Cardiovascular Toxicities of Performance-Enhancing Substances in Sports

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Athletes commonly use drugs and dietary supplements to improve athletic performance or to assist with weight loss. Some of these substances are obtainable by prescription or by illegal means; others are marketed as supplements, vitamins, or minerals. Nutritional supplements are protected from Food and Drug Administration regulation by the 1994 US Dietary Supplement Health and Education Act, and manufacturers are not required to demonstrate proof of efficacy or safety. Furthermore, the Food and Drug Administration lacks a regulatory body to evaluate such products for purity. Existing scientific data, which consist of case reports and clinical observations, describe serious cardiovascular adverse effects from use of performance-enhancing substances, including sudden death. Although mounting evidence led to the recent ban of ephedra (ma huang), other performance-enhancing substances continue to be used frequently at all levels, from elementary school children to professional athletes. Thus, although the potential for cardiovascular injury is great, few appropriately designed studies have been conducted to assess the benefits and risks of using performance-enhancing substances. We performed an exhaustive OVID MEDLINE search to identify all existing scientific data, review articles, case reports, and clinical observations that address this subject. In this review, we examine the current evidence regarding cardiovascular risk for persons using anabolic-androgenic steroids including 2 synthetic substances, tetrahydrogestrinone and androstenedione (andro), stimulants such as ephedra, and nonsteroidal agents such as recombinant human erythropoietin, human growth hormone, creatine, and β-hydroxy-β-methylbutyrate.

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AAS = anabolic-androgenic steroids; ATP = adenosine triphosphate; FDA = Food and Drug Administration; HDL = high-density lipoprotein; hGH = human growth hormone; HMB = β-hydroxy-β-methylbutyrate; LDL = low-density lipoprotein; rhEPO = recombinant human erythropoietin; THG = tetrahydrogestrinone; US DSHEA = US Dietary Supplement Health and Education Act

Performance-enhancing substances are used widely by athletes despite the potential for serious adverse effects.[1-3] Since the deaths of a Danish cyclist at the 1960 Olympics and of a UK cyclist at the 1967 Tour de France, the potential for serious or life-threatening toxicity from performance-enhancing substances in athletics has been recognized.[2] More recently, numerous media reports including the high-profile deaths of athletes such as Minnesota Vikings' Korey Stringer and Baltimore Orioles' Steve Bechler have focused needed attention on safety issues for ergogenic drugs.[4,5]

Despite the efforts of athletic regulatory and governing bodies to restrict the use of performance-enhancing substances, use of these substances has increased.[2] Meanwhile, the mechanisms and the clinical manifestations of toxicity of anabolic steroids, ephedra, erythropoietin, and other performance-enhancing agents were acknowledged. This resulted in the December 2003 Food and Drug Administration (FDA) consumer alert stating that ephedra, also called ma huang, presented an unreasonably high risk of life-threatening cardiovascular toxicity, which led to its eventual ban in the United States on April 12, 2004.[6] On January 20, 2004, the magnitude of this problem came to national attention in the United States when President George W. Bush urged professional athletes to set a better example for youth by eliminating the use of anabolic steroids and other performance-enhancing substances.

We performed an extensive OVID MEDLINE search for all existing scientific data, review articles, case reports, and clinical observations regarding the mechanisms and clinical manifestations of cardiovascular toxicity of substances marketed and sold for performance enhancement in athletes.

ANABOLIC-ANDROGENIC STEROIDS

Anabolic-androgenic steroids (AAS), which include more than 30 natural and synthetic derivatives of testosterone,[7,8] were designed in 1939 to treat conditions such as eunuchoid syndromes, impotence, depression, starvation, and cryptorchidism. It is speculated that these substances were used to enhance physical performance and aggressiveness in Nazi soldiers; they also were used extensively by weight lifters and track and field athletes from the 1950s until 1976.[7] After the Olympic ban of AAS in 1976, AAS continued to be used clandestinely by Olympic athletes, and its use spread quickly to high school, intercollegiate, and professional sports. Also, there is now widespread use among noncompetitive bodybuilders, recreational athletes, and those who simply desire an improved physique.[7]

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TABLE 1. **Commonly Used Androgenic-Anabolic Steroids**

Injectable	Oral
Boldenone	Ethylestrenol
Methenolone enanthate	Fluoxymesterone
Nandrolone decanoate	Mesterolone
Nandrolone phenpropionate	Methandrostenolon
Testosterone cypionate	Methenolone
Testosterone enanthate	Methyltestosterone
Testosterone propionate	Oxandrolone
Testosterone ester mixture	Oxymetholone
	Stanozolol

Adapted from *Med Sci Sports Exerc*,[8] with permission.

Because testosterone undergoes extensive first-pass metabolism, delayed-release systems and structural modifications are designed to increase effectiveness by bypassing the liver.[8,9] Modifications include esterification of the 17β-hydroxyl group to allow for intramuscular use; alkylation at the 17α position to allow for oral administration, inhibit hepatic metabolism, and increase bioavailability; and many other structural modifications intended to increase potency (Table 1).[8,9]

Testosterone is a potent ligand of the human androgen receptor in skeletal and myocardial tissue but also directly modulates transcription, translation, and enzymatic function in numerous other tissues.[7,9] Consequently, the adverse effects from use of AAS are widespread and affect multiple organ systems. Typical adverse effects include cardiac toxicity, hepatotoxicity including hepatic adenoma and hepatocellular carcinoma, lipid abnormalities, gynecomastia, gonadal hypertrophy, infertility, psychological abnormalities, and immunologic depression. Human immunodeficiency virus and hepatitis B and C can be transmitted by sharing needles.[10,11] In addition, women experience steroid-induced masculinization, including acne, hirsutism, amenorrhea, and clitoral hypertrophy.[9-13]

Cardiovascular Toxicity of AAS: Mechanisms

Melchert and Welder[8] proposed 4 mechanisms of AAS-induced cardiovascular toxicity: atherogenic, thrombotic, vasospastic, and direct myocardial injury. The atherogenic model involves lipoprotein abnormalities; the thrombotic model is secondary to hypercoagulability; and the vasospastic model cites endothelial dysfunction and nitric oxide changes.

Several studies suggest that AAS cause profound changes in lipid metabolism, including reductions in high-density lipoprotein (HDL) levels and elevations in low-density lipoprotein (LDL) levels.[8,11] Atherogenesis is believed to be promoted by increasing hepatic triglyceride lipase activity, which is responsible for the catabolism of very low-density lipoproteins to LDL and the catabolism of HDL. Although the changes are noted to be reversible, the risk of cardiac disease is estimated to be increased 3-fold among persons who use AAS.[7,8]

Development of an atheromatous plaque perpetuates endothelial dysfunction and promotes platelet aggregation and intracoronary thrombus formation. However, AAS also have been implicated as the primary cause of several cases of sudden death from coronary artery thrombus in the absence of intracoronary atherosclerotic plaque.[7,14,15] There appears to be a direct effect on the coagulation/fibrinolytic system, which increases levels of coagulation factors in both the intrinsic and extrinsic pathway. In addition, there is increased production of thromboxane A_2 and decreased production of prostaglandins that may cause a hypercoagulable state and promote platelet production and aggregation.[7,8]

Another cause of myocardial infarction in young patients without evidence of coronary artery disease who are using AAS is coronary vessel reactivity. The AAS are known to decrease the production of cyclic guanosine monophosphate by inhibiting guanylyl transferase. This, combined with increased levels of oxidized LDL, inhibits the ability of nitric oxide to activate guanylyl transferase and thus contributes to endothelium-dependent vascular dysfunction.[7,8]

Direct cell injury occurs by disruption of myocardial mitochondria and induction of intrafibrillar collagen dysplasia. Cell injury ensues, and scar tissue replaces dead cells, leading to fibrosis and the potential for ventricular arrhythmias.[7,8,16] Development of hypertension also occurs, followed by left ventricular hypertrophy and structural changes to the ventricular wall.[17] Increased ventricular septal thickness develops rapidly and is disproportionate to the expected degree of compensatory hypertrophy from resistance training. Other studies reveal increased incidence of diastolic dysfunction, greater left ventricular posterior wall thickness, and greater left ventricular end-diastolic dimensions.[7,8] In this setting, sudden death may have been caused by vasospasm potentiated by diastolic dysfunction–mediated ischemia.[7]

Cardiovascular Toxicity of AAS: Clinical Considerations

Many case reports and case series describe various forms of cardiac toxicity resulting from use of AAS (Table 2[15,16,18-46]), including a wide spectrum of disease ranging from lipid abnormalities to sudden death.[47] Thromboembolic phenomena originating intraventricularly as well as peripherally also have been reported.[15,16] Stroke has been reported as an embolic phenomenon in association with AAS use.[28,29] Cardiomyopathy, cardiomegaly, and biventricular dilatation induced by AAS can occur as a result of remodeling after myocyte injury and have been noted to be reversible after discontinuation of AAS.[7,15,16,46]

TABLE 2. **Case Reports and Case Series of Cardiovascular Toxicities of Ephedrine-Containing Substances and Anabolic-Androgenic Steroids**

Adverse effect	Ephedra- and ephedrine-containing substances	Anabolic-androgenic steroids
Arrhythmia, sudden death	RAND Report,[18] Haller & Benowitz,[19] Theoharides,[20] Garriott et al,[21] Backer et al,[22] Shekelle et al,[23] Samenuk et al,[24] McBride et al[25]	Nieminen et al,[26] Luke et al,[27] Frankle et al[28]
Thrombosis		Nieminen et al[26]
Peripheral embolism		Laroche,[29] McCarthy et al[15]
Myocardial infarction	RAND Report,[18] Kimmel,[30] Haller & Benowitz,[19] Shekelle et al,[23] Samenuk et al[24]	Ferenchick & Adelman,[31] Huie,[32] McNutt et al,[33] Kennedy & Lawrence,[34] Lyngberg[35]
Vasospasm	Foxford et al,[36] Lustik et al,[37] Hirabayashi et al[38]	
Hypertension	RAND Report,[18] Haller & Benowitz[19]	Lenders et al,[39] Kuipers et al[40]
Myocardial hypertrophy	Nishida et al[41] (methamphetamines)	Nieminen et al,[26] Hausmann et al,[16] Dickerman et al,[42] Luke et al[27]
Cardiomyopathy	To et al,[43] Theoharides[20]	Nieminen et al,[26] Ferenchick & Adelman,[31] Touchette,[44] McCarthy et al[15]
Myocardial necrosis	Theoharides[20]	Hausmann et al[16]
Stroke	RAND Report,[18] Kimmel,[30] Haller & Benowitz,[19] Vahedi et al,[45] Shekelle et al,[23] Samenuk et al[24]	Laroche,[29] Frankle et al[28]
Coronary artery ectasia		Tischer et al[46]

Fineschi et al[14] described 2 young men who were taking AAS and died suddenly; both had normal coronary anatomy and no evidence of coronary artery disease. The cause of death remained unclear, but pathology specimens revealed segmentation of myocardial cells suggesting sudden death from direct myocyte injury. Other cases of sudden death are described similarly. Unfortunately, because no cause is identified, etiologies considered include AAS-induced arrhythmias, direct toxicity, or underlying cardiac disease.[8,26]

ANDRO

Many chemical forms of androstenedione, collectively called andro, are available in pill form and are sold over-the-counter legally as nutritional supplements. These agents are available in sublingual, topical cream, spray, gel, and injectable forms and are marketed as a natural alternative to AAS for performance enhancement.[48,49] King et al[49] showed in a randomized controlled trial that andro was aromatized primarily to estrogens, did not enhance skeletal muscle adaptation to resistance training, and reduced HDL levels. In a meta-analysis by Nissen and Sharp,[50] androstenedione did not affect lean muscle mass or strength. It is unclear whether efficacy or adverse effects are more pronounced with long-term use or at higher doses. Andro is marketed as a nutritional supplement and protected by the 1994 US Dietary Supplement Health and Education Act (US DSHEA); thus, data on its adverse effects including cardiac toxicities are sparse.[51] Fortunately, on March 18, 2004, the FDA banned the use of andro in the United States, a departure from standard practice in which supplements are allowed to remain on the market until proven unsafe.[52]

TETRAHYDROGESTRINONE

Tetrahydrogestrinone (THG) has received considerable media attention recently for its use as a performance-enhancing substance. A purely synthetic designer steroid modified from the already banned steroids trenbolone and gestrinone, THG is structurally unrelated to the anabolic steroids that athletes used previously, such as testosterone, boldenone, or methandrostenolone.[53] The substance is popular because it is difficult to detect, and there have been many reports of its use among high-profile athletes in several sports, including track-and-field, tennis, football, and baseball. In July 2003, national and international anti-doping agencies, hoping to find a way to detect THG before the 2004 Olympics in Athens, developed a urine test based on an anonymous sample of THG. Now that THG can be detected, both the FDA and major league baseball have officially banned this substance.[54,55] Also, although not listed as a prohibited substance on the World Anti-Doping Code 2004 Prohibited List, the World Anti-Doping Agency has declared THG as prohibited.[53] On March 1, 2004, several prominent baseball players, including San Francisco Giants home run superstar Barry Bonds, were subpoenaed to testify against a company charged with supplying athletes with illegal performance-enhancing drugs, including

TABLE 3. **Scientific, Alternative, and Common Product Names for Ephedra[60-62]**

Scientific names	Other names used	Product names
E distachya	Ma huang	3-Andro Xtreme
E equisetina	Coa ma huang	Adipokinetix
E gerardiana	Muzei mu huang	Amphetra-Lean
E herba	Zhong ma huang	Animal Cuts
E intermedia	Country mallow	BetaLean
E shennungiana	Ephedrine	Brigham tea
E sinensis	Epitonin	Clenbutrx
E sinesis	Pinellia	Desert tea
E sinica	Popotillo	Diet Boost
E trifurca	Sea grape	Diet Fuel
	Sida cordifolia	Dyma-Burn Xtreme
	Yellow astringent	Dymetadrine Xtreme
	Yellow horse	Energel
		Herbal Phen-Fen
		Herbalife
		Hydroxycut
		Metabolife 356
		Metab-O-Lite
		Metacuts
		Mexican tea
		Morman tea
		Ripped Force
		Ripped Fuel
		Squaw tea
		Teamster's tea
		Thermadrene
		ThermaPro
		Thermo Speed
		Trim Fast
		Ultimate Energizer
		Ultimate Orange
		Ultra Chromaslim
		Xenadrine RFA-1
		Yellow Jacket

THG.[56] Bonds and others have repeatedly denied the allegations, but retroactive suspensions and penalties have occurred and are likely to continue. Tetrahydrogestrinone is known to be considerably more hepatotoxic than other steroids; its cardiac effects have not been investigated yet but are believed to be similar to those of other steroids.[57] Data are insufficient regarding the ergogenic effects of THG.

STIMULANTS

EPHEDRA

Ephedra contains several alkaloids including ephedrine, pseudoephedrine, norephedrine, methylephedrine, methylpseudoephedrine, and norpseudoephedrine.[58] These compounds directly and indirectly increase blood pressure, heart rate, cardiac output, and peripheral vascular resistance.[58,59] Ephedra has been used for treatment of asthma because of its β-adrenergic bronchodilatory effects, as a potent stimulant of the central nervous system in narcolepsy and in depressive states, and for treatment of Stokes-Adams attacks with complete heart block. Recently, ephedra has been marketed for weight loss and performance enhancement in a wide range of products (Table 3[60-62]). The widespread availability of over-the-counter products has led to the misconception that they are safe. There is evidence to conclude that short-term use of ephedra with or without caffeine promotes modest short-term weight loss.[23] Recently, ephedra has been shown to be ergogenic for anaerobic exercise, especially when taken with caffeine.[63] Unfortunately, the potential for toxicity is high, but the public often is told that adverse events are due to abuse or overdose.[24] Several authors have shown this information to be inaccurate, describing life-threatening toxicities in patients with no underlying cardiovascular disease who were using the product according to the manufacturers' recommendations.[20,24]

CARDIOVASCULAR TOXICITY OF EPHEDRA: MECHANISMS

The risk of cardiovascular events with use of ephedra has been reviewed independently and extensively and has been shown to be associated with both ischemic and hemorrhagic stroke, cardiac arrhythmias including ventricular tachycardia, coronary vasospasm, acute myocardial infarction, tachycardia-induced cardiomyopathy, and sudden death.[19,20,23,24,36,45,64] Coronary vasoconstriction, tachycardia, and hypertension are considered the mechanisms of induced myocardial ischemia and infarction. Hemorrhagic strokes are likely secondary to hypertension or cerebral vasculitis, whereas thrombotic strokes likely occur as a consequence of cerebral artery vasoconstriction and stasis-induced local thrombus formation. Reentrant cardiac arrhythmias are believed to develop because of adrenergic shortening of cardiac refractory periods.[19]

As proof of concept, a recent randomized, double-blind, placebo-controlled crossover study performed by McBride et al[25] showed QTc prolongation in healthy young men who received a single dose of an ephedra and caffeine product. The study revealed a statistically significant average prolongation of 27 ms, with 53% of participants experiencing prolongation longer than 30 ms. These findings are important, considering the removal of cisapride and terfenadine from the market for causing QTc prolongation ranging from 13 to 17 ms and considering that ziprasidone comes with a boldface warning on the package insert of a possible QTc prolongation of 20 ms.

CARDIOVASCULAR TOXICITY OF EPHEDRA: CLINICAL CONSIDERATIONS

In the past few years, ephedra and ephedrine-containing products have received considerable scrutiny because of safety concerns. In January 2002, Canada recalled all ephedra and ephedra-containing products, and on April 24, 2004, the FDA banned all ephedra use in the United States.[6,65]

A substantial number of case reports and case series have implicated ephedra in adverse cardiac events (Table 2). Even though a December 30, 2003, FDA report cited 155 ephedra-associated deaths and even with strong temporal association between ephedra use and adverse cardiac events, it has been difficult to establish direct causality.[6,24,65,66] The RAND Report,[18] released in February 2003 and commissioned by several governmental agencies to assess the safety and efficacy of ephedrine-containing products, based its conclusions on 52 clinical trials and thousands of case reports from the FDA, the medical literature, and Metabolife International Inc (San Diego, Calif), an ephedra manufacturer. The RAND Report cited sudden death, myocardial infarction, stroke, seizure, and psychiatric adverse effects (anxiety, mood changes, autonomic hyperactivity, and palpitations) as primary toxicities.

Haller and Benowitz[19] found that hypertension was the most frequent adverse event, followed by palpitations, tachycardia, or both. Sudden death was reported more frequently than myocardial infarction or arrhythmia. There also were several cases of cardiac arrest in young men with no associated medical history, as well as cases of ischemic and hemorrhagic stroke.[19] Fortunately, this problem was highlighted considerably in the press after the death of pitcher Steve Bechler, who died suddenly while using an ephedra product.[4]

Samenuk et al,[24] Theoharides,[20] and Haller and Benowitz[19] reported cases of sudden death in young men in whom autopsy revealed evidence of coronary artery disease, myocyte necrosis, necrotizing myocarditis, and cardiomyopathy. Although myocardial infarction and necrosis were believed to have been secondary to obstructive coronary artery disease, there was evidence of direct myocyte toxicity.[24] In these cases, the underlying cardiac abnormalities were believed to have been exacerbated by use of ephedra products and therefore to have been indirectly responsible for the patients' deaths.

Unfortunately, although ma huang, a natural source of ephedrine from the plant genus *Ephedra*, was banned, it has been replaced by "ephedra-like" and "ephedra-free" products that contain a substance called bitter orange or *Citrus aurantium*. This supplement is derived from a fruit that has been used in Chinese traditional medicines for centuries and is often added to caffeine as a "safe" alternative to ephedra. Few data exist regarding the toxicity or efficacy of this supplement, but it is known to contain synephrine, an α-adrenergic sympathomimetic agent. Bitter orange also inhibits the cytochrome P-450 system, responsible for the processing and the elimination of numerous commonly prescribed medications.[67] These effects, combined with the underlying potential for contamination, the possibility of mislabeling, and the variability in dosing inherent in the supplement industry give bitter orange an unknown safety profile.[2] Several researchers have called for a ban on this substance to prevent the same unnecessary loss of life that resulted from the delay in removing ephedra from the market.[67]

TABLE 4. **Caffeine Products Commonly Used in Combination With Ephedra[72,73]**

Common name	Botanical name
Cocoa	*Theobroma cacao*
Coffee	*Coffea arabica*
Guarana	*Paullinia cupana*
Kola nut	*Cola acuminata, Cola vera, Cola nitida*
Mate leaf	*Ilex paraguariensis*
Tea (black, green, oolong)	*Camellia sinensis*

CAFFEINE

Caffeine, a trimethylxanthine that acts as a phosphodiesterase inhibitor, is the most widely used drug in the world.[68] Consequently, it is one of only a few drugs for which the International Olympic Committee has established a urinary threshold; most other drugs are considered present or absent. The International Olympic Committee also recently moved caffeine from its 2004 Prohibited Substances List to its 2004 Monitoring Program list to detect patterns of misuse.[69]

Caffeine is used for its stimulant effects on the central nervous system to reduce the perception of fatigue. Also, it reportedly has adrenergic effects and may potentiate the effects of other stimulants by increasing levels of cyclic adenosine monophosphate.[20,70] Caffeine is believed to stimulate epinephrine release and to antagonize adenosine receptors centrally. Its peripheral effects include stimulation of acetylcholine release at the muscular level, mobilization of intracellular calcium, sensitization of myofibrils to calcium, induction of lipolysis, and direct stimulation of muscle cell. Caffeine alone or combined with ephedra has been shown to prolong time to exhaustion in endurance studies, more so for caffeine nonusers than for regular users.[63,71]

Fortunately, caffeine alone has been associated with no serious cardiovascular adverse effects. However, at high doses, caffeine acts as an ergolytic and leads to agitation, tremors, mental distraction, and paroxysmal arrhythmias; also, stroke has been reported with ephedra/caffeine combinations.[45] In many products, caffeine is often labeled as guarana or kola nut, both of which contain caffeine and other xanthine derivatives (Table 4[72,73]).[74] Interestingly, most products that contain ephedra also contain large quantities of caffeine, and the limited increase in exercise tolerance that is achieved with use of ephedra products has been attributed to the added caffeine.[70]

Concern is mounting for caffeine-containing energy drinks. One drink containing taurine, glucuronolactone, and caffeine has been linked anecdotally with 4 deaths in Europe.[75] Currently, it is banned in France, Denmark, Canada, and Iceland and has a strong advisory against its use in Sweden, where 3 of the known deaths have occurred.[75] To date, no known data confirm that this combination is cardiotoxic.[76] However, the drink is often mixed with alcohol and/or used before exercise. In this setting, there may be a potential for cardiotoxicity. Unpublished data from Swedish investigators suggest a temporary reduction in heart rate variability, which, combined with dehydration from exercise and the combined diuretic effects of taurine, caffeine, and alcohol, may have unknown cardiac effects.[77] Nevertheless, the data are inadequate to prove a direct relationship between caffeine-containing energy drinks and these deaths.

NONSTEROIDAL NONSTIMULANT PERFORMANCE-ENHANCING AGENTS

In addition to stimulants and steroids, various other substances are used for performance enhancement including creatine, erythropoietin, human growth hormone (hGH), and β-hydroxy-β-methylbutyrate (HMB). The data about cardiac toxicity are not consistent. Nevertheless, these substances are used widely and may have unknown health consequences.

Creatine

Of all the nonsteroidal, nonstimulant ergogenic aids, creatine is the most widely used and marketed.[78] Its prevalence ranges from sixth-grade students to professional athletes, and it is used without proper monitoring or proven efficacy.[78] Creatine, consisting of glycine, arginine, and methionine, is an amine found predominantly in skeletal muscle but also is synthesized in the liver, pancreas, and kidneys. Supplementation purportedly increases sustained maximal energy during anaerobic activities and delays muscle fatigue for short periods of time.[48,68] Supplementation is common, with 41% of 219 division I intercollegiate athletes reporting its use.[78]

The mechanism of action for creatine is believed to be as a substrate for hydrogen ions in the regeneration of adenosine triphosphate (ATP) from adenosine diphosphate. It is recommended to increase maximal energy production for short bursts—15 seconds—that depend on ATP regeneration before carbohydrate metabolism. Supplementation is touted as a way to increase the amount of surplus creatine phosphate, which, in theory, should lead to more rapid ATP regeneration after maximal energy expenditure. However, studies of the effect of creatine on athletic performance are equivocal. Saturated creatine stores at baseline may confound evaluation of its effectiveness in athletes who do not respond. Other factors that prevent adequate study include highly variable loading regimens, nonstandardized training regimens, and the difficulty associated with studying short bursts of maximal energy expenditure. Nevertheless, creatine, although ineffective for increasing endurance exercise, allows selected athletes to perform more repetitive, high-intensity exercises that may ultimately lead to increased muscle mass and better performance.[50,68] However, it was shown that prolonged supplementation did not increase muscle or whole-body oxidative capacity or substrate utilization during endurance cycling.[79]

Fortunately, the number of adverse effects are few and dose dependent, including weight gain, muscle cramps, and gastrointestinal distress.[80] However, other more serious adverse effects exist: muscle tears, electrolyte imbalance, severe dehydration with possible long-term renal damage in those with preexisting renal dysfunction, and rhabdomyolysis.[68,78,80-82] To date, there are no known cardiac adverse effects. Many of the known adverse effects are caused by an increase in intracellular osmotic load and may be exacerbated by dehydration. Although creatine supplementation appears safe relative to the absence of any major cardiovascular toxicities, its use should be monitored carefully, and its safety profile should be confirmed in prospective randomized trials.

Erythropoietin

Autologous and homologous blood doping has been prevalent since the 1970s and has been used at the elite level in sports that demand strenuous long-distance aerobic activities (eg, the Olympics and the Tour de France).[83] By inducing erythrocytosis, oxygen-carrying capacity and skeletal muscle performance are enhanced. Any additional volume shifts rapidly from the intravascular to the interstitial vascular compartment; therefore, there is no increase in cardiac output.[83] However, there are well-established adverse effects from polycythemia, including hypertension, congestive heart failure, and hyperviscosity that can lead to stroke.[83]

The widespread availability and ease of administration of recombinant human erythropoietin (rhEPO) has made this substance more popular than blood doping; consequently, rhEPO has been banned by all sporting federations. There are many concerns regarding the safety and use of rhEPO. Miscalculations in dosing and dehydration may result in a hematocrit level as high as 80% and can cause severe hyperviscosity leading to encephalopathy, stroke, seizures, and tissue hypoxia. Rapid clotting also may occur, leading to pulmonary embolism, myocardial infarction, and peripheral clot formation.[83] There have been case reports of sudden death, likely related to the aforemen-

tioned adverse effects.[84] Darbepoetin, a related substance, causes similar effects and was detected during the 2002 Winter Olympics in cross-country skiers, who subsequently were disqualified.[85] Because of the detectability of rhEPO and darbepoetin, a resurgence in blood doping has been seen. Newer strategies to evade detection and boost performance are likely to be used in the near future, including polymerized and cross-linked hemoglobins, hydroxyethylstarch, and 2,3-diphosphoglycerate mimetics.[2]

β-Hydroxy-β-Methylbutyrate

β-hydroxy-β-methylbutyrate is a metabolite of leucine that reportedly decreases catabolism and reduces total body fat while increasing lean body mass, strength, and performance.[50,86,87] Some authors have recommended its use in combination with creatine on the basis of some small studies.[88] Unfortunately, the data are inconclusive, and authors often report strong trends rather than statistically significant strength and endurance improvements. Also, there are extremely few data regarding hematologic, hepatic, renal, or cardiac activity. This lack of safety data does not justify recommending HMB as a dietary supplement.[80] Only after larger placebo-controlled trials of HMB have been performed and its adverse-effect profile has been better defined will it be possible to comment on the effectiveness and safety of HMB as a dietary supplement.

Human Growth Hormone and Insulin-like Growth Factor

Human growth hormone is used to increase fat-free mass, increase strength, and decrease recovery time in a nonsteroid-dependent fashion. Some athletes use synthetic hGH alone or with steroids, whereas others attempt to induce endogenous production of hGH by taking medications such as clonidine, levodopa, propranolol, or amino acid supplements. Adverse cardiac events from excessive use of hGH include hypertension, cardiomegaly, ventricular hypertrophy, and dyslipidemia.[80,89] Although a growing body of literature describes the beneficial cardiac effects of hGH in patients who are hGH deficient with or without cardiomyopathy, there are few data about the adverse effects of hGH on healthy hearts.[89,90] However, it has been established that patients with acromegaly have left ventricular hypertrophy secondary to progressive interstitial fibrosis, myocyte necrosis, and lymphomononuclear infiltration causing both systolic and diastolic dysfunction.[89] Rats with healthy hearts that were given hGH showed increases in myocardial growth, number of myocyte and nonmyocyte nuclei, length of capillaries, and left ventricular weight.[91] In humans, Karila et al[92] studied the effects of AAS on left ventricular dimension in power athletes with and without concomitant use of hGH. They concluded that AAS abuse was associated with myocardial hypertrophy, depending on dose, and that concomitant use of hGH further increased left ventricular mass and was associated with concentric remodeling.

Insulin-like growth factor, like hGH, is believed to increase lean muscle mass and improve muscle function, but no definitive studies support that claim. Adverse effects include acromegaly, myalgias, edema, dyspnea, and hypoglycemia.[80] Cardiac toxicities with use of insulin-like growth factor are believed to mimic those of hGH.[89]

DISCUSSION

Many drugs or nutritional substances are marketed to improve exercise duration or physical strength, shorten recovery time from exertion, or in other ways improve athletic performance. The efficacy of some supplements has been acknowledged by exercise physiologists, sports nutrition experts, or athletic organizations; however, formal toxicity studies have not been completed.

For the safety of athletes, there should be a meaningful commitment to the education of athletic coaches and trainers by athletic organizations regarding the health risks of performance-enhancing substances. For the integrity of athletics, the widespread use of steroids and other ergogenic substances should be curtailed through programs that include education, counseling, treatment, detection, and enforcement. Governing athletic bodies should use all available resources to enhance and coordinate existing efforts to educate athletes to take responsibility for the decisions they make regarding the use of nutritional supplements and performance-enhancing substances.

American and international sporting and medical communities are taking measures to address this pervasive problem. The first global anti-doping code was endorsed by a multitude of sports federations and more than 70 governments in March 2003.[93] In addition, with the recent ban on ephedra products by the FDA, dietary supplementation has come under scrutiny. Unfortunately, the medical and scientific communities' efforts at curtailing such ubiquitous and nonmedical uses are hindered by 3 major factors: public indifference,[3] product accessibility,[94] and lack of governmental regulation.[95,96] Substances such as AAS, rhEPO, and hGH, although banned in competitive athletics, have important medical uses, are not illegal with a prescription, and can be obtained illegally with relative ease. Compounding the problem, designer drugs such as THG are being developed constantly to escape detection.

Performance-enhancing substances that are described as supplements, vitamins, or minerals are marketed as nutritional supplements and are protected from FDA regulation by the 1994 US DSHEA.[95-98] Manufacturers of these products are not required to demonstrate proof of efficacy or

safety and lack a regulatory body responsible for evaluating their products for purity. Contamination and mislabeling occur frequently, and banned substances have been detected in over-the-counter formulations (eg, 19-norandrosterone in andro tablets).[99] Consequently, extremely few safety or efficacy data are available and even fewer randomized, double-blind, placebo-controlled trials. Furthermore, the existing scientific data are difficult to generalize to the practices of the greater population. Supranormal doses are taken frequently, and substances often are mixed either as marketed products or surreptitiously (ie, caffeine/ephedra, stimulants/alcohol, steroids/amphetamines). There is also a need for long-term, sex-specific, and pediatric data.

As long as manufacturers make nonspecific "structure-function" claims (ie, boosts immune system, increases stamina), the burden of proof lies with the FDA to prove a supplement causes "significant or unreasonable risk of illness" before it can be discontinued.[95-97,100,101] It is evident that a reevaluation of the 1994 US DSHEA will be an important part of addressing the problem of performance-enhancing substances in athletics.

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