

·Review·

# Physiological and pharmacological basis for the ergogenic effects of growth hormone in elite sports

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## Abstract

Growth Hormone (GH) is an important and powerful metabolic hormone that is secreted in a pulsatile pattern from cells in the anterior pituitary, influenced by several normal and pathophysiological conditions. Human GH was first isolated in the 1950s and human derived cadaveric GH was initially used to treat patients with GH deficiency. However, synthetic recombinant GH has been widely available since the mid-1980s and the advent of this recombinant GH boosted the abuse of GH as a doping agent. Doping with GH is a well-known problem among elite athletes and among people training at gyms, but is forbidden for both medical and ethical reasons. It is mainly the anabolic and, to some extent, the lipolytic effects of GH that is valued by its users. Even though GH's rumour as an effective ergogenic drug among athletes, the effectiveness of GH as a single doping agent has been questioned during the last few years. There is a lack of scientific evidence that GH in supraphysiological doses has additional effects on muscle exercise performance other than those obtained from optimised training and diet itself. However, there might be synergistic effects if GH is combined with, for example, anabolic steroids, and GH seems to have positive effect on collagen synthesis. Regardless of whether or not GH doping is effective, there is a need for a reliable test method to detect GH doping. Several issues have made the development of a method for detecting GH doping complicated but a method has been presented and used in the Olympics in Athens and Turin. A problem with the method used, is the short time span (24–36 hours) from the last GH administration during which the test effectively can reveal doping. Therefore, out-of-competition testing will be crucial. However, work with different approaches to develop an alternative, reliable test is ongoing. (*Asian J Androl 2008 May; 10: 373–383*)

**Keywords:** growth hormone; IGF-I; doping; doping test; athletes; maximum exercise test; supraphysiological; anabolic androgenic steroids; bone markers

## 1 Introduction

Doping with growth hormone (GH) is a well-known problem in the world of sports and has been known for decades [1]. GH was described as a potent performance-enhancing anabolic agent in *The Underground Steroid Handbook* first published in California in the early 1980s [2]. Its misuse has since increased, especially since the advent of recombinant GH in the late 1980s. It rapidly gained popularity as it was said to be “efficient, hard to detect and without major side-effects” and users

can currently be found both among elite athletes and among people training at gyms [3, 4].

It is mainly the anabolic and, to some extent, lipolytic effect of GH that is valued by users since a reduction in fat mass, especially centrally located fat mass, is a desirable GH effect in a doping situation, especially in bodybuilding competitions where a minimum of visible body fat is rewarded.

## 2 Historical background

The existence of a growth-promoting substance in the anterior hypophysis was described in animals in the 1920s [5]. Human GH was first isolated by Li *et al.* [6] in 1956 and, in the early 1970s, the structure of GH was subsequently shown to consist of a single polypeptide

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chain of 191 amino acids with two disulphide bridges and a molecular weight of 22 kDa [6–8]. It was then stated that 22 kDa GH is the major isoform of GH but a 20 kDa GH variant comprises 5%–10% of the pituitary GH and that a number of other isoforms produced by the pituitary also exist [9, 10]. The gene for GH has been cloned and characterised and synthetic GH is currently produced in bacteria using recombinant DNA technology [11].

Children with GH deficiency (GHD) have been treated with GH since the 1950s, when it was demonstrated that treatment with human GH, purified from cadaver pituitaries increased linear growth [12]. The first paper describing GH treatment in adults was presented in 1962 [13] and described the treatment of a 35-year-old GHD woman with human GH. The patient noticed “increased vigour, ambition and sense of well-being” after two months of treatment [13]. Treatment with GH was however initially restricted by the limited supply of GH and also by the recognition of the risk of Creutzfeldt-Jacobs disease with cadaveric GH, before the advent of widely available recombinant human GH in the mid-1980s. The introduction of recombinant GH made it possible to further study the effects of GH in adults and the consequences of the clinical entity of GHD, including its treatment, have been well described [14–17].

### 3 Physiology of GH secretion

GH is secreted in a pulsatile pattern from somatotrope cells in the anterior hypophysis, regulated in a complex pattern by two hypothalamic peptides; a stimulating hormone, GH releasing hormone (GHRH), and an inhibiting hormone, somatostatin [18–21].

GH secretion is influenced by several normal and pathophysiological conditions, such as gender, age, sleep, physical exercise, nutritional state and other metabolic factors.

#### 3.1 Gender

A difference between men and women in the GH release at rest, with greater release in young women than in age-matched men, has been described [22–24]. Gonadal steroids interact with GH and the administration of oestrogen increases serum levels of GH [25–29]. Testosterone and GnRH treatment in hypogonadal men has been shown to increase GH secretion [30]. Oestrogens enhance GH secretion, mainly indirectly by inducing GH resistance resulting in higher serum levels of GH in females of reproductive age, a somewhat different secretion pattern and GH production rate [21, 29].

#### 3.2 Age

It has been estimated that there is a 14% decrease in GH secretion per decade of adult life, following a peak

during puberty [31].

#### 3.3 Sleep

The GH levels are highest during slow wave sleep and lowest during rapid eye movement sleep [32].

#### 3.4 Physical exercise

Physical exercise has a stimulatory effect on GH secretion [33]. The GH levels rise in response to acute exercise, with a threshold level of approximately 70% of  $\text{VO}_2\text{-max}$  [34], and a twofold rise in GH concentrations after a year of high-intensity aerobic training has been shown in subjects who exercised consistently above the lactate threshold [35].

#### 3.5 Nutritional state and other metabolic factors

Fasting results in enhanced GH production [36], while it is suppressed by glucose [37] and fatty acids [38]. Certain amino acids such as leucine and arginine enhance GH secretion [39, 40].

#### 3.6 Hormones

Hyperthyroidism is associated with increased GH secretion [41], while hypothyroidism is associated with low GH levels [42]. The net effect of corticoids is inhibition of the GH secretion [43].

#### 3.7 Neurotransmitters

Both  $\alpha_2$ -adrenergic agonists and cholinergic agents stimulate GH secretion [44], the latter probably via suppression of somatostatin release [45].

## 4 GH and muscles

GH is an important and powerful metabolic hormone. An anabolic effect by GH in normal adults was demonstrated in 1958 by Ikkos *et al.* [46] who observed a nitrogen-retention effect after GH administration. Patients with untreated acromegaly have shown a markedly increased body cell mass estimated from assessments of total body potassium [47]. The body cell mass in acromegalic patients decreases in response to surgical treatment [48]. Furthermore, it has been shown that acromegaly causes myopathy with hypertrophic, but functionally weaker muscles [49, 50]. This could indicate that there are negative effects on muscle function following exposure to high levels of GH for a long period of time.

GH promotes the positive protein balance in skeletal muscle by increasing protein synthesis and possibly by inhibiting protein breakdown [51].

Adult GHD patients have a reduced muscle mass, isometric muscle strength and functional exercise capacity compared with healthy controls [52, 53]. Furthermore, isokinetic muscle strength and local muscle endurance

are reduced or in the lower range [52, 54–56]. The reduced muscle mass and isometric strength could be an effect of reduced muscle cross-sectional area in GHD patients [57], but it could also be caused by a reduction in the peak torque per muscle area [58], suggesting that contractile properties and neural activation might be responsible for the reduction in muscle strength in adult GHD patients.

GH replacement therapy in GHD adults increases lean body mass (LBM), exercise capacity, muscle volume, muscle mass and maximum voluntary isometric muscle strength [15, 52, 55, 59–63]. The changes in muscle mass and maximum voluntary isometric muscle strength has been shown to become apparent after approximately one year of therapy [55]. However, dynamic muscle strength has not shown any obvious increase in response to GH treatment [60, 64].

The proportion of fast-twitch, type-2 muscle fibres is increased in hypophysectomised rats [65]. However, the histology of muscles from GHD patients does not appear to differ from that of healthy adults [66] and it has not been possible to detect any changes in the proportions of muscle fibres in adult GHD patients receiving GH treatment [66, 67].

## 5 Lipolytic effects of GH

The lipolytic effects of GH have been known for decades. GH-induced lipolysis was first demonstrated in humans in 1959 [68]. Lipolytic effects have also been demonstrated in GHD and acromegaly patients. GHD patients have increased total body fat and reduced body cell mass and extracellular water (ECW) [69, 70]. GH treatment given to these patients improves the body composition [17, 54, 71]. Furthermore, patients with untreated acromegaly have a marked decrease in adipose tissue mass compared with normal individuals [47] and surgical treatment results in an increase in the fractions of adipose tissue in the subcutaneous trunk and the intra-abdominal depots, while the fractions of adipose tissue in peripheral depots decrease [48].

Meals inhibit GH release, whereas fasting conditions amplify the pulsatile pattern of GH secretion [72], indicating that the main impact of GH is in the fasting state. Dose-dependent action by GH on the induction of lipolysis has been demonstrated, with an elevation of circulatory free fatty acids (FFAs) and glycerol and increased lipid oxidation rates [73]. These effects occur despite increased insulin levels, indicating that relatively low doses of GH can overcome the lipogenic actions of insulin. GH stimulates lipolysis by activating hormone-sensitive lipase activity, with a subsequent increase in lipid oxidation [74].

## 6 Antinatriuretic effects of GH

A sodium-retention effect with the simultaneous expansion of ECW after GH administration was demonstrated in 1952 [75]. Even though it is not the main focus of attention in a doping situation, the anti-natriuretic effect of GH is still of interest.

The sodium and water-retaining effect of GH is complex. To summarise, both GH and IGF-I are capable of causing fluid retention by stimulating  $\text{Na}^+\text{K}^+\text{ATPase}$  activity in the distal nephron [76]. However, the stimulation of the renin-angiotensin-aldosterone system (RAAS) [77], the down-regulation of atrial natriuretic peptide (ANP) [78] and increased endothelial nitric oxide (NO) function have also been proposed as possible mechanisms [79].

The anti-natriuretic effects of GH explain the reduction in ECW that is found in adult patients with severe GHD and the marked increase in ECW found in acromegalic patients [47, 69]. However, the exact mechanisms behind these effects are unknown. ECW is increased by as much as 25% in untreated acromegaly patients, an increase that normalises after successful treatment [80]. After treatment, the excess ECW correlates with the GH concentrations [80]. Further studies of acromegalic patients suggest a curve-linear dose-response relationship between GH concentrations and excess ECW [80, 81].

## 7 GH effects on bone

GH has a stimulating effect on both osteoblasts and osteoclasts and is thereby involved in the regulation of bone metabolism [82–84], leading to both bone formation and resorption [85, 86]. The osteoclasts, osteoblasts and components of the bone matrix release several peptides and proteins into the circulation during bone resorption and formation: peptides and proteins that can be used as biochemical markers of bone metabolism.

In adult GHD patients, both normal [87] and reduced [88] serum levels of biochemical markers of bone turnover have been shown. Several studies of hypopituitary patients have shown that GH treatment accelerates bone turnover [85, 89, 90]. Furthermore, it has been shown that biochemical markers of bone formation and bone resorption increase within a few weeks after the initiation of GH treatment in GHD adult patients [91].

## 8 GH doping among athletes and in the gyms

GH-doping is mostly seen in sporting disciplines that favour strength and explosivity, that is among weightlifters, body builders, football players (American football) and sprinters, but to some extent also in endurance athletes. It is also used by some female athletes, who want to avoid the androgenic side-effects of the AAS. The exact figures of GH-doping among elite athletes and among people training in gyms are not known and there is a lack of studies

on the prevalence of GH usage. One study has reported that 5% of male American high-school students used or have used GH as an anabolic agent [3]. However, this study was published in 1992 and whether the results are valid today is not sure. Furthermore, the figures in this study are based on self-reports in a survey and there might be a risk of an overestimation of the usage, since GH might have been considered as an anabolic steroid, resulting in a higher prevalence. GH is often administered 3–10 mg/day, 3–4 times per week when taken alone, and 1–3 mg daily if combined with AAS, thus well above the doses given in cases of adult GH-deficiency. The administration is usually taken in cycles that vary from 6–12 weeks to 6–12 months in length. However, different patterns and doses have been described.

The fact that most abusers probably use GH in combination with AAS and that this combination possibly has an anabolic effect, due to synergistic actions between the two agents, is important to take into account when discussing GH as a doping agent.

## 9 Doping with GH

This misuse of GH is forbidden for both medical and ethical reasons. Several issues have made the development of a method for detecting GH doping complicated [92]. It is, for example, not possible to distinguish exogenous recombinant GH from endogenous GH in a blood or urine test. Furthermore, GH secretion is influenced by many different factors such as exercise, food intake, sleep and stress [23]. A test method based on the different GH isoforms has been presented and used in the Olympics in Athens and Turin [93, 94]. However, there are some disadvantages with this method. The previous lack of an official method to discover GH doping, might partly explain the strong position GH is thought to enjoy as a doping agent in elite sports.

The GH-2000 project was initiated by the International Olympic Committee (IOC) with the aim of developing a method for detecting GH doping among athletes. The project was funded by the European Union (EU) BioMed2 Research Programme, with additional support from industry and the IOC.

Prior to the start of the GH-2000 project, Wallace *et al.* [95–98] studied the effects of exercise and supra-physiological GH administration on the GH/IGF-I axis and bone markers in 17 athletic adult males. To summarise, acute exercise increased all the molecular isoforms of GH, with 22 kDa GH constituting the major isoform, with a peak at the end of acute exercise [95]. The proportion of non-22 kDa isoforms increased after exercise, due in part to the slower disap-

pearance rates of these isoforms. With supra-physiological GH administration, these exercised-stimulated endogenous GH isoforms were suppressed for up to four days [96]. Moreover, all the components of the IGF-I ternary complex transiently increased with acute exercise and GH pre-treatment augmented these exercise-induced changes [97]. Furthermore, acute exercise increased the serum concentrations of the bone and collagen markers, bone-specific alkaline phosphatase, carboxy-terminal cross-linked telopeptide of type I collagen (ICTP), carboxy-terminal propeptide of type I procollagen (PICP) and procollagen type III (P-III-P), while osteocalcin was unchanged. GH treatment resulted in an augmented response to exercise of the bone markers PICP and ICTP [98].

A forthcoming method to discover GH abuse will probably necessitate the use of specific markers of the GH/IGF-I axis and bone markers, with the prerequisite that these variables are more sensitive to exogenous GH administration than to exercise. As a result, it will be important closely to study how the levels of these variables are influenced by a maximum exercise test in comparison to rest and by other factors such as gender, age, fitness, type of sport, medication, menstrual status or illness. Furthermore, it will be important to closely study the effects of different types of injuries, for example fractures, on the specific markers.

## 10 GH and exercise

Physical training has been shown to change circulating levels of GH and, more inconsistently, IGF-I in normal subjects in relation to improvements in oxygen uptake and muscle strength [99–102].

It is well known that acute exercise above a certain intensity is one of the most potent stimulators of GH secretion and the magnitude of the GH response is closely related to the peak intensity of exercise, rather than to total work output [33, 34, 103]. Exercise not only mediates the acute effects on GH secretion. It has been shown that one year of endurance training above the lactate threshold, increases the basal 24-h pulsatile GH release [35]. Interestingly, subjects training below the lactate level did not show any change in the GH release, indicating that the training intensity may be important in regulating the GH-axis as well as fitness. This physiological GH increase in response to exercise and to other stimuli such as hypoglycemia makes it difficult to use measurements of GH itself in blood as a doping marker, as it would be difficult to discriminate a high exercise-derived endogenous GH level from that resulting from exogenous GH.

In addition, bone markers have been shown to respond to exercise and the effects of low-intensity

endurance-type activity or brief high-intensity or resistance exercise have shown no acute change [104–106], increased markers [107, 108] or transient decreased markers [106]. Furthermore, studies of high-intensity exercise showed no rise in PICP or ICTP in response to exercise [104, 106, 108]. This could suggest that the duration of exercise is important in the response by bone markers to acute exercise.

## 11 Variability

Acute exercise above a certain intensity is one of the most potent stimulators of GH secretion. It is well known that elite athletes are able to train at much higher intensities than the normal population and that, during a training season, there are significant differences in training intensity, which might influence GH secretion. Many of the GH-related mediators, binding proteins and markers do not exhibit the same fluctuations as GH and there is a real lack of knowledge about the seasonal stability of markers of the GH/IGF-I axis and circulating bone markers in athletes. A study of seasonal patterns of sleep stages and secretion of cortisol and GH during 24-hour periods in northern Norway revealed no difference in GH secretion as a function of season of the year [109]. Another study reveals no circannual rhythm of plasma GH in pre-pubescent subjects [110].

There is some evidence that biological rhythms of bone turnover over long periods, such as circannual variation, exist [111–118]. Woitge *et al.* [118] have shown that seasonal variation contributes to the biological variability in bone turnover and needs to be taken into account when interpreting the results of bone marker measurements.

## 12 Supraphysiological doses of GH: effects on muscles, power, exercise capacity and body composition

GH plays a regulatory role in the maintenance of normal body composition through its well-known anabolic, lipolytic and antinatriuretic actions. These effects are easily demonstrated when GH-substitution therapy is initiated in patients with GHD, reversing muscle atrophy and decreasing central abdominal adiposity and dry skin, signs typically associated with GHD [15, 17, 119]. The anabolic actions of GH include stimulated protein synthesis through the mobilisation of amino-acid transporters, which is reflected *in vivo* by an increase in the metabolic clearance rate of amino acids. IGF-I also directly stimulates protein synthesis, albeit to a lesser extent than GH, while insulin inhibits protein breakdown [120–124].

Even though GH has been regarded as an effective ergogenic drug among athletes since the 1980s, only

a few controlled studies of the effectiveness of GH in relation to physical performance and the effects on body composition in athletes have been performed. A study of 16 young, healthy adults revealed no differences between the GH or placebo group in terms of muscle size, strength or muscle protein synthesis after GH (40 µg/kg/day) or placebo treatment for 12 weeks combined with heavy-resistance exercise. However, fat free mass (FFM) and total body water (TBW) increased in both groups but significantly more among the GH recipients [125]. Another study of 22 power athletes assigned in a double-blind manner to either GH treatment (30 µg/kg/day) or placebo for a period of six weeks revealed no difference between the groups in terms of maximum voluntary strength (biceps or quadriceps) and no change in body weight or body fat, but a remarkable increase in IGF-I was noted [126]. Crist *et al.* [127] found increased fat free weight and decreased body fat in eight well-trained adults when given 2.67 mg of GH 3 days/week for six weeks. A study of healthy, experienced male weightlifters before and at the end of 14 days of subcutaneous GH administration (40 µg/kg/day) revealed no increase in the rate of muscle protein synthesis or reduced whole body protein breakdown, metabolic alterations that would promote muscle protein anabolism [128]. In a placebo-controlled study by Healy *et al.* [129] including 11 endurance-trained athletes, who received supraphysiological GH-doses (67 µg/kg/day) or placebo during four weeks, it was concluded that GH had a net anabolic effect on whole body protein metabolism at rest and during and after exercise. The whole body protein metabolism was measured with a 1-(<sup>13</sup>C) leucine method. Although no muscle power test was performed in the study, it was thus speculated that the acute excess GH administration might have short-term benefits for physical performance. Finally, in two studies from our own group, we found that treatment with supraphysiological doses of GH during one month given to healthy individuals resulted in a decrease in body fat, an increase in ECW but no visible effect in ICW, indicating limited anabolic effect on muscles. Furthermore, no improvements in power output or oxygen uptake in a bicycle exercise test before and after treatment were observed [130, 131].

Some studies performed on elderly men show the same results. A study of healthy, sedentary men with low serum IGF-I levels who followed a 16-week progressive resistance-exercise program (75%–90% max strength, 4 days/week) after random assignment to either a GH (12.5–24.0 µg/kg/day) or placebo group showed that resistance-exercise training improved muscle strength and anabolism, but these improvements were not enhanced when exercise was com-

bined with daily GH administration [132]. Further supportive findings of the lack of effect are found in elderly but not particularly GH-deficient men. Taffee *et al.* [133, 134] were unable to see any increase in strength, muscle mass or fibre characteristics after GH treatment during a resistance-exercise training programme.

There is a discrepancy between GH's rumour as a strong anabolic agent and the lack of effects seen in the studies performed. There are some different explanations to this that might be taken into consideration. The doses used in the different studies might be too low, even though being supraphysiological and thought to be equal to the doses used by GH abusers. Furthermore, most abusers probably use GH in combination with AAS and this combination might have an anabolic effect, due to synergistic actions between the two agents.

The reduction in fat mass, especially centrally located fat mass, has also been suggested as a desirable GH effect in a doping situation, especially in bodybuilding competitions where a minimum of visible body fat is rewarded.

### 13 Side-effects of GH

The fear of the well-known side-effects of GH also reduces its use in the gyms. The fluid retention symptoms with swollen hands and feet and carpal tunnel syndroms reduce the exercise performance, thereby limiting the potential of GH as a powerful doping agent.

Long-term use also increases the risk for ordinary acromegalic symptoms. Due to high costs of the "clean" rhGH, some athletes use the cheaper cadaveric GH, with the potential risk of ending up in fatal Creutzfeldt-Jacobs disease.

### 14 GH doping: current and future aspects

The use of GH as a doping agent is widespread and doping with GH has become an increasing problem in sports and among young people at ordinary gyms during the last 10–15 years [3, 4, 135]. The actual use of GH as a doping agent is not known, but 5% of male high-school students in the USA have been reported to have used it [3]. The GH abusers primarily aim to benefit from the potential anabolic effects of GH, mostly in combination with AAS, in order to increase muscle mass and muscle power. It has also been popular among female athletes, who wish to avoid the androgenic side-effects of anabolic steroids. However, our own interviews with hormone abusers (to be published elsewhere) indicate a more differentiated pattern of GH doping, revealing that its effect is preferentially on muscle volume, and not on muscle strength, thereby making it more popular among body-

builders than among weightlifters.

Although previous reports from GH-abusing athletes uniformly describe the positive effects of GH doping on muscle volume and strength [135], the effectiveness of GH as a doping agent has been questioned during the last few years. There is a lack of scientific evidence that GH in supraphysiological doses has additional effects on muscle exercise performance than those obtained from optimized training and diet itself [125, 126, 128, 134, 136–138]. These data have initiated speculations that the reputation of GH as an effective doping agent is highly exaggerated, at least when taken alone. However, in elite athletes, even a small increase in muscle power or exercise performance might make the difference between a gold or silver medal. Furthermore, there is a great deal of counterfeit, inactive GH present on the black market, complicating the real picture of the effectiveness of GH as a doping agent.

There are risks involved with GH abuse. Several potential risk factors have been suggested by observations in GH-supplemented and acromegalic patients, including carpal tunnel syndrome and pitting edema [139], myocardial hypertrophy, and cancer [140, 141]. Because GH needs to be injected there is also a risk of hepatitis and HIV if the abusers share syringes. Finally, cadaver-derived GH is still present on the black market and abusers using this could acquire the fatal Creutzfeldt-Jacob disease [4, 142].

Taken as a whole, there is no published evidence of any anabolic effect on muscles or positive effects on physical performance as a result of GH alone or combined with exercise [136–138].

It has been claimed that one main function of GH is its stimulating effect on collagen synthesis and that this might have positive consequences for athletes [143, 144]. In a review, Doessing and Kjaer [143] concluded that supraphysiological doses of GH do not appear to increase the synthesis of myofibrillar protein, but that it is possible that a supraphysiological GH level has an effect on connective tissue. It is known that the GH/IGF-I level is associated with pathological changes in connective tissue in patients with clinical conditions involving a change in GH activity [145–150]. Furthermore, studies of healthy subjects treated with GH have revealed an increase in levels of whole body collagen synthesis [98, 151], indicating that there is a stimulatory effect on connective tissue in normal healthy subjects.

Tendons heal more rapidly in rats treated with GH [152] and anecdotal reports have suggested that GH prevents tendon and muscle ruptures, especially if combined with AAS [153]. By protecting the myotendinous junction regarded as a "weak link in the chain" in athletes training at high intensity and in those with fast-

growing muscles due to heavy resistance training and/or AAS abuse, GH could therefore enable training at even higher intensity with shorter recovery periods.

## 15 Test methods

Regardless of the effectiveness of GH, there is a huge need for the development of a test method to detect GH doping. The problem of developing a reliable method has been described in several papers and work on different approaches is ongoing [2, 92, 154, 155].

### 15.1 Isoform method

There are currently two main approaches to developing a method for detecting GH doping. The first is an isoform method, developed by the Strasburger group, based on the knowledge that normal, endogenous GH exists in a variety of isoforms. In the pituitary, the most abundant isoform is 22-kDa GH, but other isoforms (non-22-kDa GH) are present in varying amounts [156]. Recombinant GH, in contrast, is solely made up of the 22-kDa isoform. Wallace *et al.* [96] have shown that all the measured isoforms of GH increased during and peaked at the end of acute exercise, with 22-kDa GH constituting the major isoform in serum during exercise. They also found that the proportion of non-22-kDa isoforms increased after exercise, due in part to slower disappearance rates of 20-kDa GH and perhaps other non-22-kDa GH isoforms. Furthermore, it has been shown that supraphysiological doses of GH in trained adult males suppressed exercise-stimulated endogenous circulating isoforms of GH for up to 4 days and that the clearest separation of treatment groups required the simultaneous presence of high exogenous 22-kDa GH and suppressed 20-kDa or non-22-kDa GH concentrations [95].

Consequently, even if it is not possible directly to distinguish exogenous recombinant GH from endogenous GH in a blood or urine test, the method developed by the Strasburger group, which was used in the Athens Summer Olympics (2004) and in the Turin Winter Olympics (2006), is based on the change in the normal ratio of 22/non-22-kDa GH isoforms after treatment with exogenous GH. One disadvantage with this isoform-based method, however, is that it is only able to detect GH up to 24 h after the last treatment and, therefore, out-of-competition testing will be crucial.

### 15.2 GH marker-based method

The other approach to detecting GH misuse is to use longer-lasting GH-dependent markers. This approach, used by the GH-2000 group, involves markers that are more sensitive to exogenous GH substitution than exercise-induced GH increase. Several papers from GH-2000 have been published [129, 151, 157–160] and the results

from the GH-2000 group have resulted in mathematical, statistical formulae that have been presented as a potential test for detecting GH doping [160]. This method has then been further validated in a study stating that the test proposed by the GH-2000 study group can be used to detect subjects receiving exogenous GH [161].

However, some questions still remain before an accurate, reliable method is found. The test proposed by the GH-2000 study group requires further evaluation and discussion before it can be finally accepted as a doping test. Any test to detect drug abuse in sport must minimize the risk of a false positive result.

## 16 Conclusion

The role of GH as an effective anabolic muscle doping agent, when taken alone, is questioned. GH might be effective, in lower doses, when taken together with AAS. GH doping does not seem to have any positive effect on cardiac performance. Fluid retention and other acromegalic side-effects further reduce its use. However, GH seems to stimulate collagen synthesis, which might have a positive, protective effect on ruptures of muscles and tendons, and allow harder training with a shorter recovery period, thus explaining its ongoing use in doping areas. It cannot be excluded that this effect on collagen synthesis might be useful in a few years in clinical practice for the treatment of muscle and tendon ruptures.

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