGH stimulates IGF-1 gene expression in all tissues.[95] However, hepatic production of IGF-1 is regulated by factors other than HGH, such as nutritional status, and circulating IGF-1 levels should be considered more as a marker of HGH action on the liver than as the mechanism by which HGH exerts its effects.[95]

Research on actual IGF-1 in humans has been unconvincing of an anabolic effect. Yarasheski and colleagues found that even in individuals who doubled their circulating IGF-1 levels, there was no effect on the rate of protein synthesis, and no increase in strength.[99] Like HGH, however, OTC products that claim to contain IGF-1 are either precursors or alternate formulations that are unproven as performance enhancers. Adverse effects of these OTC products have not been studied, but elevated IGF-1 levels have been linked to lung cancer and colorectal cancer.[97,100] Injectable subcutaneous IGF-1 can cause temporomandibular joint discomfort, weight gain, dyspnoea and sinus tachycardia.[91]

Regarding HGH and IGF-1, neither agent can be classified as ergogenic unless further study is done on an athletic population, the necessity of which is questionable. The problem the clinician faces is marketing. What is marketed is not the actual researched drug, and patients are often unaware of this important fact. It is also unlikely that either agent would ever be legalised by a major sports organisation.

8. Proteins and Amino Acids

Arguably, proteins and amino acids are the most heavily marketed category of sports supplements. Despite the known role of amino acids and protein synthesis in the development of muscle hypertrophy and strength, the necessity of additional supplementation beyond diet is highly questionable. It is generally accepted that athletes have a greater daily protein requirement than sedentary people. The recommended daily allowance is 0.8 g/kg/day for adults, but ranges from 1.2–1.8 g/kg/day for athletes, with the higher range being reserved for strength athletes.[101-103]

Despite the acceptance of the additional protein needs of athletes, most athletes eat well enough to obtain this in their diet,[101,104] and there is little evidence to support additional consumption of protein or amino acids as performance enhancing. Williams et al.[105] studied seven untrained individuals supplemented with a glucose/amino acid product for 10 weeks. They utilised a clever design whereby alternate legs within the same individuals were trained on successive days, so each individual in a

training group served as his or her own control. This minimised the inter-individual variability inherent in other small sample size studies. The investigators found no strength benefits of the supplementation. In another study, Jentjens et al.[106] found that the addition of protein and amino acids to a carbohydrate diet did not enhance post-exercise muscle glycogen synthesis. A widely cited, double-blind, crossover study by Lemon et al.[104] in 1992 found that supplemental protein intake did not increase muscle mass or strength in novice bodybuilders.

The branched chain amino acids (BCAAs) are leucine, isoleucine, and valine. Theoretically, they decrease protein-induced degradation, which can lead to a greater fat-free mass.[102] The data on BCAAs as an ergogenic aid are not convincing. Davis et al. studied the effects of BCAA administration to a sports drink in individuals who performed intermittent, high-intensity running, with no beneficial effect noted.[107] Some studies have suggested that BCAAs may reduce exercise-induced muscle damage based on creatine phosphokinase and lactate dehydrogenase levels, but did not address performance.[108,109] Simply put, BCAAs, while an essential component of diet, are not ergogenic when taken in mass quantities as a dietary supplement. In fact, Wagenmakers makes an interesting argument that BCAAs may be ergo*lytic* (detrimental to performance) due to impedance of aerobic oxygenation.[110]

It is common for a new amino acid complex with a catchy brand name to be touted as the next magic bullet. The fact is that while proteins and amino acids are essential components of diet, studies on supplemental protein are not convincing. Patients wishing to take amino acid or protein supplements should be told that a proper diet is sufficient, and that dietary protein provides 20 essential and nonessential amino acids, including those that are marketed as 'ergogenic', such as leucine, isoleucine, lysine, alanine and glutamine.

9. Pyruvate

Pyruvate is a carboxylic acid produced by the metabolism of glucose. In 1990, Stanko et al. published two studies that involved upper and lower extremity endurance capacity in individuals who consumed pyruvate.[111,112] The results of these studies caught the eye of the supplement industry and pyruvate was aggressively marketed by supplement companies as being performance enhancing for endurance events. The proposed but unproven mechanism was that pyruvate enhances glucose oxidation.

Analysis of these studies, however, shows that both involved untrained individuals and very small sample sizes (8–10 individuals), and neither study used pyruvate alone. The upper extremity study[112] utilised dihydroxyacetone and pyruvate, while the lower extremity study[111] utilised dihydroxyacetone, pyruvate and a pre-event high carbohydrate diet. The dose of pyruvate utilised (25g) was also much higher than that marketed by supplement companies, which is usually 5g. High doses can cause gastric distress, which also brings into question the feasibility of such studies truly being double-blind. Furthermore, pyruvate is usually marketed alone. The pyruvate/dihydroxyacetone combination product is commonly known as DHAP.

Morrison and colleagues[113] did a recent study that incorporated a randomised double-blind crossover design (n = 7), and found that 7g of pyruvate for 7 days did not improve cycling performance time (approximately 90 minutes of cycling). Equally important, blood pyruvate levels did not even increase despite the supplementation. In a separate study by Morrison, published in the same paper,[113] nine recreationally active individuals ingested 7, 15, and 25g of pyruvate, but again no effect was found on blood pyruvate, glucose or lipid metabolism. This is of particular interest because pyruvate is also marketed as a weight-loss and cholesterol-lowering agent, neither of which has been proven.[114] Unlike the studies by Stanko et al., both of Morrison et al.'s studies involved trained individuals, which most sports clinicians find clinically more relevant.

Pyruvate cannot be classified as being ergogenic, and one review even called the marketing of pyruvate as 'economic fraud'.[114] The studies by Stanko et al.[111,112] may reveal some potential of high dose pyruvate/dihydroxyacetone in untrained individuals, but the doses necessary cast significant

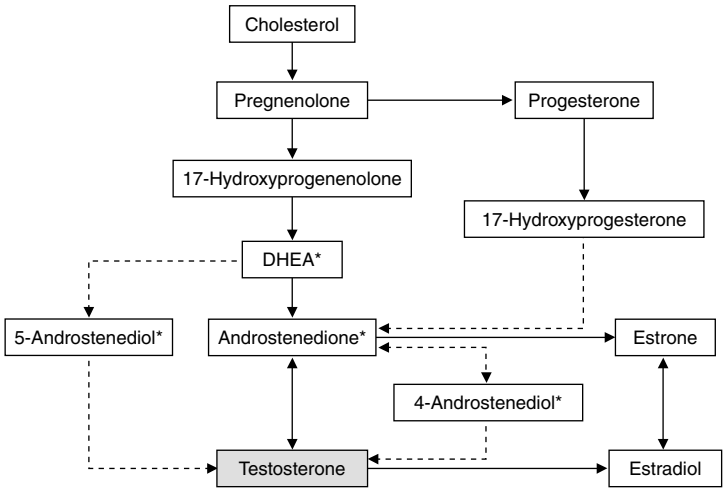

Fig. 1. The androgen and estrogen biosynthesis pathway. **DHEA** = dehydroepiandrosterone; * indicates androgenic precursors available over the counter.

doubt on the practicality of this regimen, least of all by trained athletes.

10. Androstenedione

If there were any doubts that society embraces its sports heroes, such doubts were quickly dispelled when sales of 'andro' skyrocketed after the revelation that a Major League Baseball player was using the supplement during a season where he broke the single season home run record. Research has shown, however, that this accomplishment cannot be attributed to the use of androstenedione.

It is common for an athlete to ask if androstenedione is a steroid. It is an 'androgenic' steroid, but it has not been proven to be an 'anabolic' (muscle building) steroid. In other words, it is not ergogenic. Specifically, androstenedione is an androgen/testosterone precursor (figure 1). Testosterone is synthesised from cholesterol via the δ-4 or δ-5 pathway, each of which involves androgenic precursors as intermediaries between cholesterol and the final testosterone product.[115,116] In the US, androgenic precursors are sold OTC, with androstenedione and dehydroepiandrosterone (DHEA) being the most popular.[115]

Oddly enough, androgenic precursors are not classified as drugs in the US and therefore fall under the loose guidelines of the Dietary Supplement Health and Education Act of 1994, meaning no FDA verification of product claims. There were no published studies on androstenedione prior to the 1998 McGwire story, but JAMA quickly published two well designed studies[117,118] that did not support an ergogenic effect, and only one of the two[117] demonstrated any increase in serum testosterone. Both studies, however, found significant increases in estradiol/estrogen synthesis, which is not surprising given estradiol's relationship to the biosynthesis of testosterone (figure 1).

In an extensive study, Broeder et al.[119] studied the effects of 200mg androstenedione daily for 12 weeks in men aged 35–65 years, who participated in a high-intensity resistance training programme. They found that serum testosterone levels increased at 1 month, but despite continued supplementation, returned to baseline levels by week 12, likely due to down-regulation of endogenous testosterone synthesis. More relevant is the fact that there was no change in body composition or strength compared with placebo. There were also adverse effects on high-density lipoprotein levels and coronary heart disease risk. Furthermore, estradiol levels increased by 97% in the treatment group due to a sustained increase in aromatisation leading to increases in estrogen synthesis.

Finally, a study by Rasmussen et al.[120] used isotopic tracer procedures to demonstrate that androstenedione does not promote muscle protein synthesis. In fact, under non-resistance training, Rasmussen found that the androstenedione group produced a greater degree of muscle protein breakdown than synthesis.

The lack of evidence supporting an ergogenic effect of androstenedione, combined with its adverse effects and legal ramifications, puts androstenedione on the not-recommended list of sports supplements. Additionally, androstenedione has been shown to cause a positive urine test for the anabolic steroid nandrolone.[121]

11. Dehydroepiandrosterone

DHEA is also an androgen precursor (figure 1). It is produced by the adrenal glands. As a precursor to androgenic steroids, DHEA may increase the production of testosterone and is marketed as having an anabolic steroid effect.

Brown et al.[122] examined the effects of DHEA on serum androgen levels and resistance training. Ten men (average age 23 years), were given a single 50mg dose of DHEA, and within 60 minutes had increased their androstenedione concentration by 150%. However, testosterone levels did not increase. Additionally, Brown et al. evaluated the effects of 150 mg/day of DHEA in 19 men (average age 23 years), while engaging in an 8-week resistance training programme. No changes in body composition or strength were found.[123]

While studies on adverse effects are lacking, there are reports of irreversible virilisation in women, including hair loss, hirsutism and voice deepening.[124] Men have reported irreversible gynecomastia, which may result from an elevation in estrogen levels. There is also concern that DHEA may increase the risk of uterine and prostate cancer due to prolonged unopposed estrogen and testosterone.[124]

Like androstenedione, DHEA is not classified as a drug, but rather a dietary supplement, and is therefore available OTC. Athletes should also be warned that any androgen precursor could alter the testosterone-epitestosterone ratio enough to exceed the 6 **:** 1 limit, which the IOC and NCAA enforce in their screening for exogenous testosterone use. It would be unfortunate for an athlete to be disqualified from competition for taking a product that does not have evidence to support an ergogenic effect to begin with.

12. Anabolic Steroids

Anabolic steroids began the athletic world's obsession with ergogenic aids. Anabolic steroids are simply the synthetic derivatives of the prototypical anabolic steroid, testosterone. They come in oral and injectable forms. Popular names include dianabol, nandrolone and stanozolol. The United States Congress classified anabolic steroids as a class III controlled substance in 1991. While it took many years for the medical community to admit it, the evidence is in: anabolic steroids work, but at a price.[125,126]

There have been several extensive reviews of anabolic steroids and their use in sport, and each has drawn similar conclusions regarding their anabolic effect as well as numerous adverse effects.[125-128] Briefly, anabolic steroids increase muscle mass by increasing muscle protein synthesis.[129] The exact mechanism is related to the increased nitrogen retention as a result of androgen excess. Via the metabolism of testosterone in the liver, an androgen receptor complex is formed which initiates the cellular transcription necessary for protein synthesis and muscle accretion.[125,128] There is also evidence to suggest that anabolic steroids increase erythropoiesis.[125]

Anabolic steroids are banned by the IOC, and the most utilised test is the ratio of testosterone to its metabolite, epitestosterone (T **:** E ratio), which is 1 in most men. The cut-off being 6 **:** 1 is generous and likely tempts athletes to test the limits.

Some recent studies have shed more light on anabolic steroids and their potential uses and abuses. Tamaki and colleagues demonstrated that anabolic steroids increase exercise tolerance.[130] While this was a rat model, it was the first study to address the relationship between protein synthesis and mitotic activity in skeletal muscle after anabolic steroid treatment, with and without exercise. There are also

potential medical uses of anabolic steroids, such as its use in genetic or HIV-induced muscle wasting disorders.[125,131]

Some concern has been voiced that elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels should not be dismissed as always being steroid-induced in an anabolic steroid user. Dickerman et al. found that resistance training alone can lead to elevations in AST and ALT, but not glutamyl transpeptidase (GGT).[132] Clinicians should take note of this and include a GGT in the workup of any anabolic steroid user.

While there can be no denying the legitimate medical uses of anabolic steroids and the sometimes biased attitudes of physicians towards users, the ergogenic effect of anabolic steroids cannot justify their use in sport. Adverse health consequences are well established and include increased virilisation in women, menstrual irregularities, premature closure of growth plates, hirsutism, acne, aggressive behaviour, liver dysfunction and increased cardiovascular event risk.[125-128] A recent study found that only 17% of anabolic steroid users had normal spermatozoa.[133] There are also significant psychosocial aspects related to anabolic steroid use that cannot be overlooked. Kindlundh et al.[134] found significant associations between anabolic steroid use and immigrant status, low self-esteem, low school achievement, and use of prescription sedatives. On an encouraging note, Nilsson and colleagues[135] studied 16- to 17-year-old male anabolic steroid users, and found that discussion about appearance and attitudes helped to decrease steroid abuse. The take-home message is that clinicians should make every effort to counsel their patients.

13. Misleading Marketing

A discussion about sports supplements would not be complete without mentioning the dangers of misleading marketing. Green and colleagues evaluated 12 OTC anabolic-androgenic supplements using high pressure liquid chromatography.[136] Eleven of the 12 products (92%) had less product than what was labelled. Similar misleading labels (six of seven) were found in Catlin et al.'s study.[121] These findings are discouraging, but not surprising. It reflects the significant impact of the Dietary Supplement Health and Education Act of 1994. The passage of this Act, which allows any product not classified as a drug to bypass the FDA approval process, appears to have opened the door to unscrupulous business practices, and the studies by Green and Catlin suggest that a close re-evaluation of the Act is warranted. Most other countries, similar to the US, do not have strict regulation of supplements.

14. Conclusion

Many products are marketed as ergogenic despite a lack of evidence to support such claims. While a few have ergogenic potential, their applicability is limited to certain types of exercise and individual variability is a significant factor.

Antioxidants, proteins and amino acids are essential components of diet; however, additional oral supplementation does not increase endurance or strength. Caffeine is ergogenic in certain aerobic activities and is relatively safe. Laboratory studies on creatine show promise in repetitive anaerobic cycling sprints and maximal voluntary muscle contraction, but the research on running and swimming is not convincing of an ergogenic effect. Ephedrine and pseudoephedrine may have ergogenic potential but with a very high risk of adverse cardiovascular effects, and are appropriately banned by most sport governing bodies. EPO increases $\dot{V}O_{2max}$ and time to fatigue, but increases the risk of thromboembolic events. HMB may increase strength but more data are needed on trained individuals. HGH and IGF-1 decrease body fat and may increase lean muscle mass when given subcutaneously. Pyruvate is not ergogenic. The androgenic precursors androstenedione and DHEA have not been shown to increase any parameters of strength and have potentially significant adverse effects. Anabolic steroids increase protein synthesis and muscle mass but with many adverse effects, some irreversible. Labels describing content of supplements can be inaccurate and misleading. It must be emphasised that the population being 'treated' is not sick or diseased in any way, so it is important for the sports clinician to stay abreast

of the information in order to better advise their active patient population.

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