Doping in sport: effects, harm and misconceptions

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Abstract

Doping in sport is a widespread problem not just among elite athletes, but even more so in recreational sports. In scientific literature, major emphasis is placed on doping detection, whereas detrimental effects of doping agents on athlete's health are seldom discussed. Androgenic anabolic steroids are well known for their positive effects on muscle mass and strength. Human growth hormone also increases muscle mass, although majority of that is an increase in extracellular fluid and not the functional muscle mass. In recreational athletes, growth hormone does not have major effect on muscle strength, power or aerobic capacity, but stimulates anaerobic exercise capacity. Erythropoietin administration increases oxygen carrying capacity of blood improving endurance measures, whereas systemic administration of beta-adrenergic agonists may have positive effect on sprint capacity, and beta-adrenergic antagonists reduce muscle tremor. Thus, there are certain drugs that can improve selective aspects of physical performance. However, most of the doping agents exert serious side effects, especially when used in combination, at high doses, and for long duration. The extent of long-term health consequences is difficult to predict but likely to be substantial, especially when gene doping is considered. This review summarises main groups of doping agents used by athletes, with main focus on their effects on athletic performance and adverse effects.

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Introduction

Doping in sport is a well-known phenomenon and is now reported on a daily basis by the media worldwide. Most reports, however, focus on elite athletes. Little attention has been devoted to the use of performance-enhancing and body-image-enhancing drugs in recreational athletes, the group with the highest rates of drug misuse. There is no doubt that doping among elite athletes will always be in focus. The power of a dream (Citius, Altius, Fortius) and potentially lucrative rewards may drive athletes to seek victory at any cost despite the Olympic creed that "the essential thing is not to have conquered, but to have fought well". Spectators appreciate observing athletes at their fastest, highest and strongest; but expect that this reflects their athletic ability and not their doping skills. Many elite athletes who abuse performance-enhancing substances have escaped detection and many recreational athletes are never going to be tested. Thus, we only can speculate how widespread doping actually is in elite and recreational sports.

Substantial research effort has been devoted to the development of reliable doping detection assays, as summarized elsewhere [1]. What is rarely discussed is the adverse effects and long-term health consequences of performance-enhancing drugs. This lack of emphasis on health risks of doping agents in the scientific literature has resulted in a prevalent belief among athletes that the only adverse consequence of doping is the risk of being caught. In a survey when athletes were asked if they are willing to misuse performance-enhancing drugs that would guarantee an Olympic medal if they could not be caught, 98% of athletes said yes [2]. When asked if they would take the drug even if they then died from its adverse effects but with a guarantee that they won every competition for the next 5 years without getting caught, an amazing 50% also replied yes [2]. In a recent paper summarizing athletes' attitudes, it was reported that reasons for doping include not only athletic success, financial gain and improved recovery after injury, but also the assumption that other athletes also use them [3].

Coaches appear to be the main influence and source of information for athletes, and many athletes feel pressed to dope [4]. Thus, there is a need to change the attitude towards doping in sport. Educational programs are warranted, particularly for recreational athletes to grasp the health consequences of performance-enhancing and body-image-enhancing drugs.

There is an extensive list of prohibited substances by the World Anti-Doping Agency (WADA) (http://www.wada-ama.org/Documents/World_Anti-Doping_Program/WADP-Prohibited-list/2014/WADA-prohibited-list-2014-EN.pdf). This review will summarise the main groups of performance-enhancing agents used by athletes, with a particular focus on their effects on athletic performance and potential adverse effects.

Anabolic androgenic steroids

Anabolic androgenic steroids (AAS) are the most commonly used substances to improve exercise performance and/or body image of an athlete. AAS are used often in combination with other substances to increase anabolic/performance-enhancing effect (growth hormone, insulin, IGF-I), to enhance fat and water loss (diuretics, β2 adrenoreceptor agonists), or to reduce side effects of androgens (aromatase inhibitors, Selective Estrogen Receptor Modulators - SERMs). Athletes commonly combine different steroids (called stacking) and use ASS in cycles. A recent meta-analysis of 187 studies determined a 3.3% global lifetime prevalence of AAS use in mixed population, with the prevalence rate for males being significantly higher for that in females (6.4% and 1.6%, respectively) [5]. AAS abuse has been reported in 11% of adult gym users, 39% of bodybuilders and a staggering 67% of powerlifters [6, 7]. Thus, AAS abuse rates may be extremely high, and health professionals should be alert to this practice.

Effects on muscle mass and strength

The effect of testosterone on muscle mass is dose-dependent. The evidence comes from a study by Bhasin and colleagues showing that high dose testosterone administration in healthy

adults results in an increase in lean body mass (LBM) in a dose-depended manner, with the highest dose of 600 mg/week, (approximately six times the physiological rate of testosterone production) resulting in 9 kg increase in LBM over 20 weeks of testosterone administration [8]. AAS administration also increases muscle strength, as summarised elsewhere [9]. Circulating testosterone levels positively correlate with the change in muscle strength and testosterone potentiates the effect of exercise on muscle strength [8, 10]. Thus, testosterone exerts not only an anabolic effect but also a substantial effect on muscle strength.

Although the effect of AAS on muscle strength is well-known, androgens have not been shown to improve endurance VO2 max or lactate threshold in healthy adults [11, 12]. Studies in elderly subjects show improvement in aerobic capacity with testosterone administration, especially when used in combination with growth hormone, however in healthy adults with normal testosterone levels AAS may not increase aerobic capacity beyond normal. Potential positive effects on physical performance by AAS may also relate to the capacity of testosterone to increase haemoglobin and haematocrit, reduce reaction time, and increase tolerance for hard training.

Side effects of AAS (Fig 1)

AAS use in supra-physiological doses is associated with cardiovascular complications, with recent reports of sudden cardiac death in young otherwise healthy athletes who have been abusing testosterone for several years [13, 14]. A study that investigated the cause of death among AAS users reported that around 35% of AAS users had chronic cardiac changes [15]. The most common findings are concentric cardiac hypertrophy, dilated cardiomyopathy, fibrosis and myocytolysis; with significantly lower left ventricular ejection fraction and diastolic dysfunction [13, 16, 17]_ENREF_13. Left ventricular hypertrophy may persist even after AAS cessation. Finally, AAS abuse is linked to acute myocardial infarction and fatal

ventricular arrhythmias [18]. As many AAS users also abuse growth hormone (GH), the effect on myocardial hypertrophy is potentiated by concomitant use of GH [19].

Other side effects relate to suppression of the hypothalamic-pituitary-testicular (HPT) axis. Although suppression of pituitary gonadotropin secretion is potentially reversible, largely depending on the duration of AAS abuse, hypogonadism may persist for prolonged periods of time after androgens are discontinued [20]_ENREF_21. AAS users may have reduction in testicular size, sperm count, sexual dysfunction, and other symptoms like gynecomastia that results from an increase in oestrogen aromatised from testosterone. In women, AAS abuse associates with breast atrophy, hirsutism, clitoral enlargement, and menstrual irregularity. Other androgen-related side effects include acne, male pattern balding and an increase in haemoglobin. Hepatic dysfunction and neoplasms have been reported, mostly in relation to oral testosterone abuse [21]. Muscle rupture, tendon and ligament injuries are also reported, which may result from disproportionate increase in muscle mass without an increase in strength of supporting tissue [22, 23].

Special attention should be drawn to psychiatric side effects. Many studies have reported an association between AAS use and aggression, violent behaviour, mood swings and mania [24]. In AAS-dependent users the psychological/psychiatric symptoms are more prevalent and severe, with twice as many subjects reporting anxiety and major depression compared to AAS users without dependence [25]. There is also an increased risk of other drug and alcohol abuse, and increased risk of suicidal and homicidal death. The use of AAS associates with antisocial behaviour and violence, and there is a complex interaction with criminal activity. When 6362 police cases and 5779 prison inmates were analysed, 33.5% of the cases from the police and 11.5% of the inmates tested positive for AAS [26]. Other drug abuse was detected in 60% of these cases, indicating a frequent polysubstance abuse among AAS users [26].

In a recent review on AAS and polypharmacy, in weightlifters lifetime opioid abuse is reported up to 3 times higher in AAS users than in non-users, and 50% of those with

androgen dependence also abuse opioids [24]. It is reported that 27% of AAS users also abuse human GH, and within the subgroup of heaviest AAS users (diagnosed with androgen dependence), 70% had used hGH and/or insulin-like growth factor-1 (IGF-1) [27]. AAS use may also be combined with over-use of alcohol, caffeine, ephedrine, β-adrenoreceptor agonists, thyroid hormones, or cannabis, and AAS users are up to 30 times more likely to report past-year cocaine or heroin use compared to non-users [24]. Animal studies show that AAS tolerance/dependence is related to opioid mechanisms and the higher the dose of testosterone the higher the death rates [28].

There is an increase in mortality rates in AAS abusers. In competitive powerlifters suspected to have abused AAS for several years, risk of death is up to 5 times that of controls [29]. A study that investigated the cause of death among AAS users reported that out of 34 male AAS abusers, 27% were victims of homicide, 32% committed suicide, 35% death were classified as accidental [15]. Deaths were related to impulsive behaviour characterized by violent rages, mood swings and other drug intake. Thus, it is difficult to separate the specific adverse effects of AAS abuse from broader issues of lifestyle and risk-taking behavior among users.

Growth hormone

Human GH is one of the major anabolic hormones and is abused together with AAS in about 25% of AAS users [27]_ENREF_38. GH abuse is popular among athletes probably because of the perceived benefit on muscle mass and function, as well as difficulty of detection. GH increases whole body protein synthesis in healthy young men and conserves protein during exercise, however this effect appears to be lost in highly trained athletes [30, 31]. GH has no additional effect on quadriceps muscle protein synthesis rate in men undertaking resistance training [30]. Moreover, GH administration in healthy young men stimulated collagen but not myofibrillar protein synthesis [32]. These findings suggest that although GH stimulates whole

body protein accretion it probably does not result in a specific anabolic effect on skeletal muscles, especially in highly trained athletes.

Effects of GH on body composition

A systematic review reported that GH increases LBM in healthy adults [33]. Importantly, the GH-induced increase in LBM is accompanied by a concomitant expansion of the extracellular water (ECW) volume [11]. As the LBM consists of ECW plus a functional cellular compartment (body cell mass) when the ECW component is removed from the LBM, no significant increase in body cell mass is observed with GH administration [11]. Thus, fluid retention accounts for most of the increase of LBM induced by GH. The effect of GH on LBM is potentiated by androgens_ENREF_57, and combined administration of GH and testosterone does increase body cell mass [11]. These findings suggest that only when GH is combined with testosterone, an increase in functionally active muscle mass occur.

Effects of GH on physical performance

A systematic review of 27 studies comprising a total number of 303 healthy adults in whom the effects of GH on various measures of athletic performance, such as muscle strength and endurance were analysed, concluded that claims that GH enhances physical performance are not supported by the scientific literature [33]. In the largest study of nearly 100 recreational athletes, both muscle strength and muscle power were not affected by 8 weeks of blinded GH administration [11]. Moreover, 12 weeks of GH administration combined with exercise did not enhance muscle strength compared to exercise alone [30]. These studies show that in healthy adults, administration of GH does not significantly improve muscle strength and power.

Studies have found no significant effect of GH on VO_2max [33]. In a study involving 30 healthy young men and women, no significant effect was observed on VO_2max or on maximum achieved power output during exercise after 4 weeks of GH treatment [34]. Furthermore, changes in IGF-I did not correlate with changes in oxygen uptake or maximum achieved power output [34]. In recreational athletes, GH administration alone or with

testosterone for 8 weeks also had no effect on VO_2max [11]. Thus, all the double blind placebo controlled studies in healthy adults show no effect on VO2 max, muscle strength or power with GH administration in doses up to 67 μg/kg/d (Table 1).

Recently a novel enhancing effect of GH on anaerobic muscle performance has been discovered [11]. Sprint capacity (which relies significantly on anaerobic muscle function) was increased significantly with GH administration in the group of men and women combined by 3.9%, and in men co-administered GH and testosterone by 8.3%. The increase in sprint capacity was no longer present 6 weeks after GH discontinuation [11].

Potential benefits of GH in athletes

Evidence suggests that during early stages of acromegaly, GH excess may initially improve physical performance, increasing tolerance for hard training and shortening recovery time after exercise [35]. GH may also be beneficial in accelerating recovery from soft tissue injury. It is well known that GH stimulates connective tissue formation. Two weeks of GH administration increased collagen synthesis in skeletal muscle and tendon by up to 6-fold in a placebo-controlled study in healthy young men [32], and animal studies show that tendons heal faster after treatment with IGF-I, a mediator of GH action[36]. Thus, GH may be important in strengthening the supporting connective tissue of muscle.

It is important to consider the potential role of the placebo effect in any studies of drug effects on athletic performance. In a blinded, placebo-controlled study of GH and testosterone effects in recreational athletes [11] all the participants were asked to indicate whether they thought that they received placebo or active treatment. Remarkably, 81 % of men and 31 % of women perceived improved performance and thought they have received active treatment when they in fact received placebo [37]. Moreover, changes in measured performance were also higher for those participants in the placebo group who believed they were on active treatment, with a significant increase in a measure of muscle power [37]. These results suggest that for

some people, and especially for men, the placebo effect may be responsible for the perceived athletic benefit of doping with GH.

Adverse effects of GH

Between 40 to 80% of healthy adults who have received GH in controlled prospective studies report side effects. Most of the acute side effects of GH administration arise from fluid retention (Fig 2). These include oedema, paraesthesia, carpal tunnel syndrome and arthralgias [33]. Other side effects reported are sweating, fatigue, dizziness, and insulin resistance/hyperglycaemia_ENREF_72. High doses of GH can induce rapid negative effects on cardiac morphology and function, significantly increasing left ventricular wall thickness due to concentric remodelling [38]_ENREF_86. Interestingly, GH doping is associated with increase in fatigue, muscle pain after exercise and reduced concentration, which is opposite to the effect of physiological GH replacement in GH deficient patients. Thus, excess GH may induce worsening of quality of life. Evidence from patients with acromegaly show that prolonged excess of GH causes myopathy with hypertrophic, but functionally weaker muscles, hypertension, cardiac, metabolic and articular complications, increased risk of diabetes, malignant neoplasms, and reduction in life expectancy.

Concomitant administration of AAS with GH results in additive toxicity; particularly fluid retention and myocardial injury. Both hormones may also interact to induce insulin resistance, prostate hypertrophy, and possibly cancer[39, 40]_ENREF_88.

Other Doping Agents

Insulin, IGF-I

Insulin and insulin-like growth factor 1 (IGF-I) are increasingly used as doping agents. IGF-I is produced in the liver and is the primary mediator of the effects of GH. The actions of insulin and IGF-I that may enhance performance include protein anabolism, glucose uptake, and glycogen storage in muscle. Insulin promotes net amino acid uptake and protein

anabolism in skeletal muscle by reducing protein breakdown, whereas IGF-I stimulates protein synthesis [41]. Effects of IGF-I on glucose metabolism largely resembles those of insulin. However, upon IGF-I infusion, insulin levels drop and so does the fat-sparing effect of insulin [42]. Thus, insulin and IGF-I stimulate muscle anabolism and may increase glucose availability for exercising muscle to use.

Increasing number of body builders and other athletes abuse insulin_ENREF_98_ENREF_99. A web-based survey identified 41 non-diabetic insulin users, out of which 95 % also used AAS and practiced polypharmacy [43]. Most of the subjects reported the side-effect of hypoglycaemia (57%) and one reported unconsciousness. Other reports also indicate that insulin abuse can lead to hypoglycaemia and even coma and death [44, 45].

There are two types of IGF-I preparations, IGF-I used alone and with its binding protein IGFBP-3. Combining IGF-I with IGFBP-3 results in less severe side effects and longer half-life resulting in sustained increase in circulating IGF-I levels [46]. Effect of IGF-I on physical performance in healthy adults has not yet been studied in appropriately designed trials. Similar to insulin, the most common side effect of IGF-I abuse is hypoglycaemia. As IGF-I promotes cell proliferation, inhibits apoptosis, and interacts with pathways that have an established role in carcinogenesis, IGF-I abuse has a potential to increase cancer risk [47]. In human breast cancer cells, AAS causes a dose-dependent increase in aromatase expression and oestradiol production, the effect potentiated by concomitant IGF-I treatment [48]. Moreover, AAS and IGF-I co-administration induce significant cancer cell proliferation [48]. In humans, a positive relationship between circulating IGF-I and the incidence of prostate and colorectal cancers has been reported [49, 50]. Thus, insulin and IGF-I abuse would seem to entail a significant theoretical increase in cancer risk.

Erythropoetin (EPO)

Many of the elite athletes in cycling have been implicated in discoveries of erythropoietin (Epo) doping. It is abused because of its ability to increase oxygen carrying capacity of blood. The efficacy in stimulating erythropoiesis is dose dependent. As summarized in a paper by Heuberger and colleagues, Epo administration in untrained or trained athletes elevates haemoglobin by up to 12% and haematocrit by up to 19%, the effects associated with an increase in VO2 max and significant improvement in endurance measures [51]. Prolonged administration of Epo improved submaximal exercise performance by about 50%, independently of the increase in VO2 max [52]. Similar approaches of doping include altitude training and blood transfusions. Altitude training increases Epo and erythrocyte volume, without affecting blood volume [53]. Target altitude between 2,000 and 2,500 metres has been shown to produce an optimal acclimatization response for sea level performance, with a positive relationship between altitude and increase in VO2 max [53]. Thus, by increasing blood oxygen carrying capacity, exercise performance is expected to improve.

Epo abuse however can result in serious health consequences. Adverse effects of recombinant human Epo include injection site reactions, nausea, headache, dizziness, arthralgia, allergic and anaphylactic reactions. Epo can elevate blood pressure, at least in part by lowering systemic and cerebral vascular conductance that is independent of its effect on haematocrit [54]. As Epo increases blood viscosity, coagulation and platelet reactivity, risk of thrombosis is elevated, as summarized elsewhere [51], along with increased risk for myocardial infarction and stroke. A meta-analysis in more than 9 thousand cancer patients indicated that treatment with Epo increases the risk of thrombosis [55]. Whether this is true in healthy athletes is less clear, although cerebral sinus thrombosis has been described in a professional cyclist after 3 months of doping with Epo and concomitant polypharmacy, including GH abuse [56]. Pure red cell aplasia is also reported, which is characterized by a progressively developing severe anaemia, with almost complete absence of red cell precursors and presence of Epo autoantibodies [57]. Epo may promote angiogenesis, increase tissue oxygenation and inhibit

apoptosis, hence Epo might favour cancer progression and aggressiveness [58, 59]. Thus, abuse of recombinant Epo may increase aerobic exercise capacity, but this effect comes in combination with increased risk for thrombosis, autoimmune reactions and possibly cancer.

Beta-adrenergic agents

β_2-adrenoreceptor (AR) agonists are targets for doping in sport, because of their bronchodilator, anabolic and anti-inflammatory actions [60]. Majority of studies however have demonstrated limited effect of inhaled β_2-AR agonists on aerobic exercise performance despite an improvement in lung function. Moreover, 6 weeks of salbutamol inhalation in male athletes did not result in significant improvement in endurance, strength or muscle power [61]. A systematic review concluded that there are no significant effects for inhaled β_2-AR agonists on endurance, strength or sprint performance, whereas systemic β_2-AR agonists may have a positive effect on physical performance in healthy subjects [62]. Combined inhalation of β_2-AR agonists (salbutamol, formoterol and salmeterol) also did not improve swim performance in elite swimmers, but there was an increase in swim ergometer sprint performance [63]. In contrast, oral salbutamol has been shown to have a significant positive effect on sprint capacity in recreational athletes, increasing sprint capacity by almost 15% after acute salbutamol administration [64]. The improvement in maximal anaerobic power has been shown in both trained and untrained men. Thus, there may be a significant positive effect on certain aspects of performance, particularly with oral β_2-AR agonists.

There are side effects with frequent use of β_2-AR agonists. Major concern relates to cardiovascular stimulatory effects. Tachycardia is a common feature of β_2-AR agonists, but more serious adverse effects, including supraventricular and ventricular arrhythmias, myocardial ischemia and even sudden cardiac failure have been reported [65, 66]. This however

at least partly can be avoided by using highly selective β_2-AR agonists, like formoterol, which may improve the safety profile.

β_2-AR antagonists also are abused by athletes, mostly to relieve anxiety and muscle tremor. However, besides negative effect on metabolism and body composition, β_2-AR antagonists also reduce endurance and sprint capacity [67]. Thus, doping with β_2-AR antagonists may be detrimental for muscle anabolism and strength, aerobic and anaerobic exercise capacity, but may alleviate muscle tremor and therefore be abused in sports, such as archery and shooting.

Gene doping

There is no conclusive evidence that gene doping has been used in sport, although the extent of current and future use of gene therapy among athletes is difficult to predict. Gene doping is defined as the transfer of genetic material to improve athletic performance. Main techniques used for delivering genes include direct injection of a gene into a muscle; intravenous or intramuscular injection of a virus containing a gene of interest; or ex vivo gene transfer into cells that are subsequently transplanted into the recipient.

For gene doping practically every known gene can be used, with most likely targets being the genes that play major role in stimulating endurance, muscle strength and power, recovery after injuries, pain tolerance, psychological wellbeing and motivation. Evidence for selection of target genes comes from studies exploring the role of gene polymorphism in determining athletic performance [68]. Potential targets for gene doping are considered Epo, IGF-I, myostatin, vascular endothelial growth factor (VEGF), fibroblast growth factor, α actinin 3 (ACTN3), peroxisome proliferator-activated receptor-delta (PPARδ), cytosolic phosphoenolpyruvate carbohykinase (PEPCK-C), endorphin, enkephalin, brain-derived neurotrophic factor (BDNF), and others [68-70]. IGF-I is a very attractive candidate for gene therapy, as animal studies show increased muscle mass, accelerated muscle and nerve

regeneration in IGF-I transgenic mice models [71], and muscle strength response to training is influenced by IGF-I genotype in humans [72]. However, prolonged IGF-I over-expression has high potential to induce unwanted side effects, such as cardiac hypertrophy, systolic dysfunction and cancer development. Since mutation in the gene encoding myostatin, a member of the transforming growth factor β (TGF-β) family, increases muscle growth and strength [73], myostatin inhibitors would be a potential doping agents of interest. Moreover, studies on ACTN3 polymorphism have also generated much interest, indicating that by increasing ACTN3 copies sprinting ability may be stimulated, whereas by diminishing ACTN3 copies endurance may be enhanced [70]. Modulation of psychological factors, such as pain perception (endorphins, enkephalins), response to stress (BDNF), mood and motivation (monoamines, BDNF), is another highly attractive area for gene therapy in sport [69].

There are only few studies that have used gene therapy in humans, as development of gene therapy is restricted to certain types of diseases. Local VEGF gene transfer show good results in patients with lower limb ischemia [74]. There are also short-term increases in Epo serum levels after re-implantation of dermal core samples transfected with Epo cDNA into the skin of the patients with chronic renal failure [75]. However gene therapy poses potential major health risks, such as liver damage, tumour development or development of autoimmune disease, as both the virus used and the protein itself can cause an immune reaction. For example, following intramuscular Epo gene administration, non-human primates develop severe autoimmune anaemia [76]. These are predictable potential side effects, however alterations of gene expression may bring unknown risks to the athlete's health. Gene doping could also affect germ cells, producing permanent alterations that could be transmitted to future generations. Thus, adverse effects of gene therapy are difficult to predict. As studies in humans are lacking, long-term consequences are unknown and complications of gene doping may be apparent only many years later.

CONCLUDING REMARKS

Certain doping agents can improve specific aspects of physical performance in athletes. Serious health risks are associated with doping in healthy adults, although our knowledge on this may be just a tip of an iceberg compared to what harm it causes in reality. Athletes often abuse substances in much higher doses than in the available placebo controlled studies, and often combine several agents. Thus, data from research studies may in fact underestimate the side effects of doping agents. Educational programs should be implemented to improve athlete's knowledge on health risks of performance- and body image-enhancing agents. It is also important for health professionals to be alert to clinical presentations which might be caused by doping, as the patient will often not willingly disclose this as the likely aetiology of their complaint.

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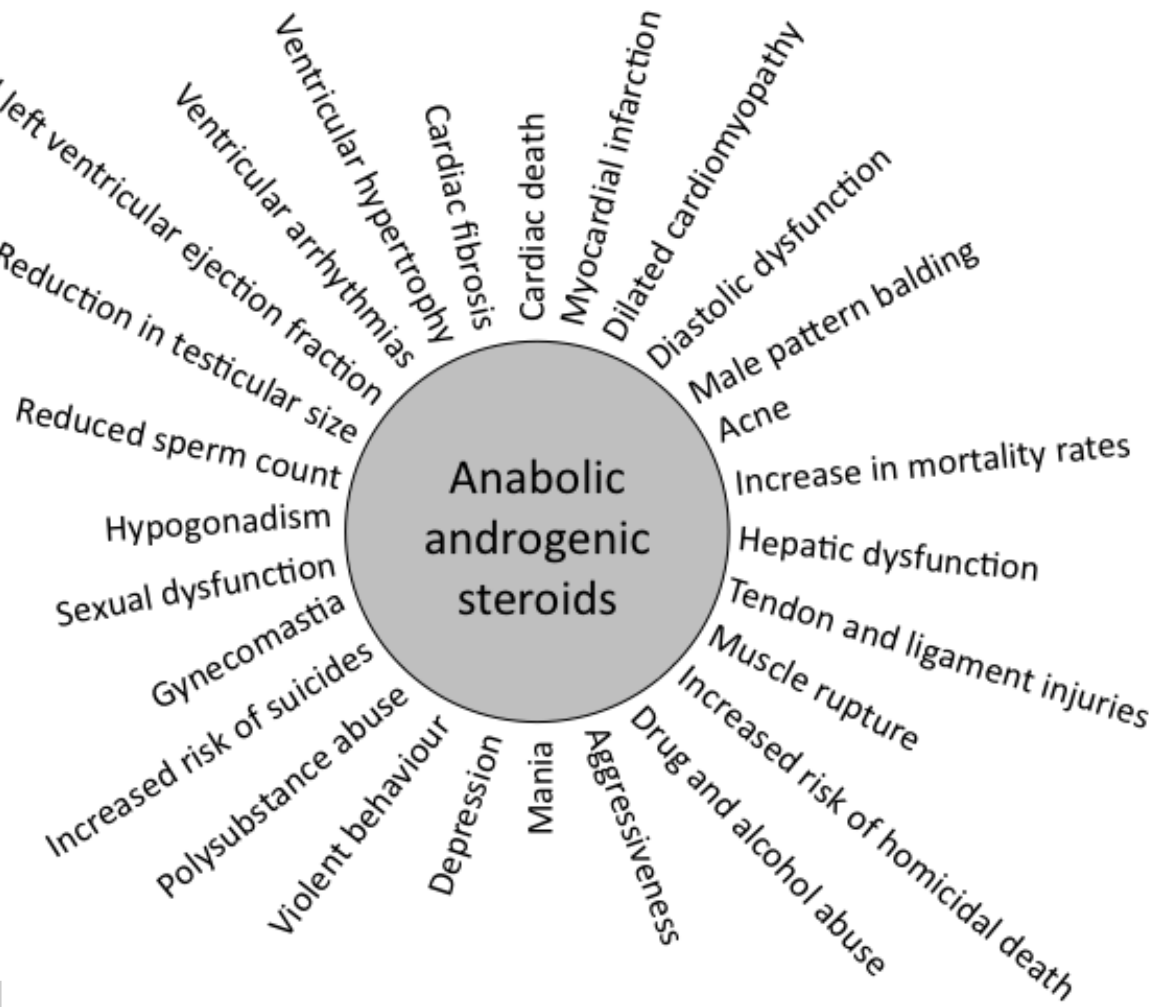
Table 1

The effects of growth hormone on physical performance reported in double-blind placebo controlled studies in healthy adults

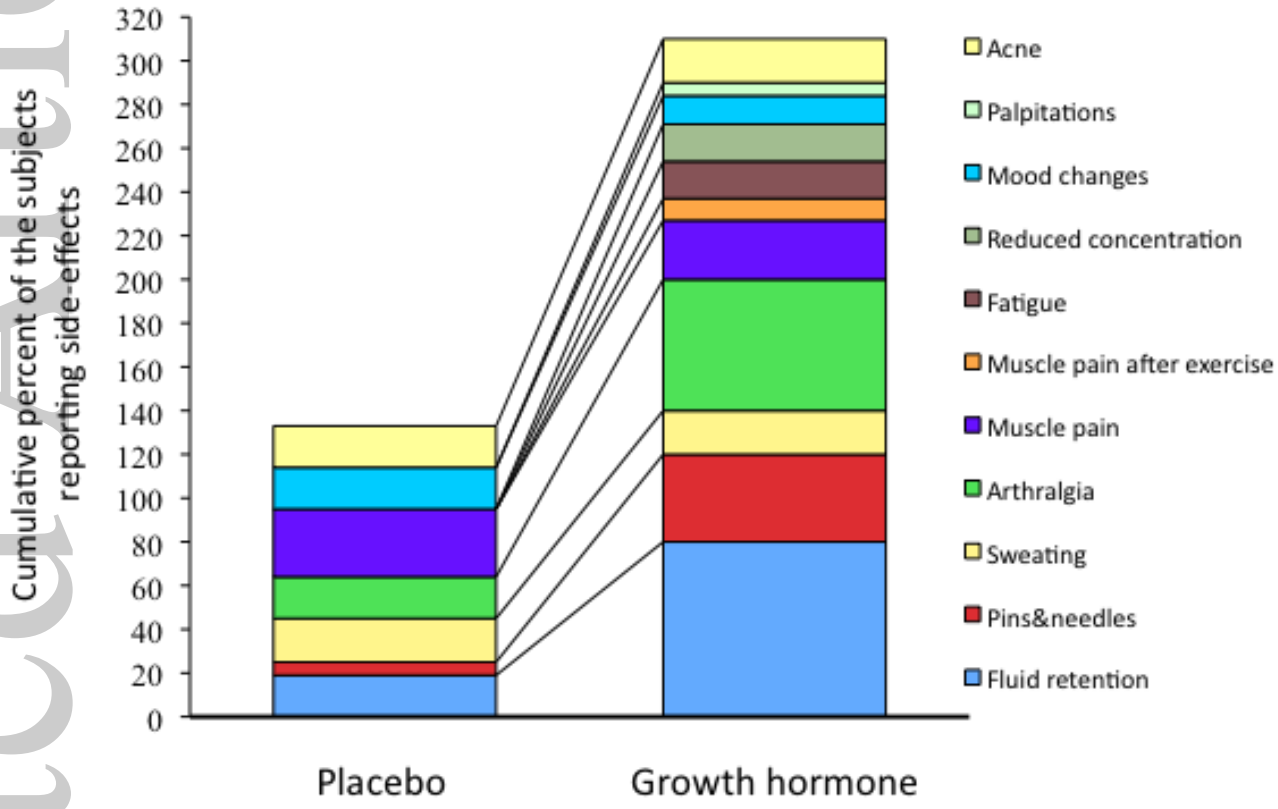
Study	Participants	GH treatment	GH dose	Outcome measures
[77]	Highly trained men (7)	4 hours pre-exercise	2.5 mg	VO_2max did not change; GH prevented 2 subjects from completing the exercise protocol
[78]	Fit lean men (9)	0.75 to 3.75 hours pre-exercise	10 μg/kg	VO_2max reduced, no change in power output
[34]	Active volunteers (15 men, 15 women)	4 weeks	33 μg/kg/d 67 μg/kg/d	VO_2max, power output, muscle mass did not change
[79]	Highly trained men (22)	6 weeks	30 μg/kg/d	No effect on muscle strength
[11]	Recreational athletes (63 men, 33 women)	8 weeks	2 mg/d	VO_2max, muscle strength, power did not change; anaerobic exercise capacity increased
[30]	Untrained men (18)	12 weeks combined with exercise	40 μg/kg/d for 5 d/week	Muscle strength improved with exercise, but similar improvement in placebo and GH groups

Figure 1



The most frequently reported adverse effects of AAS abuse.

Figure 2



Summary of side effects reported in double-blind placebo controlled studies in healthy adults of GH administration. Data are presented as cumulative percent of the subjects reporting side effects during GH and placebo administration [11, 30, 34, 38, 80-82].