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REVIEW ARTICLE

Performance-Enhancing Substances in Sports: A Review of the Literature

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Abstract Performance-enhancing substances (PESs) have unfortunately become ubiquitous in numerous sports, often tarnishing the spirit of competition. Reported rates of PES use among athletes are variable and range from 5 to 31 %. More importantly, some of these substances pose a serious threat to the health and well-being of athletes. Common PESs include anabolic–androgenic steroids, human growth hormone, creatine, erythropoietin and blood doping, amphetamines and stimulants, and beta-hydroxy-beta-methylbutyrate. With recent advances in technology, gene doping is also becoming more conceivable. Sports medicine physicians are often unfamiliar with these substances and thus do not routinely broach the topic of PESs with their patients. However, to effect positive change in the sports community, physicians must educate themselves about the physiology, performance benefits, adverse effects, and testing methods. In turn, physicians can then educate athletes at all levels and prevent the use of potentially dangerous PESs.

Key Points

Performance-enhancing substance (PES) use among athletes remains high and can pose a threat to the health and well-being of athletes.

Sports medicine physicians should be knowledgeable on the variety of PESs available in order to better advise athletes on the risks and benefits.

Through early education and awareness programs, health professionals can curb the use of banned or illicit PESs.

1 Introduction

Performance-enhancing substances (PESs) have become widespread and a serious issue in sports. Often referred to as 'doping', the use of PESs refers to the use or manipulation of substances, synthetic or autologous, with the intention of altering sports performance. Greater media coverage coupled with improved and more frequent testing has brought further attention to the use of PESs by professional athletes over the past few decades. However, athletes at all levels, seeking to attain the highest performance, continue to use PESs despite the potential health risks and penalties [1, 2]. Physicians need to be aware of the prevalence of PESs in sports and their potential deleterious effects. With greater understanding, physicians can better educate athletes on PESs and curb the use of substances that may ultimately harm the athlete.

The concept of PESs has been a part of competitive sport since its inception. Both Greek athletes competing in

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the ancient Olympics and Roman gladiators used certain wines, herbal teas, and mushrooms to help enhance performance [1, 2]. Since then, PESs have evolved with advances in pharmaceutics. In 1998, a large number of PESs were found during a raid at the Tour de France. This event triggered the creation of the World Anti-Doping Agency (WADA) in 1999 as an independent international agency with the mission to create a doping-free sporting environment. WADA labels a substance as banned in competition if two of the following three criteria are met: (1) enhances sport performance, (2) poses a risk to health, or (3) violates the spirit of the sport [3]. WADA publishes the World Anti-Doping Code, which has been adopted by several sporting organizations across the world, including the International Olympic Committee (IOC). WADA works closely with smaller anti-doping agencies on several fronts, including the implementation of the code and accreditation of testing laboratories. Although WADA may establish guidelines for sanctions, the ultimate decision is left to the specific league in which the athlete participates.

In addition to the Tour de France, recent investigations surrounding Major League Baseball (MLB) have brought greater attention to PESs and drawn attention from the US Congress. The commissioner of the MLB appointed George Mitchell, a former Democratic senator, to investigate the use of PESs in the MLB. After a lengthy investigation, the Mitchell Report was released, which named 89 baseball players alleged to have used PESs [4]. Seeing this issue as a national health policy concern, the US government decided to hold congressional hearings, during which specific high-profile players were interrogated.

The purpose of this article is to summarize the prevalence of PESs among athletes, the physiology and effects of common PESs, and the evolution of drug testing (Table 1). Furthermore, we discuss ways to prevent PES use. PubMed searches were performed corresponding to each section in this manuscript with associated keywords such as 'anabolic steroids' or 'gene doping.' An emphasis was placed on highlighting literature published within the last decade to provide readers with current, evidence-based medicine. The authors also cited articles based on the strength of the study design.

2 Epidemiology

Although numerous studies have attempted to determine the prevalence of PES use, much of the data are limited to self-reported surveys, which are subject to response error. Nonetheless, the overall incidence of PES use among athletes at all levels appears to be high. Current reported rates of PES use among athletes are variable and range from 5 to 31 % [5–10].

Dietz et al. [11] conducted an anonymous questionnaire to gauge the rate of use of illicit or banned substances among triathletes in Germany. Among 2,987 respondents, 13.0 % reported the use of illicit or banned substances to improve physical performance. Furthermore, the study also reported a 15.1 % rate of cognitive doping—that is, the use of substances that enhance focus, learning performance, and memory.

Another study in Germany evaluated the rate of doping and illicit drug use by elite athletes and compared it with outcomes of official doping tests. The athletes were questioned using either an anonymous standardized questionnaire or interviewed using a randomized response technique. The authors reported a 6.8 % doping rate, which is in stark contrast to the 0.81 % positive test results from official doping tests conducted by the WADA and National Anti-Doping Agency (NADA) [12].

Buckman et al. [10] conducted a study on 234 male student athletes at one university to evaluate the risk profile of those who use PESs. The study based its definition of a PES on a published National Collegiate Athletic Association (NCAA) classification that included both licit and illicit substances. The study reported a 31 % usage rate of PES in the year prior to the survey. Among those using PESs, 31 % reported using banned substances. The study concluded that those using PESs were more likely to engage in other substance use behaviors (e.g., binge drinking). The study cited the limited number of subjects as a potential weakness.

PES use has also been examined with respect to sex and sport by a recent NCAA survey study [13]. The percentage of female athletes who reported anabolic steroid use in the previous 12 months was 0.1 % during the 2013 year compared with 0.7 % of male athletes. Particular substances were found to be associated with certain men's sports: anabolic–androgenic steroids (AAS) with lacrosse (1.7 %), American football (0.7 %), and baseball (0.7 %); human growth hormone (hGH) with baseball (1.3 %) and lacrosse (1.1 %); and creatine with wrestling (28.5 %), baseball (28.1 %), and American football (27.5 %).

3 Substances

Commonly used PESs among athletes include AAS, hGH, creatine, erythropoietin (EPO), blood doping, amphetamines and stimulants, and beta-hydroxy-beta-methylbutyrate (HMB). Gene doping has also received concern recently as technology allows it to become more conceivable.

3.1 Anabolic–Androgenic Steroids

AAS have traditionally received the greatest attention among PESs in sports. Examples of AAS include

Table 1 Reference guide to performance-enhancing substances

Performance-enhancing substance	Desired effects	Major adverse effects	Minor adverse effects	Status	Route of administration	Testing/detection method	Mechanism of action
Anabolic–androgenic steroids	Increase muscle size, strength, lean body mass; decrease body fat	Testicular atrophy, CV disease, atherosclerosis, myocardial disease, liver dysfunction, cancer	Acne, gynecomastia	Banned by IOC and all major sporting bodies	Oral, topical, injectable	Urine immunoassay, chromatography, mass spectrometry	Upregulation of genes responsible for muscle growth, counteracts catabolic effects of glucocorticoids
Creatine	Increase in strength, power output, sprint performance, total work to fatigue, peak force/power; decrease lactate threshold; increase weight and lean body mass	Heatstroke	Dehydration	Allowed	Oral	N/A	Provides an energy substrate to allow for contraction of skeletal muscle
Human growth hormone	May increase lean body mass and decrease fat mass	Carpal tunnel syndrome, pseudotumor cerebri, CV disease, hyperlipidemia, insulin resistance	Arthralgias	Banned by IOC and International Federations	Injectable	Recombinant hGH: naturally derived hGH ratio	Promotes growth through action of insulin-like growth factor-1, protein anabolism, lipolysis
Amphetamines/stimulants	Increase in alertness and metabolism; may increase strength, muscular power, speed, acceleration, aerobic power, anaerobic capacity, endurance	Arrhythmias, heat exhaustion, seizures, myocardial infarction, sudden death	Agitation, GI upset, nausea, headaches, insomnia, hallucinations	Banned by IOC, NCAA, NFL	Oral, injectable, inhalable	Urine quantitative analysis	Central nervous system stimulant through stimulation of norepinephrine
Erythropoietin/blood doping	Increase in oxygen-carrying capacity, endurance	Hypertension, myocardial infarction, pulmonary embolism, immune reaction	Headaches	Banned by IOC and all major sporting bodies	Injectable	Athlete biologic passport (hemoglobin mass)	Stimulates increased production of erythrocytes leading to increased hematocrit and higher oxygen-carrying capacity
Beta-hydroxy-beta-methylbutyrate	May increase lean body mass, muscle strength, power; enhance recovery	Unknown	Unknown	Allowed	Oral	N/A	Upregulation of mTOR/p70S6 K pathway, promoting protein synthesis and muscle hypertrophy, decreased proteolysis, decreased LDH production

Table 1 continued

Performance-enhancing substance	Desired effects	Major adverse effects	Minor adverse effects	Status	Route of administration	Testing/detection method	Mechanism of action
Gene doping	Dependent on targeted protein	Immune reaction, cancer, overexpression of gene product, germ line modification	N/A	Banned by IOC	Injectable, inhalation	No WADA-approved detection methods exist	Transcription and production of specific targeted protein

CV cardiovascular, *GI* gastrointestinal, *hGH* human growth hormone, *IOC* International Olympic Committee, *LDH* lactate dehydrogenase, *mTOR* mechanistic target of rapamycin, *N/A* not applicable, *NCAA* National Collegiate Athletic Association, *NFL* National Football League, *WADA* World Anti-Doping Agency

testosterone, methyltestosterone, and danazol. A recent meta-analysis by Sagoe et al. [14] reported a global lifetime prevalence of the use of AAS of 6.4 % for males and 1.6 % for females. Moreover, the prevalence of AAS use was highest among recreational and competitive athletes, and the odds of AAS use increased by 91 % with participation in at least one sport. The study also found that the prevalence of AAS use was slightly higher in the 2000s than in the 1990s. Even among adolescents, the rate of AAS use is high. In a questionnaire study of high school varsity football players in the USA, 6.3 % reported that they were either current or former AAS users, with the average age at first use being 14 years [15].

Designer steroids have also played a greater role in sports medicine over the past two decades [16, 17]. These steroids are chemically modified from known banned anabolic steroids in an attempt to avoid detection. Tetrahydrogestrinone (THG) has become one of the most popular and widely known designer steroids [14, 15].

Androstenedione, a precursor to testosterone, has also become popular, especially after MLB player Mark McGuire admitted to using it [18]. The mechanism of action is believed to be related to its degradation into testosterone.

3.1.1 Physiology

The human body naturally produces testosterone, an endogenous anabolic steroid responsible for male secondary sexual characteristics and muscle and bone metabolism. AAS are synthetic derivatives of testosterone. AAS bind to an androgen receptor (AR) in the cytoplasm of target tissues, triggering a molecular cascade that results in androgenic and anabolic effects similar to those caused by testosterone. Specifically, the AR is involved in the regulation of transcription of genes responsible for muscle growth. Furthermore, the enzyme 5-alpha-reductase plays a crucial role by converting AAS into dihydrotestosterone, which can also act on the AR. In addition, AAS displace cortisol from its receptors and thus counteract the catabolic effects of glucocorticoids [19].

3.1.2 Performance

Due to the lack of consistency with regard to dosing and methods in previous studies, it is difficult to compare clinical trials studying performance and AAS. Studies have shown that the main benefit of AAS on performance is related to increased muscle size, strength, and lean body mass [20–22].

Bhasin et al. [20] showed that men who took supraphysiologic doses of testosterone, coupled with exercise, increased fat-free mass and muscle size and strength. In

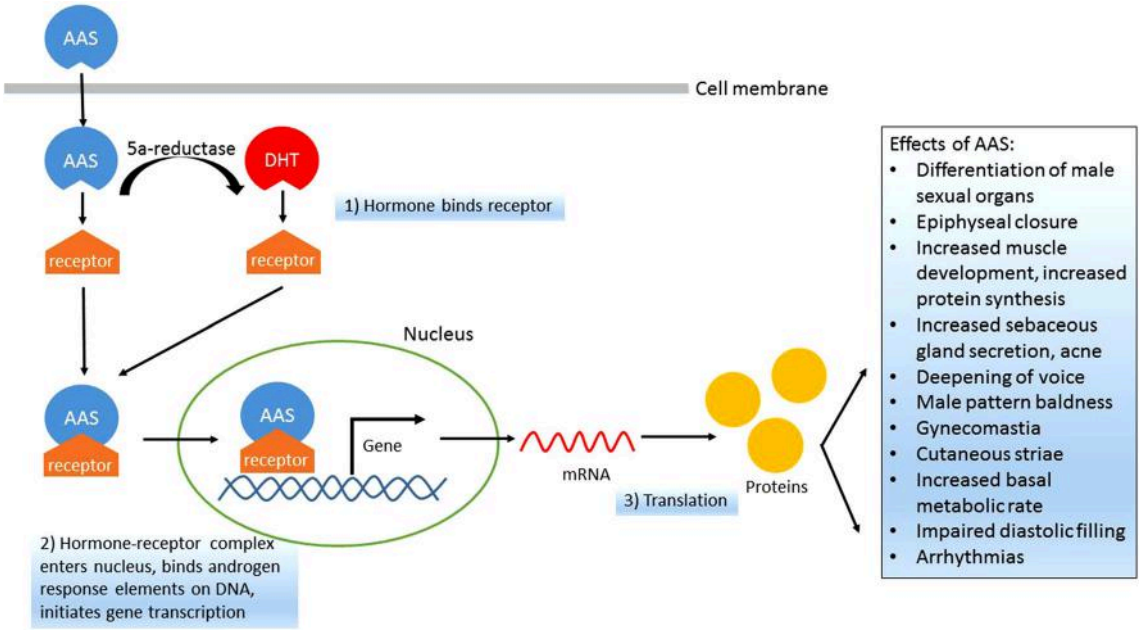

Fig. 1 The physiology of anabolic–androgenic steroids and their downstream effects. *AAS* anabolic–androgenic steroids, *DHT* dihydrotestosterone, *DNA* deoxyribonucleic acid, *mRNA* messenger ribonucleic acid

another study, Giorgi et al. [22] randomly assigned 21 male weight training subjects to either a testosterone or a placebo group. Over a 12-week period, those in the testosterone group demonstrated significantly greater increases in muscle strength and circumference and decreases in abdominal skinfold measurements than the placebo group. No studies to date have demonstrated beneficial effects of AAS on endurance performance [23].

Specifically, with regard to androstenedione, no studies have demonstrated any significant ergogenic effect. In a double-blinded study of 50 men who participated in a 12-week high-intensity resistance program, androstenedione was not shown to enhance adaption to resistance training in terms of body composition or strength [24]. Other studies have reached similar conclusions [25, 26].

3.1.3 Adverse Effects

Common side effects of AAS use include acne, testicular atrophy, gynecomastia, cutaneous striae, and injection site pain. Additionally, life-threatening side effects include cardiovascular disease with impaired diastolic filling, arrhythmias, stroke, blood clots, liver dysfunction, and cancer [27].

The most important cardiovascular changes involve increases in triglyceride levels, increases in concentrations of several clotting factors, and changes in myocardium, including increases in left ventricular mass and dilated cardiomyopathy. These effects vary depending on the type and dose of AAS and may be reversible with cessation of use. Other adverse effects include reductions in endogenous testosterone, gonadotropic hormones, and sex hormone-binding globulin. Reductions in these hormone levels result in decreased testicular size, sperm count, and sperm motility [28]. The physiology of AAS and their downstream effects are shown in Fig. 1.

Due to concern for neurotoxic effects from AAS use, a study was conducted to evaluate for cognitive deficits among long-term AAS users when compared with nonusers. A long-term user was defined as an individual who had used AAS for at least 2 years. Long-term users and nonusers did not differ significantly in response speed, sustained attention, and verbal memory. However, visuospatial performance was significantly lower among those who reported long-term use of AAS. Furthermore, within the user group, visuospatial performance negatively correlated with the total lifetime dose of AAS [29].

3.1.4 Testing

Testing for steroids is often performed with a urine immunoassay used to calculate a testosterone: epitestosterone ratio. Epitestosterone is a metabolite that is not affected by exogenous steroids. Increases in this ratio, therefore, help determine AAS use. Ratios are typically less than 2:1; the WADA has set the upper limit at 6:1 [30]. Much of the focus on urinary metabolites has focused on long-term metabolites, which allow for a longer detection window.

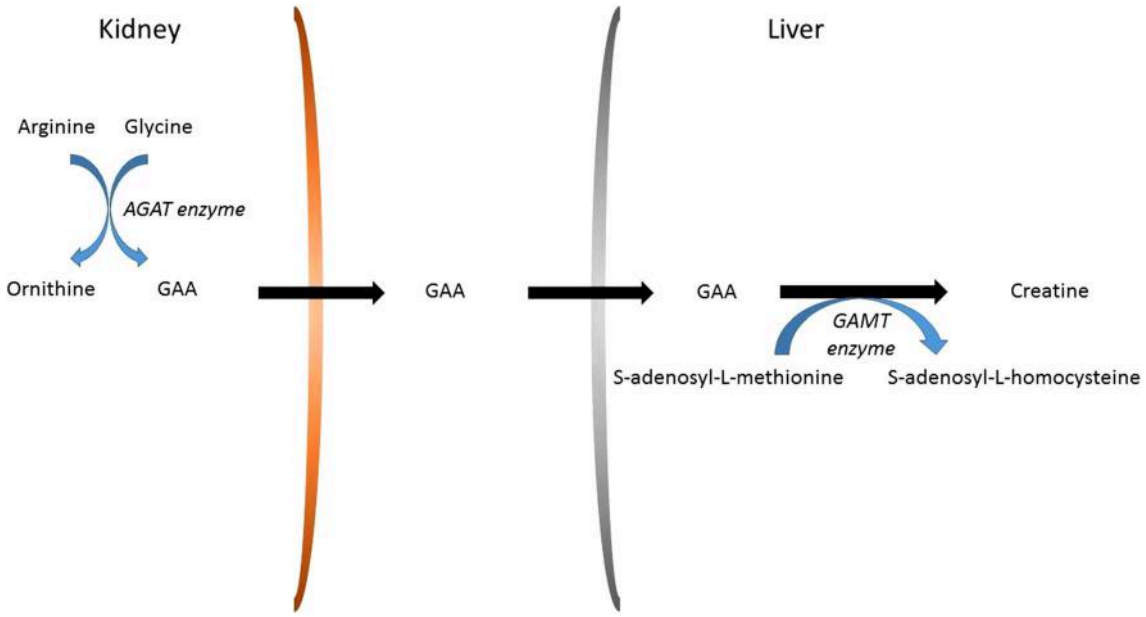

Fig. 2 The creatine pathway. *GAA* guanidinoacetate, *AGAT* arginine:glycine amidinotransferase, *GAMT* guanidinoacetate methyltransferase

Recently, more attention has been directed at chromatographic and mass spectrometric techniques, which can help differentiate natural and synthetic endogenous steroids.

Designer steroids remain difficult to detect. Strategies to combat designer steroid use have focused on two methods. One method centers on a non-targeted approach. The basis for this approach is that designer steroids have common chemical structures to known endogenous steroids. Thus, by searching for these commonalities, one may identify abnormally high levels of certain steroids. Another method involves an indirect approach, examining the effects of exogenous steroids on the profile of endogenous steroids. For example, it is known that the administration of AAS suppresses endogenous steroid concentrations, and such a finding in an athlete may trigger a search for designer steroid use [30].

3.2 Creatine

Creatine is one of the most common sports supplements used today, with sales estimated around $US400 million annually [31]. Creatine monohydrate is a naturally occurring compound synthesized endogenously and consumed in most diets. It has been studied since the 1920s and gained notoriety by its mainstream use in the 1992 Barcelona Summer Olympics [32].

In a large-scale survey of approximately 21,000 student athletes, the NCAA reported that creatine use in the 12 months prior to the survey was 14.0 % among all athletes. Usage rates were highest among wrestlers at 29 % [13].

3.2.1 Physiology

Creatine is an amino acid formed from arginine and glycine through a transferase enzyme that produces ornithine and guanidinoacetate. The guanidinoacetate is then methylated by S-adenosyl-L-methionine to form creatine. This process occurs largely in the kidney, except for methylation, which occurs in the liver (Fig. 2). A total of 95 % of the creatine formed is stored in skeletal muscle, specifically in fast twitch type II fibers [31].

Creatine serves as an energy substrate for the contraction of skeletal muscle. Those cells with a high energy demand utilize creatine in the form of phosphocreatine, which functions as a donor of phosphate to produce adenosine triphosphate (ATP) from adenosine diphosphate (ADP). Skeletal muscle cells store enough phosphocreatine and ATP for about 10 s of high-intensity action [33].

3.2.2 Performance

Numerous studies have been performed on creatine supplementation and its role in enhancing sports performance. Increases in strength, power output, sprint performance, total work to fatigue, peak force, and peak power performed during multiple sets of maximal-effort contractions have been shown [27].

Specifically, in cyclists, several studies have shown that creatine helps maintain force and power output [34–36]. Oliver et al. [37] examined the effect of creatine on blood lactate levels during cycling. A total of 13 recreationally active men were placed on a 6-day creatine

supplementation program and tested before and after with maximal, incremental cycling. Blood tests demonstrated that creatine supplementation decreased lactate levels and tended to raise lactate threshold. The lactate threshold was defined as 4 mmol/L, above which it becomes very difficult to maintain exercise performance.

The beneficial effects of creatine have also been demonstrated in other sports. Weight lifters have reported increased single repetition maximum weight of approximately 20–30 % [38, 39]. Track and field athletes have demonstrated a decrease in mean sprint times [40]. However, competitive swimmers did not demonstrate improvements in sprint performance with creatine supplementation [41]. With regard to body composition, weight and lean body mass tend to increase by about 1–2 kg [27, 42, 43].

Most studies have examined short-term (less than 1 week) creatine use. A recent study by Claudino et al. [44] examined chronic (7 weeks) creatine supplementation in elite soccer players. Although jumping performance was lower in the placebo group, the difference did not reach statistical significance. However, the study was limited by a small sample size.

Results have been inconsistent with regard to the effects of creatine [18]. Some athletes appear to be 'responders' while others are 'nonresponders.' These discrepancies can likely be explained by the idea of preloading muscle creatine—that is, those with higher baseline levels of creatine before supplementation will exhibit less of an increase in muscle creatine with supplementation than those with lower baseline levels of creatine [45, 46].

3.2.3 Adverse Effects

Short-term creatine use is regarded as safe and without significant adverse effects [27]. However, the number of long-term studies is limited, and caution should be exercised in the setting of renal and liver disease [27].

There is a theoretical risk of dehydration caused by the use of creatine, as its osmotic effect can lead to water being drawn into muscles. Athletes are encouraged to maintain adequate hydration while using creatine. Bailes et al. [47] postulate that creatine may be linked to subclinical dehydration and heatstroke. Wen et al. [48] report two cases of otherwise healthy athletes sustaining venous thromboembolisms (VTE) and suspect a link to creatine. They report that the dehydration, caused by the creatine, was a precipitating factor for the VTE.

There are also concerns with regard to renal function due to the large creatine load, but one study that monitored creatine supplementation for up to 5 years did not reveal a decrease in glomerular filtration rate [49].

3.2.4 Testing

Creatine is available as an over-the-counter nutritional supplement and is found in various forms. It is not tested for nor banned by any major athletic organization. However, the NCAA does have a policy that none of its member teams will provide creatine to their players [50].

3.3 Human Growth Hormone

The use of hGH as a supplement for performance enhancement has received worldwide attention over the past decade. Athletes from numerous sports have admitted to the use of hGH [13]. Further attention was brought upon hGH after the Mitchell report, which identified numerous MLB players as having used PESs, one of which was hGH [4].

One study published in 1992 surveyed high school students and reported a 5 % use of hGH in male students, while 31 % of males reported knowing someone who was using hGH. These users also were more likely to abuse anabolic steroids. The average age at first use was between 14 and 15 years [51]. A 2013 NCAA survey study reported that 0.4 % of student athletes admitted to using hGH in the previous year [13].

3.3.1 Physiology

hGH is released by the somatotrope cells of the anterior pituitary gland, and it promotes growth through the actions of insulin-like growth factor-1. These hormones cause an increase in lipolysis and protein anabolism, ultimately resulting in a decrease in fat mass and an increase in lean mass [27]. In adolescence, the pulsatile release of hGH is regulated by a number of factors, including growth hormone-releasing hormone, sleep, exercise, L-dopa, and arginine [18].

3.3.2 Performance

Few studies have been conducted regarding performance and hGH use. Postulated benefits include improved athletic performance via increased muscle mass and improved exercise capacity [52]. However, scientific evidence has failed to demonstrate an ergogenic effect with supraphysiologic doses of hGH, although doses studied may be lower than those used by athletes [53].

With regard to body composition, lean body mass increases while fat mass decreases significantly with hGH. However, the overall increase in weight is not significant [52]. One study investigated strength outcomes in 22 healthy men. A double-blind protocol was employed with

an hGH group and a placebo group. Urine specimens were tested to ensure no concurrent AAS use. hGH was not shown to increase biceps or quadriceps strength with one repetition maximum strength testing [54]. In another study, changes in muscle circumference between groups treated with hGH versus placebo were not shown to be significant [55]. Furthermore, no benefits in maximal oxygen consumption (VO_{2max}), respiratory exchange ratio, energy expenditure, bicycling speed, or power output have been shown [52]. The major limiting factor in these studies involves the lack of dosing standardization.

Use of hGH appears to continue despite the lack of evidence-based medicine to support its use in athletes. Many of the purported benefits may stem from the theoretical benefits from known physiologic pathways. However, such effects may apply only to those who are growth hormone deficient and not to athletes.

3.3.3 Adverse Effects

Chronic use of hGH can lead to multiple adverse effects. Because hGH activates the renin-angiotensin system, it can cause fluid accumulation, thus leading to arthralgias, carpal tunnel syndrome, and pseudotumor cerebri. Reported effects also include cardiovascular disease, hyperlipidemia, cancer, and insulin resistance [56].

3.3.4 Testing

hGH exhibits a very short half-life in blood and a low concentration in urine, making it difficult to detect. Furthermore, due to the pulsatile nature of hGH secretion, there are wide fluctuations in circulation. hGH is also often affected by sleep, exercise, stress, and nutrition [57].

Nonetheless, the most reliable method that currently exists focuses on the ratio of concentrations of recombinant hGH versus naturally derived isotopes of hGH. Limits are set based upon ratios collected in routine hGH testing of athletes [58].

3.4 Amphetamines and Stimulants

Stimulants have been used in sports to enhance performance throughout history, but in the past decade these drugs have gained attention due to the deaths of two professional athletes who were reportedly using ephedrine [18]. Commonly used stimulants include amphetamines, caffeine, ephedrine, pseudoephedrine, phenylephrine, and methamphetamines.

In a recent survey of nearly 21,000 students in grades 8–10 in the USA, an increased use of amphetamines was seen among males who participated in lacrosse (adjusted odds ratio 2.52) and wrestling (adjusted odds ratio 1.74) [59]. In contrast, no association among females and sporting type was found for amphetamine use. Stimulants have accounted for nearly 10 % of adverse analytical findings by the WADA in 2010. Furthermore, they have been the second most common reason for a positive test in recent years [27]. Another study involving drug testing of several high schools in the USA found that 543 (16.6 %) of 3,000 samples were positive for drugs of abuse. Most commonly, these positive results were for central nervous system (CNS) stimulants. However, sampling was not limited to athletes [15].

3.4.1 Physiology

Amphetamines are CNS stimulants and chemically related to catecholamines. They exhibit an indirect sympathomimetic action by causing the release of norepinephrine from storage vesicles in the sympathetic nerve endings. Norepinephrine then leads to the classic sympathetic effects, including increased arousal, heart rate, blood pressure, and respiratory rate [27]. Half-lives have been reported in pharmacology studies: 19.4 h for amphetamines [60], 5.7 h for caffeine [61], 6.1 h for ephedrine [62], and 7 h for pseudoephedrine [63]. The route of administration for these substances is usually oral, but they can also be injected.

3.4.2 Performance

One study that has closely examined amphetamine use and athletic performance is by Chandler and Blair [64]. Six male college students were tested, and amphetamine use was associated with increased strength, muscular power, speed, acceleration, aerobic power, and anaerobic capacity. There was also an increased time to exhaustion, although no increase in VO_{2max} was seen. In another study, pseudoephedrine was shown to increase maximum torque, peak power, and lung function during a maximal cycle performance [65]. Some studies have demonstrated improved times for medium distance runs with the pre-ingestion of caffeine and ephedrine [66, 67].

Specifically, caffeine has been widely studied with regard to performance in sports. It has been shown to reduce reaction time and delay fatigue in taekwondo [68], improve cycling time trials in triathletes [69], and decrease times in cross country double poling [70]. However, other studies have not shown significant improvement with caffeine. In a study with 11 female athletes performing repeated sprint cycling, neither ingestion of caffeine plus placebo nor caffeine plus carbohydrate improved repeated sprint performance with short rest intervals [71]. Many athletes use caffeine to counter sleep deprivation, but a study on semi-professional tennis players showed that caffeine did not

make up for lost sleep with regard to serving accuracy [72]. Further studies should be performed to elucidate the prevalence of caffeine use by athletes with respect to insufficient sleep.

Other stimulants such as ephedrine and ephedra alone have shown little efficacy or benefit in athletic performance [73]. Shekelle et al. [74] performed a meta-analysis of 52 controlled trials and 65 case reports regarding ephedrine and ephedra. When examining outcomes as related to athletic performance, there were no significant effects. However, the analysis did find that these drugs promoted a modest short-term weight loss.

3.4.3 Adverse Effects

The side effects of stimulants relate to their effects on increasing CNS stimulation. Common side effects include restlessness, agitation, gastrointestinal upset and nausea, headaches, rebound fatigue; serious adverse effects include heat exhaustion, arrhythmias, seizures, hallucinations, and dependence [27, 75]. From 1994 to 1997, the Food and Drug Administration reviewed over 800 cases of ephedra adverse effects, which included hypertension, myocardial infarction, arrhythmias, anxiety, tremors, stroke, and death [76].

3.4.4 Testing

Several classes of amphetamines are banned by the IOC, and the National Football League (NFL) has banned the use of ephedrine. Testing for amphetamines and stimulants involves quantitative tests to detect their presence in urine. Specifically, the NCAA has limited caffeine levels to 15 μg/ml in urine, which is equivalent to approximately six regular sized cups of coffee [77].

3.5 Erythropoietin and Blood Doping

Athletes, especially endurance athletes, benefit from improved delivery of oxygen to their tissues. Such improved oxygen delivery affords athletes improved aerobic capacity. One method by which athletes attempt this is by living or training at high altitudes, which is often thought of as a natural way to improve oxygen delivery [78]. Another method used involves blood transfusions, most commonly autologous. Such a transfusion would artificially increase hematocrit and thus oxygen-carrying capacity. Another artificial method by which athletes have been known to gain an advantage is through the administration of EPO, which is responsible for erythropoiesis.

The rate of use of EPO or blood doping is difficult to quantify. However, it is estimated that such techniques have been widely used throughout endurance sports [18]. One Spanish doping investigation revealed that several athletes had employed the systematic use of autologous blood transfusions. Officials discovered several frozen blood units in addition to calendars with reinfusion dates [79].

3.5.1 Physiology

EPO is a glycoprotein hormone that plays an important role in the differentiation, survival, and proliferation of erythroid cells. EPO is produced mostly in the kidney. In response to hypoxic stress, the body produces a greater amount of EPO. The EPO then binds to the EPO receptor on the red cell progenitor surface. Such binding stimulates a cascade that leads to the increased production of erythrocytes. Such increases in hematocrit lead to higher oxygen-carrying capacities [80].

3.5.2 Performance

Several studies have documented the performance enhancement benefits of blood doping. In one study, after an autologous transfusion of 750 ml of red blood cells, the VO_{2max} increased by 12.8 %, and performance times on a treadmill test to exhaustion improved significantly [81]. Other studies have shown decreased times in cross country skiers [82] and in runners during a 10 km race [83].

A double-blind, placebo-controlled study by Birkeland et al. [84] evaluated cycling performance after administration of recombinant human erythropoietin (rhEPO). Mean VO_{2max} increased by 7 % in the EPO group from 63.6 to 68.1 mL kg^{-1} min^{-1}, while mean hematocrit increased from 42.7 to 50.8 %. Both of these changes were significant. Another study, by Berglund and Ekblom [85], showed similar results.

3.5.3 Adverse Effects

The side effects of EPO should not be underestimated. These adverse effects include hypertension, headaches, and an increased risk for a thromboembolic event due to the rise in hematocrit and viscosity [77]. Furthermore, with large doses, EPO may cause death [80]. During the first year EPO was released, five Dutch cyclists died of unexplained causes. In a 4-year span, between 1997 and 2000, 18 cyclists died from stroke, myocardial infarction, or pulmonary embolism [18].

With regard to blood transfusions, similar risks may be encountered when elevating hematocrit and thus blood viscosity. When homologous transfusions are employed, there is also the risk for transfer of infection such as hepatitis and HIV and major transfusion reactions from blood type incompatibility [86].

3.5.4 Testing

Testing for autologous blood transfusions remains difficult. No direct detection method has been implemented by the WADA. Sophisticated algorithms help detect possible autologous blood transfusions, and these algorithms are based on the total amount of circulating hemoglobin and the percentage of reticulocytes. Because of lower variability with total hemoglobin mass compared to hemoglobin, it has been proposed as a parameter in the Athlete Biologic Passport (ABP). The ABP entails measuring certain biological parameters over time for an athlete. The assumption is that these variables will remain stable over time. Any changes in the ABP would trigger a suspicion for doping. Thus, instead of solely relying on direct testing for banned substances, organizations can incorporate the ABP to help indirectly identify athletes who may be doping [87].

A number of detection methods for rhEPO exist, but it remains difficult to detect exogenous EPO. Such tests include measurement of hematologic parameters, gene-based detection methods, use of peptide markers, electrophoresis, and isoelectric focusing among numerous other methods [80].

3.6 Beta-Hydroxy-Beta-Methylbutyrate

HMB is a metabolite of the amino acid leucine and is a precursor to cholesterol. It is believed to attenuate protein breakdown after workouts and has recently gained greater attention among athletes [88]. A 2013 NCAA survey study reported a 0.2 % rate of use among all student athletes [13]. However, it appears that HMB is increasingly being added to many training regimens [88].

3.6.1 Physiology

There are several proposed mechanisms by which HMB acts. One of the primary mechanisms involves the up-regulation of the mechanistic target of rapamycin/p70S6K signaling pathway, which promotes protein synthesis and muscle hypertrophy [89].

Other studies have focused on the anti-catabolic effects of HMB. Smith et al. [90] demonstrated that HMB preserved lean body mass and decreased proteolysis through the down-regulation of the increased expression of certain components of the ubiquitin–proteasome proteolytic pathway. Some studies have examined HMB and its effect on muscle by measuring markers of muscle breakdown. Wilson et al. [91] demonstrated that when non-resistance-trained males received HMB pre-exercise, the rise of lactate dehydrogenase (LDH) levels reduced, and HMB tended to decrease soreness. Knitter et al. [92] showed a decrease in LDH and creatine phosphokinase (CPK), a byproduct of muscle breakdown, by HMB after a prolonged run.

3.6.2 Performance

Several studies have been performed with regard to HMB and performance. However, it is difficult to compare the various studies due to different dosing schedules and amounts of HMB, previous training levels of participants, and different performance outcomes.

Kraemer et al. [93] showed that HMB intake in healthy men who underwent a 12-week course of heavy resistance training increased lean body mass, muscle strength, and power with regard to squatting and bench press when compared with a placebo group. Nissen and Sharp [94] performed a meta-analysis and found that HMB increased strength and lean tissue through resistance training. However, when specifically examining trained subjects, some studies have shown no effect. In one study of American collegiate football players [95], no significant effect of HMB on creatine kinase, power, or muscle soreness was observed. In another study on trained American collegiate football players, no effects were demonstrated by HMB when studying bench press, power cleans, squats, or sprint performance [96].

Despite differences in these studies, it does appear that HMB overall enhances muscular hypertrophy, strength, and power. In fact, the International Society for Sports Nutrition, in a position statement, writes that HMB can be used to enhance recovery by reducing skeletal muscle damage after exercise in athletically trained and untrained people. The utility of HMB does seem to be affected by timing of intake prior to workouts and dosage [97]. Further, chronic consumption of HMB appears safe [97].

3.6.3 Adverse Effects

No serious adverse effects from HMB consumption have been reported. In one study, 37 college males took HMB for an 8-week period during resistance training. No adverse effects were seen with regard to blood glucose, blood urea nitrogen, hemoglobin, hepatic enzymes, lipid profile, leukocytes, urine pH, urine glucose, or urine protein excretion [98]. Similarly, Nissen et al. [99] evaluated nine studies and found that HMB was a safe ergogenic aid. In fact, HMB lowered total cholesterol, low-density lipoprotein cholesterol, and systolic blood pressure, thus demonstrating potential cardioprotective effects.

3.6.4 Testing

Currently, HMB is available as an over-the-counter supplement. The drug is not tested for nor banned by any sporting organization.

3.7 Gene Doping

As the field of genetics continues to advance and techniques to modify human genes become more readily available, gene doping draws closer to reality. Gene doping is defined as the "transfer of nucleic acid sequences or the use of normal or genetically modified cells to enhance sports performance" [100]. To date, there is no evidence that gene doping has been employed for sports enhancement.

3.7.1 Physiology

Numerous proteins have been identified for targets of gene doping based on potential and include EPO, insulin-like growth factor, hGH, myostatin, vascular endothelial growth factor, fibroblast growth factor, endorphin, and encephalin [100].

Methods such as injection or inhalation could be used to deliver genetic material containing specific genes into the athlete's body. Once the genetic material is incorporated into the DNA in the nucleus of the cell, the specific gene sequences would be transcribed, resulting in the increased expression of the specific protein encoded by the delivered gene [101]. Various delivery methods have been proposed and studied for such a process. In general, the athlete's cells are isolated from the body, modified in vitro, and transplanted back into the athlete (direct transplant) [102]. There are two methods to modify the athlete's cells in vitro. One method involves DNA transfection, through which non-viral transporters such as liposomes deliver plasmid DNA containing the gene material into the cells. The transfection method would likely have a short duration of action on the order of days to weeks [103]. A second method involves transduction with inactive viral vectors. Such a technique would likely lead to a longer duration of action on the order of months to years (Fig. 3) [104].

3.7.2 Adverse Effects

Because gene doping is still in the infancy stage, much of the potential adverse effects are theoretical. Nonetheless, such risks are substantial and may compromise the health of athletes who look to obtain an edge without considering the consequences. One potential adverse effect is an immune reaction. The virus or the protein itself may trigger an immune response, which may even lead to destruction of the endogenous protein. Another problem is that the virus may integrate such that it leads to the increased production of proto-oncogenes, thereby increasing the risk of cancer. Also, gene doping may affect germ cells, and its effects, both intended and unintended, may be passed on to offspring. Finally, the expression of the gene is difficult to

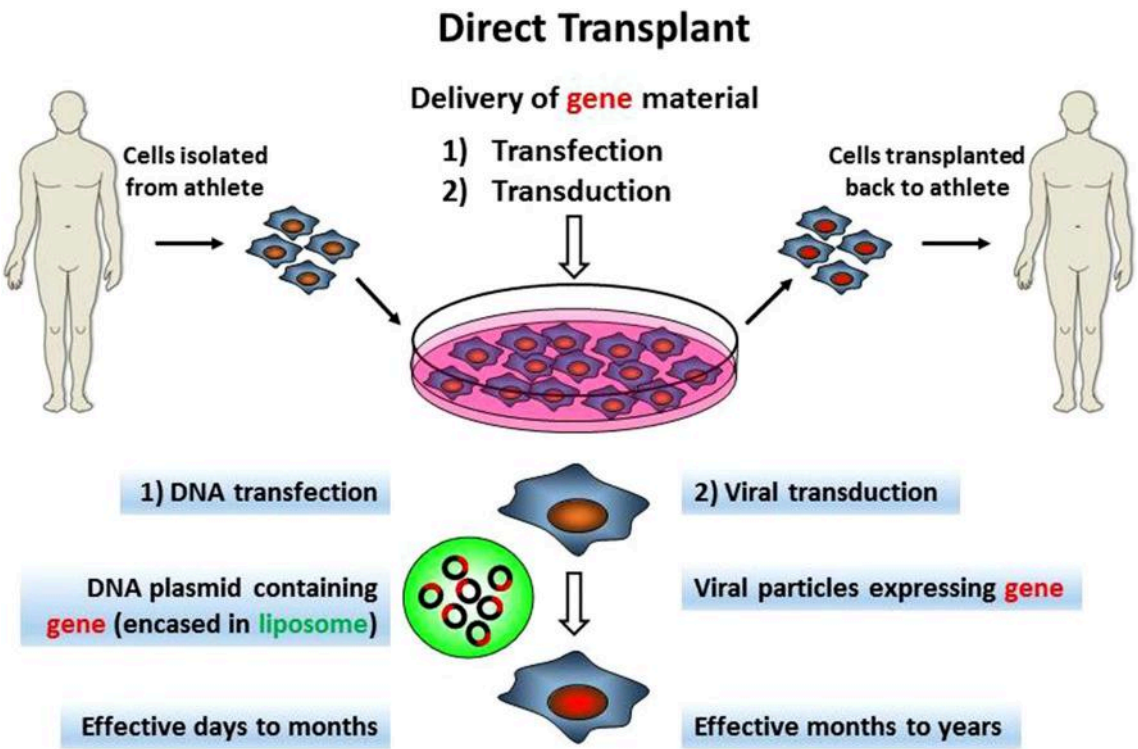

Fig. 3 Gene doping pathways via transfection or transduction

control, and overexpression may lead to an overabundance of protein that could reach toxic levels [100].

3.7.3 Testing

The detection of gene doping will prove to be very difficult. Currently, no WADA-approved detection methods exist for gene doping. The WADA currently prohibits any form of gene or cell doping.

4 Therapeutic Use Exemption

In certain situations, an athlete may require the use of a substance that is banned by WADA for an acute or chronic medical condition. The Therapeutic Use Exemption (TUE) program has been created to allow for athletes to use such substances without facing penalties. In order to meet the requirements for a TUE, four conditions must be met: (1) the banned substance is needed by the athlete for a chronic or acute medical condition and withholding the substance may pose a significant impairment to the health of the athlete, (2) the use of this substance is unlikely to increase athletic performance beyond what is anticipated by the return of the athlete to his or her normal health, (3) no reasonable therapeutic alternative exists, and (4) the need for this banned substance is not the consequence of prior use of a banned substance [105].

In order to obtain a TUE, the athlete and physician must complete appropriate paperwork and submit it to the governing agency. Table 2 lists the common substances by class for which athletes sought TUEs in 2013. These data were obtained from the Anti-doping Administration and Management database [106].

Table 2 Requests for Therapeutic Use Exemption by substance class

Substance	Percentage
Glucocorticosteroids	36
Stimulants	21
Hormone and metabolic modulators	14
Diuretics and other masking agents	8
Narcotics	6
Beta-2 agonists	5
Peptide hormones, growth factors, and related substances	4
Anabolic agents	3
Chemical and physical manipulation	1
Beta-blockers	1
Cannabinoids	<1
Manipulation of blood and blood components	<1

5 Prevention

Despite advances in PES detection, the prevalence of doping persists throughout sports. Some studies have examined preventive techniques, but much work remains in order to protect the health and safety of athletes.

Foremost, education appears to be the keystone to any prevention program. In a 2004 Swedish study, a health promotion program for 16- and 17-year-old adolescents focused on awareness and discussion of attitudes on AAS use over 2 years. The use of AAS tended to decrease after the program [15]. In another study in a low-income community, a short-term nutrition and sport supplement educational program was shown to improve nutrition and sport supplement knowledge [107]. However, these students were not necessarily athletes, and no objective testing data from prior to and after the educational program were available to assess drug use.

Whitaker et al. [108] conducted semi-structured interviews on athletes' perceptions of their role in doping prevention. The study concluded that prevention programs would need to focus on changing the broader group and community norms on doping. Furthermore, anti-doping programs may need to be specialized based on the sport. Harcourt et al. [109] report on a technique by which drug use was reduced in elite Australian football ('Australian Rules'). The authors surmised that player education and a greater number of tests conducted along with a "harm minimization" rather than a "punitive" strategy would lead to a decreased use of prohibited PESs.

Further studies are needed to help formulate an effective program on preventing the use of banned PESs. Such programs will need to start early while the athletes are young and focus on education and awareness. Nevertheless, physicians must be aware of the incidence of PES use despite prevention techniques. When PES use is suspected, the physician must broach the subject with the athlete. Warning signs of PES use may include increased aggressiveness, increased weight, acne, and skin changes from needle marks. Guidelines need to be established to help direct physicians who suspect the use of banned substances by their patients. At this point, testing for banned substances and subsequent reporting should be left to the sport's governing body.

6 Conclusion

The current rate of PES use among athletes is disturbing. The majority of studies are limited by response errors, and the true prevalence of PES use may be much higher. Further studies are needed to evaluate the true prevalence of PES use among athletes and differentiate sport-specific

rates. Such studies may stem from randomized testing of athletes. Further randomized controlled studies are also needed to resolve conflicting data on specific substances and their effects on sports performance.

As methods of doping continue to advance, the sports medicine physician will need to play an even greater role in protecting athletes from harm. Physicians should be knowledgeable about the types of PESs available and the potential performance benefits and health risks of such substances. Only after the physician gains such knowledge can he or she effectively educate athletes on PESs and effect positive change in the sports community.

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References

1. Botre F, Pavan A. Enhancement drugs and the athlete. Neurol Clin. 2008;26:149–67.
2. De Rose EH. Doping in athletes: an update. Clin Sports Med. 2008;27:107–30.
3. WADA. World anti-doping code (online). 2015. https://wada-main-prod.s3.amazonaws.com/resources/files/wada-2015-world-anti-doping-code.pdf. Accessed 11 Aug 2014.
4. Mitchell G. Report to the Commissioner of Baseball of an independent investigation into the illegal use of steroids and other performance enhancing substances by players in Major League Baseball (online). http://files.mlb.com/mitchrpt.pdf. Accessed 11 Aug 2014.
5. Nilsson S. Androgenic anabolic steroid use among male adolescents in Falkenberg. Eur J Clin Pharmacol. 1995;48:9–11.
6. Korkia P, Stinson GV. Indication of prevalence, practice and effects of anabolic steroid use in Great Britain. Int J Sports Med. 1997;18:557–62.
7. Simon P, Striegel H, Aust F, et al. Doping in fitness sports: estimated number of unreported cases and individual probability of doping. Addiction. 2006;101:1640–4.
8. Striegel H, Simon P, Frisch S, et al. Anabolic ergogenic substance users in fitness-sports: a distinct group supported by the health care system. Drug Alcohol Depend. 2006;81:11–9.
9. Kanayama G, Gruber AJ, Pope HG Jr, et al. Over-the-counter drug use in gymnasiums: an unrecognized substance abuse problem? Psychother Psychosom. 2001;70:137–40.
10. Buckman JF, Yusko DA, White HR, et al. Risk profile of male college athletes who use performance-enhancing substances. J Stud Alcohol Drugs. 2009;70:919–23.
11. Dietz P, Ulrich R, Dalaker R, et al. Associations between physical and cognitive doping: a cross-sectional study in 2,997 triathletes. PLoS ONE. 2013;8:e78702.
12. Striegel H, Ulrich R, Simon P. Randomized response estimates for doping and illicit drug use in elite athletes. Drug Alcohol Depend. 2010;106:230–2.
13. Rexroat M. NCAA national study of substance use habits of college student-athletes (online). http://www.ncaa.org/sites/default/files/Substance%20Use%20Final%20Report_FINAL.pdf. Accessed 11 Aug 2014.
14. Sagoe D, Molde H, Andreassen CS, et al. The global epidemiology of anabolic-androgenic steroid use: a meta analysis and meta-regression analysis. Ann Epidemiol. 2014;24:383–98.
15. Gregory AJ, Fitch RW. Sports medicine: performance-enhancing drugs. Pediatr Clin North Am. 2007;54:797–806.
16. Pereira HM, Padilha MC, Neto FR. Tetrahydrogestrinone analysis and designer steroids revisited. Bioanalysis. 2009;1:1475–89.
17. Teale P, Scarth J, Hudson S. Impact of the emergence of designer drugs upon sports doping testing. Bioanalysis. 2012;4:71–88.
18. Tokish JM, Kocher MS, Hawkins RJ. Ergogenic aids: a review of basic science, performance, side effects, and status in sports. Am J Sports Med. 2004;32:1543–53.
19. Evans N. Current concepts in anabolic-androgenic steroids. Am J Sports Med. 2004;32:534–42.
20. Bhasin S, Storer TW, Berman N, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med. 1996;335:1–7.
21. Forbes GB, Porta CR, Herr BE, et al. Sequence of changes in body composition induced by testosterone and reversal of changes after drug is stopped. JAMA. 1992;267:397–9.
22. Giorgi A, Weatherby RP, Murphy PW. Muscular strength, body composition and health responses to the use of testosterone enanthate: a double blind study. J Sci Med Sport. 1999;2:341–55.
23. Duntas LH, Popovic V. Hormones as doping in sports. Endocrine. 2013;43:303–13.
24. Broeder CE, Quindry J, Brittingham K, et al. The Andro Project: physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high-intensity resistance training program. Arch Intern Med. 2000;160:3093–104.
25. King DS, Sharp RL, Vukovich MD, et al. Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men: a randomized controlled trial. JAMA. 1999;281:2020–8.
26. Wallace MB, Lim J, Cutler A, et al. Effects of dehydroepiandrosterone vs androstenedione supplementation in men. Med Sci Sports Exerc. 1999;31:1788–92.
27. Liddle DG, Connor DJ. Nutritional supplements and ergogenic AIDS. Prim Care. 2013;40:487–505.
28. Bahrke MS, Yesalis CE. Abuse of anabolic steroids and related substances in sport and exercise. Curr Opin Pharmacol. 2004;4:614–20.
29. Kanayama G, Kean J, Hudson JJ, et al. Cognitive deficits in long-term anabolic-androgenic steroid users. Drug Alcohol Depend. 2013;130:208–14.
30. Geyer H, Schanzer W, Thevis M. Anabolic agents: recent strategies for their detection and protection from inadvertent doping. Br J Sports Med. 2014;48:820–6.
31. Brudnak MA. Creatine: are the benefits worth the risk? Toxicol Lett. 2004;150:123–30.
32. Eichner ER. Ergogenic aids: what athletes are using and why. Phys Sportsmed. 1997;25:70–83.
33. Greydanus DE, Patel DR. Sports doping in the adolescent athlete the hope, hype, and hyperbole. Pediatr Clin North Am. 2002;49:829–55.
34. Balsom PD, Soderlund K, Sjodin B, et al. Skeletal muscle metabolism during short duration high-intensity exercise: influence of creatine supplementation. Acta Physiol Scand. 1995;154:303–10.
35. Birch R, Noble D, Greenhaff PL. The influence of dietary creatine supplementation on performance during repeated bouts of maximal isokinetic cycling in man. Eur J Appl Physiol Occup Physiol. 1994;69:268–76.

36. Dawson B, Cutler M, Moody A, et al. Effects of oral creatine loading on single and repeated maximal short sprints. Aust J Sci Med Sport. 1995;27:56–61.
37. Oliver JM, Joubert DP, Martin SE, et al. Oral creatine supplementation's decrease of blood lactate during exhaustive, incremental cycling. Int J Sport Nutr Exerc Metab. 2013;23:252–8.
38. Earnest CP, Snell PG, Rodriguez R, et al. The effect of creatine monohydrate ingestion on anaerobic power indices, muscular strength and body composition. Acta Physiol Scand. 1995;153:207–9.
39. Stone MH, Sanborn K, Smith LL, et al. Effects of in-season (5 weeks) creatine and pyruvate supplementation on anaerobic performance and body composition in American football players. Int J Sport Nutr. 1999;9:146–65.
40. Aaserud R, Gramyik P, Olsen SR, et al. Creatine supplementation delays onset of fatigue during repeated bouts of sprint running. Scand J Med Sci Sports. 1998;8:247–51.
41. Mujika I, Chatard JC, Lacoste L, et al. Creatine supplementation does not improve sprint performance in competitive swimmers. Med Sci Sports Exerc. 1996;28:1435–41.
42. Balsom PD, Ekbolm B, Soderlund K, et al. Creatine supplementation and dynamic high-intensity intermittent exercise. Scand J Med Sci Sports. 1993;3:143–9.
43. Balsom PD, Soderlund K, Ekblom B. Creatine in humans with special reference to creatine supplementation. Sports Med. 1994;18:268–80.
44. Claudino JG, Mezencio B, Amaral S, et al. Creatine monohydrate supplementation on lower-limb muscle power in Brazilian elite soccer players. J Int Soc Sports Nutr. 2014;11:e1–6.
45. Lemon PW. Dietary creatine supplementation and exercise performance: why inconsistent results? Can J Appl Physiol. 2002;27:663–81.
46. Dawson B, Vladich T, Blanksby BA. Effects of 4 weeks of creatine supplementation in junior swimmers on freestyle sprint and swim bench performance. J Strength Cond Res. 2002;16:485–90.
47. Bailes JE, Cantu RC, Day AL. The neurosurgeon in sport: awareness of the risks of heatstroke and dietary supplements. Neurosurgery. 2002;51:283–6.
48. Wen TC, Hae Tha M, Joo Ng H. Creatine supplementation and venous thrombotic events. Am J Med. 2014; 127;e7–e8.
49. Poortmans JR, Francaux M. Long term oral creatine supplementation does not impair renal function in healthy athletes. Med Sci Sports Exerc. 1999;31:1108–10.
50. NCAA Academic and Membership Affairs Staff. NCAA 2014-2014 division I manual (online). http://www.ncaapublications.com/productdownloads/D114.pdf. Accessed 11 Aug 2014.
51. Rickert VI, Pawlak-Morello C, Sheppard V, et al. Human growth hormone: a new substance of abuse among adolescents? Clin Pediatr. 1992;31:723–6.
52. Liu H, Bravata DM, Olkin I, et al. Systematic review: the effects of growth hormone on athletic performance. Ann Intern Med. 2008;148:747–58.
53. Baumann GP. Growth hormone doping in sports: a critical review of use and detection strategies. Endocr Rev. 2012;33:155–86.
54. Deyssig R, Frisch H, Blum WF, et al. Effect of growth hormone treatment on hormonal parameters, body composition and strength in athletes. Acta Endocrinol. 1993;128:313–8.
55. Yarasheski KE, Campbell JA, Smith K, et al. Effect of growth hormone and resistance exercise on muscle growth in young men. Am J Physiol. 1992;262:e261–7.
56. Rennie MJ. Claims for the anabolic effects of growth hormone: a case of the emperor's new clothes? Br J Sports Med. 2003;37:100–5.
57. Saugy M, Robinson N, Saudan C, et al. Human growth hormone doping in sport. Br J Sports Med. 2006;40:i35–9.
58. Hanley J, Saarela O, Stephens D, et al. hGH isoform differential immunoassays applied to blood samples from athletes: decision limits for anti-doping testing. Growth Horm IGF Res. 2014;24:205–15.
59. Veliz P, Boyd C, McCabe SE. Adolescent athletic participation and nonmedical Adderall use: an exploratory analysis of a performance-enhancing drug. J Stud Alcohol Drugs. 2013;74:714–9.
60. Ebert MH, Kammen DP, Murphy DL. Plasma levels of amphetamine and behavioral response. In: Gottschalk LA, Merlis S, editors. Pharmacokinetics of psychoactive drugs: blood levels and clinical response. New York: Wiley; 1976. p. 157–69.
61. Statland BE, Demas TJ. Serum caffeine half-lives: healthy subjects vs. patients having alcohol hepatic disease. Am J Clin Pathol. 1980;73:390–3.
62. Haller CA, Jacob P III, Benowitz N. Pharmacology of ephedra alkaloids and caffeine after single-dose dietary supplement use. Clin Pharmacol Ther. 2002;71:421–32.
63. Pentel P. Toxicity of over-the-counter stimulants. JAMA. 1984;252:1898–903.
64. Chandler JV, Blair SN. The effect of amphetamines on selected physiological components related to athletic success. Med Sci Sports Exerc. 1980;12:65–9.
65. Gill ND, Shield A, Blazevich AJ, et al. Muscular and cardiorespiratory effects of pseudoephedrine in human athletes. Br J Clin Pharmacol. 2000;50:205–13.
66. Bell DG, Jacobs I. Combined caffeine and ephedrine ingestion improves run times of Canadian Forces Warrior Test. Aviat Space Environ Med. 1999;70:325–9.
67. Bell DG, McLellan TM, Sabiston CM. Effect of ingesting caffeine and ephedrine on 10-km run performance. Med Sci Sports Exerc. 2002;34:344–9.
68. Santos VG, Santos VR, Felippe LJ, et al. Caffeine reduces reaction time and improves performance in simulated-contest of taekwondo. Nutrients. 2014;6:637–49.
69. Hodgson AB, Randell RK, Jeukendrup AE. The metabolic and performance effects of caffeine compared to coffee during endurance exercise. PLoS One. 2013;8:e1–10.
70. Stadheim HK, Kvamme B, Olsen R, et al. Caffeine increases performance in cross-country double-poling time trial exercise. Med Sci Sports Exerc. 2013;45:2175–83.
71. Lee CL, Cheng CF, Astorino TA, et al. Effects of carbohydrate combined with caffeine on repeated sprint cycling and agility performance in female athletes. J Int Soc Sports Nutr. 2014;11:e1–12.
72. Reyner LA, Horne JA. Sleep restriction and serving accuracy in performance tennis players and effects of caffeine. Physiol Behav. 2013;120:93–6.
73. Lattavo A, Kopperud A, Rogers PD. Creatine and other supplements. Pediatr Clin North Am. 2007;54:735–60.
74. Shekelle PG, Hardy ML, Morton SC, et al. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta analysis. JAMA. 2003;289:1537–45.
75. McDuff DR, Baron D. Substance use in athletics: a sports psychiatry perspective. Clin Sports Med. 2005;24:885–97.
76. Greydanus DE, Patel DR. Sports doping in the adolescent: the Faustian conundrum of Hors de Combat. Pediatr Clin North Am. 2010;57:729–50.
77. Spriet LL, Graham TE. Caffeine and exercise performance (online). http://www.acsm.org/docs/current-comments/caffeineandexercise.pdf. Accessed 22 Nov 2014.
78. McLean BD, Gore CJ, Kemp J. Application of 'live low-train high' for enhancing normoxic exercise performance in team sport athletes. Sports Med. 2014;44:1275–87.

79. Morkeberg J. Blood manipulation: current challenges from an anti-doping perspective. Hematol Am Soc Hematol Educ Program. 2013;2013:627–31.
80. Citartan M, Gopinath SC, Chen Y, et al. Monitoring recombinant human erythropoietin abuse among athletes. Biosens Bioelectron. 2014;63:86–98.
81. Robertson RJ, Gilcher R, Metz KF, et al. Effect of induced erythrocythemia on hypoxia tolerance during physical exercise. J Appl Physiol Respir Environ Exerc Physiol. 1982;53:490–5.
82. Berglund B, Hemmingson P. Effect of reinfusion of autologous blood exercise performance in cross-country skiers. Int J Sports Med. 1987;8:231–3.
83. Brien AJ, Simon TL. The effects of red blood cell infusion on 10-km race time. JAMA. 1987;257:2761–5.
84. Birkeland KI, Stray-Gundersen J, Hemmerbach P, et al. Effect of rhEPO administration on serum levels of s TfR and cycling performance. Med Sci Sports Exerc. 2000;32:1238–43.
85. Berglund B, Ekblom B. Effect of recombinant human erythropoietin treatment on blood pressure and some haematological parameters in healthy men. J Intern Med. 1991;229:125–30.
86. Leigh-Smith S. Blood boosting. Br J Sports Med. 2004;38:99–101.
87. Morkeberg J. Detection of autologous blood transfusions in athletes: a historical perspective. Transfus Med Rev. 2012;26:199–208.
88. Palisin T, Stacy JJ. Beta-hydroxy-beta-methylbutyrate and its use in athletics. Curr Sports Med Rep. 2005;4:220–3.
89. Pimentel GD, Rosa JC, Lira FS, et al. Beta-hydroxy-beta-methylbutyrate (HMB) supplementation stimulants skeletal muscle hypertrophy in rats via the mTOR pathway. Nutr Metab. 2011;8:e1–7.
90. Smith HJ, Mukerji P, Tisdale MJ. Attenuation of proteasome-induced proteolysis in skeletal muscle by beta-hydroxy-beta-methylbutyrate in cancer-induced muscle loss. Cancer Res. 2005;65:277–83.
91. Wilson JM, Kim J, Lee SR, et al. Acute and time effects of beta-hydroxy-beta-methylbutyrate (HMB) on indirect markers of skeletal muscle damage. Nutr Metab. 2009;6:e1–8.
92. Knitter AE, Panton I, Rathmacher JA, et al. Effects of beta-hydroxy-beta-methylbutyrate on muscle damage after a prolonged run. J Appl Physiol. 2000;89:1340–4.
93. Kraemer WJ, Hatfield DL, Volek JS, et al. Effects of amino acids supplement on physiological adaptations to resistance training. Med Sci Sports Exerc. 2009;41:1111–21.
94. Nissen SI, Sharp RL. Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. J Appl Physiol. 2003;94:651–9.
95. Hoffman JR, Copper J, Wendell M, et al. Effects of beta-hydroxy-beta-methylbutyrate on power performance and indices of muscle damage and stress during high-intensity training. J Strength Cond Res. 2004;18:747–52.
96. Kreider RB, Ferreira M, Greenwood M, et al. Effects of calcium b-HMB supplementation during training on markers of body composition, strength, and spring performance. J Exerc Physiology-online. 2000;3:48–59.
97. Wilson JM, Fitschen PJ, Campbell B, et al. International Society of Sports Nutrition position stand: beta-hydroxy-beta-methylbutyrate (HMB). J Int Soc Sports Nutr. 2013;10:e1–14.
98. Gallagher PM, Carrithers JA, Godard MP, et al. Beta-hydroxy-beta-methylbutyrate ingestion, part I: effects on strength and fat free mass. Med Sci Sports Exerc. 2000;32:2109–15.
99. Nissen S, Sharp RL, Panton L, et al. Beta-hydroxy-beta-methylbutyrate (HMB) supplementation in humans is safe and may decrease cardiovascular risk factors. J Nutr. 2000;130:1937–45.
100. Van der Gronde T, de Hon O, Haisma HJ, et al. Gene doping: an overview and current implications for athletes. Br J Sports Med. 2013;47:670–8.
101. Fischetto G, Bermon S. From gene engineering to gene modulation and manipulation: can we prevent or detect gene doping in sports? Sports Med. 2013;43:965–77.
102. Brill-Almon E, Stern B, Afik D, et al. Ex vivo transduction of human dermal tissue structures for autologous implantation production and delivery of therapeutic proteins. Mol Ther. 2005;12:274–82.
103. Wang W, Li W, Ma N, et al. Non-viral gene delivery methods. Curr Pharm Biotechnol. 2013;14:46–60.
104. Sinn PL, Sauter SL, McCray PB Jr. Gene therapy progress and prospects: development of improved lentiviral and retroviral vectors—design, biosafety, and production. Gene Ther. 2005;12:1089–98.
105. WADA. Therapeutic use exemptions (online). 2015. https://wada-main-prod.s3.amazonaws.com/resources/files/WADA-2015-ISTUE-Final-EN.pdf. Accessed 22 Nov 2014.
106. Vernec A. Therapeutic use exemptions: principles and practice (online). https://wada-main-prod.s3.amazonaws.com/resources/files/01-_vernec_alan_-_tue_symposium_paris_vernec_october_23_2014.pdf. Accessed 22 Nov 2014.
107. Little JC, Perry DR, Volpe SL. Effect of nutrition supplement education on nutrition supplement knowledge among high school students from a low-income community. J Community Health. 2002;27:433–50.
108. Whitaker L, Backhouse SH, Long J. Reporting doping in sport: national level athletes' perceptions of their role in doping prevention. Scan J Med Sci Sports. 2014;24(6):e515–21.
109. Harcourt PR, Unglik H, Cook JL. Strategy to reduce illicit drug use is effective in elite Australian football. Br J Sports Med. 2012;46:943–5.