Review

# Growth hormone and physical performance

**Vita Birzniece, Anne E. Nelson and Ken K.Y. Ho**

Pituitary Research Unit, Garvan Institute of Medical Research and Department of Endocrinology, St Vincent's Hospital, Sydney, NSW 2010, Australia

**There has been limited research and evidence that GH enhances physical performance in healthy adults or in trained athletes. Even so, human growth hormone (GH) is widely abused by athletes. In healthy adults, GH increases lean body mass, although it is possible that fluid retention contributes to this effect. The most recent data indicate that GH does not enhance muscle strength, power, or aerobic exercise capacity, but improves anaerobic exercise capacity. In fact, there are adverse effects of long-term GH excess such that sustained abuse of GH can lead to a state mimicking acromegaly, a condition with increased morbidity and mortality. This review will examine GH effects on body composition and physical performance in health and disease.**

## GH abuse in athletes

Doping with GH is a well-known problem in the world of sports and GH abuse has increased since the availability of recombinant GH in the late 1980 s. Human GH (hGH) is abused by athletes in the hope of improving their performance and to shorten recovery after injury. The increasing popularity of GH among athletes stems from its anabolic and lipolytic properties, and the difficulty of detection [1]. Exogenous hGH is indistinguishable from the GH produced in the pituitary gland, and given the short half-life of hGH (approx 25 min), the window of detection is fairly small. The test implemented for hGH is based on the GH isoform approach [2] and is a major breakthrough in the fight against doping with hGH. The test is based on immunological detection and differentiation between pure 22 kDa recombinant GH from a mixture of GH isoforms secreted from the pituitary gland. New tests have recently been developed using a GH marker approach which increases the window for detection of doping with hGH [3,4]. This approach is based on detecting changes in the blood levels of GH-dependent markers, such as IGF-I and collagen peptides.

GH is listed in the 2010 Prohibited List (http://www.wada-ama.org/rtecontent/document/2010_Prohibited_List_FINAL_EN_Web.pdf) because of its theoretical potential to enhance sports performance and because of the health risks that it poses. Abuse of GH can start at a young age. An early survey of 10$^{th}$ grade boys in the US indicated that 5% had taken GH, with more than half using GH in conjunction with steroids [5]. A web-based survey reported use of GH together with anabolic androgenic steroids by 25% of steroid users [6]. There is anecdotal evidence that hGH is abused in doses ranging from approximately 10 to 25 IU per day, 3–4 times per week, equating to 5–15-fold above the daily production rate [7,8]. Ironically, despite the large doses being administered, the evidence for a beneficial effect on physical performance is weak.

There are limited and conflicting data on the effects of GH on body composition and physical function in healthy adults, despite strong evidence of benefit in adults with GH deficiency. This review will examine the consequences of GH deficiency, the impact of replacement, and the effects of GH supplementation in healthy adults on protein metabolism, body composition and physical function including muscle strength, aerobic and anaerobic exercise capacity. The review will also examine the health risks posed by long-term hGH abuse.

## Role of GH in adult life

The effects of GH replacement in GH-deficient adults provide a good model for understanding its role in adult life. In adults with GH deficiency (GHD) there is deterioration of cardiovascular health, physical performance and general well-being. GHD results in a reduction of lean body mass, and an increase in fat mass (FM) and central abdominal obesity [9] arising from a loss of anabolic and lipolytic activity [10]. GH replacement returns body composition to normal [11,12]. In adults with GHD, GH replacement results in a reduction in FM by up to 20% and an increase in lean body mass (LBM) by up to 7% [12–16]. Adults with GHD have reduced protein synthesis compared with healthy controls [17]. Short-term GH replacement in GHD adults results in a reduction in protein loss, whereas the anabolic effects associated with long-term replacement appear to be related to increased partitioning of amino acids for protein synthesis [15,18–20]. Thus, GH plays an important role in optimizing fat and protein metabolism, and body composition in adult life.

Adults with GHD have reduced muscle strength [21] characterized by a reduction in muscle mass [22] and in contractile properties [23]. The evidence suggests that short-term GH replacement increases muscle strength in GHD subjects, but the effect varies widely between studies [21,24,25]. A recent meta-analysis of nine randomized placebo-controlled studies observed no significant improvement in muscle strength following GH replacement over a mean duration of 6 mo [26]; over 12 mo there was an improvement in muscle strength by up to 10% [27]. After 3 yr of GH replacement, the improvement in muscle strength

*Corresponding author:* Ho, K.K.Y. (k.ho@garvan.org.au)

  doi:10.1016/j.tem.2011.02.005 

was maintained, but at only 66% that of healthy controls [28]. Other studies also show small but persistent increase in muscle strength after 5 yr of GH replacement [29]. Therefore, long-term GH replacement in excess of 12 mo seems to be required for improved muscle strength.

In addition to reduced muscle strength, aerobic exercise capacity, typically measured as $VO_2$max, is impaired in GH-deficient adults. $VO_2$max is reduced in GHD patients by about 20% of predicted $VO_2$max for age, gender and height [21]. In a double-blind placebo-controlled study, GH replacement for 6 mo increased $VO_2$max, maximal power output and exercise time compared to placebo-treated patients [30]. In another 6 mo study $VO_2$max increased by 17% compared to only 6% in a placebo group [31]. After 5 yr of GH replacement $VO_2$max was maintained to the level close to the expected $VO_2$max for age and gender [32]. Meta-analysis of 11 randomized placebo-controlled studies showed that GH replacement improves $VO_2$max and maximal power output in GH-deficient subjects, with no association between GH dose and the degree of improvement [33]. Thus, aerobic capacity is impaired in GH deficiency and restored by replacement therapy.

Several factors could contribute to the reduced exercise capacity observed in GHD. Respiratory muscle weakness [34] and a reduction in cardiac function, such as left ventricular ejection fraction and diastolic filling at rest, occur in patients with GH deficiency [35]. In addition, GHD is associated with an increase in plasma viscosity and a reduction in plasma volume that can affect oxygen delivery and availability to the tissues [36,37]. Central effects, such as reduction in general well-being, as assessed by a standardized quality-of-life questionnaire, could also contribute to the reduced exercise capacity in GH-deficient patients [21]. Thus, following GH replacement, upon improvement of cardiorespiratory function and general well-being, exercise capacity could improve as well. In summary, replacement of GH in GH-deficient patients improves aerobic exercise capacity, although whether this is due to the direct effect on muscle function or on other factors influencing cardiovascular function, well-being and motivation, remains to be seen.

## GH, exercise and fuel utilization

The link between GH and exercise suggests a physiological role of GH in the regulation of physical health. Fitness correlates positively with GH status. Physical training increases levels of GH and IGF-I in healthy subjects [38–41]. A peak of GH concentration is detected at the end of exercise [41] with a minor gender difference in the timing of the peak GH response, which occurs earlier in female athletes [39]. Even though exercise increases GH secretion, it is not known whether GH mediates in part the beneficial effect of exercise on muscle strength. It is possible that GH administration combined with exercise could increase muscle strength beyond that of exercise alone. However, this is not supported by a study in healthy untrained men, which showed that addition of GH to resistance exercise training for 12 wk did not further improve muscle strength compared to that achieved by training alone [42]. Thus, GH offers no benefit to the major gain in muscle strength achieved through physical training. The corollary is that the effects of physical training on muscle strength far outweigh any putative effect of GH.

Exercise requires the use of metabolic fuels, such as glucose and fatty acids (FA). FA and pyruvate, a substrate of glucose derived through glycolysis, are utilized in the tricarboxylic acid cycle (TCA) cycle to produce ATP via the mitochondrial respiratory chain. GH could improve exercise performance through increased delivery of fuels, in other words GH increases plasma free FA and glycerol levels, reflecting its lipolytic effects [43]. Thus, administration of GH to athletes could increase the availability of FAs to exercising muscle, sustaining the ability to exercise. GH also elevates blood glucose levels through several mechanisms [44,45]. This could increase the amount of pyruvate derived from glucose to be used for ATP synthesis. However, gene-expression studies in muscle show that GH administration downregulates genes governing oxidative mitochondrial energy production [46]. This finding suggests that pyruvate utilization for ATP synthesis is inhibited by GH. This is supported by a finding that GH reduces pyruvate dehydrogenase [47], an enzyme that converts pyruvate to acetyl-CoA, a substrate for the TCA cycle. Thus, GH administration could be predicted to increase cell pyruvate content without stimulating oxidative mitochondrial energy production. In the cytoplasm, pyruvate can also be reduced to lactate, a process indicative of anaerobic metabolism. Indeed, GH augments the increase in lactate levels during exercise in young men [47]. The view that lactate impairs muscle force and contractility has been challenged [48]. There is strong evidence that lactate enhances muscle excitability during intensive exercise. It is an active metabolite that can move between cells and tissues where it can be recycled as a fuel through conversion to pyruvate and glucose [48,49]. Collectively, the data suggest that GH enhances glucose utilization and promotes anaerobic metabolism. Thus, during exercise, rising GH levels could shift utilization of metabolic fuels, such as glucose, to enhance certain aspects of exercise capacity.

## GH regulation of protein metabolism in healthy adults

GH exerts protein anabolic effects. This is supported by tracer studies at the tissue and whole-body levels. An increase in whole-body protein synthesis upon treatment with GH is clearly demonstrated in healthy young men [42]. GH reduces whole-body protein oxidation, indicating a protein-sparing effect [50]. During exercise, GH administration results in a smaller increase in protein oxidation compared to that induced by exercise alone [50]. Thus, GH could conserve protein during exercise. Although the whole-body protein anabolic effect is enhanced with GH administration in men undertaking resistance training, GH did not have any additional effect on quadriceps muscle protein-synthesis rate [42]. While GH induces whole-body protein synthesis in untrained men, this effect appears to be lost in highly trained athletes. When a high dose of GH (40 μg/kg/d) was administered for 2 wk to experienced athletes during weight-training routines, no change in whole-body protein synthesis was found [51]. There is further recent evidence from molecular studies that GH might not stimulate muscle protein synthesis. Administration of GH in healthy young

**Table 1. Effects of GH administration in GHD and healthy adults**

| | GH administration to GHD adults | GH administration to healthy adults |
|---|---|---|
| Body Composition | | |
| Fat mass | Reduced | Reduced |
| LBM | Increased | Increased |
| Extracellular water | Increased | Increased |
| Body cell mass | Increased | No change |
| | | |
| Physical performance | | |
| Ability to exercise | Increased | Reduced (if GH given shortly before the exercise) |
| Muscle strength | Increased (long-term therapy), no change (short-term therapy) | No change |
| $VO_2$max | Increased | No change |
| Anaerobic exercise | Not known | Increased |
| | | |
| Perceived quality of life | Increased | Not known |
| Sleep requirements | Reduced | Not known |
| Ability to concentrate | Increased | Reduced |
| Fatigue | Reduced | Increased |
| Cardiac output | Increased | Not known |

The summary of evidence from original studies, reviews and meta-analyses [10,21,25,26,33,42,43,47,53,59,60,86].

men significantly increased collagen synthesis but not myofibrillar protein synthesis, as assessed by mRNA expression in skeletal muscle biopsies [52]. These findings suggest that GH stimulation of whole-body protein metabolism is unlikely to reflect a major anabolic stimulus in skeletal muscle, especially in highly trained athletes.

## Effects of GH on body composition in healthy adults

As in adults with GH deficiency, GH exerts significant effects on body composition in healthy adults (Table 1). A meta-analysis indicated a small but overall non-significant reduction in fat mass by 0.9 kg in normal subjects with an average duration of GH administration of 4 wk [43]. In recreational athletes, 8 wk of GH treatment resulted in a mean 10% fall of fat mass versus placebo [53], confirming the observations of previous studies.

The LBM consists of extracellular water (ECW) and a functional cellular compartment predominantly composed of muscle, the body cell mass. There is strong evidence that GH increases LBM. A systematic review reported that GH increases LBM by an average of 2.1 kg in normal subjects [43]. Our recent double-blind randomized placebo-controlled study for 8 wk in recreational athletes demonstrated that treatment with GH (2 mg/d) increased LBM in men by 2.9 kg and in women by 2.5 kg versus placebo [53]. Most of the increase in LBM was accompanied by a concomitant expansion of the ECW volume – by 2.4 l in men and by 1.2 l in women. The increase in ECW is consistent with the known antinatriuretic properties of GH and is also supported by other studies reporting that GH administration increases ECW [54,55]. After removing the ECW component from the LBM measurement, no significant increase in body cell mass after GH administration was observed [53]. The data provide strong evidence that fluid retention accounts for most of the increase of LBM induced by GH.

There is anecdotal evidence that many athletes dope with a cocktail of performance enhancing drugs. It is well-known that the effect of GH on LBM is potentiated by androgens [56,57]. This is supported by our recent study of recreational athletes in whom combined administration of GH and testosterone resulted in a significantly greater increase in LBM compared to either hormone alone [53]. Furthermore, following combined GH and testosterone treatment in men there was a significant increase in body cell mass of 6% (absolute increase 2.3 kg) versus placebo [53]. Thus, combined administration of GH and testosterone could increase the functionally active compartment of LBM.

In summary, GH significantly increases LBM and decreases fat mass in healthy adults. The evidence suggests that fluid retention accounts for most of the increase in LBM induced by GH, rather than an increase in muscle mass, although there is evidence for an increase in body cell mass following combined administration of GH and testosterone.

## Effects of GH on physical performance in healthy adults

The effect of GH on physical performance in healthy adults has not been extensively studied. Systematic review was performed of 27 studies comprising 303 physically fit participants in whom the effects of GH on various measures of athletic performance were analyzed, such as muscle strength and endurance [43]. From these data, the study concluded that claims that GH enhances physical performance are not supported by the scientific literature, but noted that limited evidence is available regarding the effects of GH on key athletic performance outcomes, such as muscle strength, power, and aerobic exercise capacity [43]. There has been evidence for improved physical performance following short-term GH administration in a single-blind study, however this study was undertaken using the specific model of abstinent anabolic androgenic steroid dependents, who could be in a metabolic state exhibiting a modified response to GH [58]. Here we review double-blind placebo-controlled studies evaluating the effects of GH on physical performance in healthy subjects. Effects of GH in this section will be discussed according to different measures of physical performance, namely muscle strength and power, aerobic and anaerobic exercise capacity.

**Table 2. The effects of GH on physical performance in healthy adults**

| Study | Participants | GH dose | Treatment duration | Outcome measures | Ref |
|---|---|---|---|---|---|
| Double-blind placebo-controlled cross-over study | 7 highly trained men | 2.5 mg | 4 h pre-exercise | $VO_2$max did not change; GH prevented two subjects from completing the exercise protocol | [47] |
| Placebo-controlled, randomized within subject design | 9 fit lean men | 10 μg/kg | 0.75–3.75 h pre-exercise | $VO_2$max reduced, no change in power output | [86] |
| Double-blind placebo-controlled study | 30 active volunteers (15 men, 15 women) | 33 μg/kg/d 67 μg/kg/d | 4 wk | $VO_2$max, power output, muscle mass did not change | [60] |
| Double-blind placebo-controlled study | 18 untrained men | 40 μg/kg/d for 5 d/wk | 12 wk of GH combined with exercise | Muscle strength improved with exercise, but similar improvement in placebo and GH groups | [42] |
| Double-blind placebo-controlled study | 22 lean highly trained men | 30 μg/kg/d | 6 wk | No effect on biceps and quadriceps muscle strength | [59] |
| Double-blind placebo-controlled study | 96 recreational athletes (63 men, 33 women) | 2 mg/d | 8 wk | $VO_2$max, muscle strength, power did not change; anaerobic exercise capacity increased | [53] |

*Effects on muscle strength*

Few data are available on the effects of GH on muscle strength in healthy adults (Table 2). To the best of our knowledge, only three placebo-controlled studies have evaluated muscle strength [42,53,59]. GH administration for 12 wk combined with exercise did not enhance muscle strength compared to exercise alone [42]. Similarly, 6 wk of GH treatment revealed no positive effect on maximal voluntary strength of biceps and quadriceps muscles in 8 subjects tested [59]. In the largest study of nearly 100 recreational athletes by our group, both muscle strength, assessed by dead lift dynamometer, and muscle power, assessed by jump height, were not affected by GH (2 mg/d) for 8 wk [53]. In these trained men, coadministration of testosterone with GH in pharmacological doses also failed to improve muscle strength or power [53]. These studies show that, in healthy adults, administration of GH does not significantly improve muscle strength and power.

*Effects on aerobic exercise capacity*

Aerobic exercise capacity depends not only on muscle function but also on cardiorespiratory function and on motivation. Several studies have found no significant effect of GH on $VO_2$max [43]. Only two studies have investigated effects of longer-term GH administration on $VO_2$max in healthy adults. In a study involving 30 healthy young men and women, no significant effect was observed on $VO_2$max or on maximum achieved power output during exercise after 4 wk of GH treatment [60]. There was also no relationship between changes in IGF-I and changes in oxygen uptake or maximum achieved power output [60]. Our recent study of 96 recreationally-trained male and female athletes showed that GH administration for 8 wk did not significantly change $VO_2$max [53]. Furthermore, GH coadministration with testosterone failed to increase $VO_2$max in men [53]. There was no significant correlation between the change in IGF-I and $VO_2$max. Thus, GH administration in healthy adults does not increase aerobic exercise capacity.

*Effects on anaerobic exercise capacity*

Anaerobic capacity assesses the ability to generate a relatively high power output of brief duration and represents the capacity to exercise using predominately anaerobic sources of energy derived from phosphocreatinine degradation and glycogenolysis. It is usually measured by the Wingate test, a 30 s all-out sprint capacity test; however the effect of GH on this aspect of performance has not previously been assessed. We identified a novel enhancing effect of GH on muscle performance that is dependent on the anaerobic metabolism [53]. Sprint capacity increased significantly with GH in the group of men and women combined by 3.9%, and in men coadministered GH and testosterone by 8.3%, compared to placebo. The stimulation of sprint capacity was no longer present 6 wk after GH discontinuation [53]. This study provides the first evidence that GH enhances anaerobic exercise capacity. Thus, GH treatment could improve ability to derive acute energy requirements from anaerobic metabolism.

In summary, there appears to be no evidence that GH enhances muscle strength, power, or aerobic capacity in trained adult athletes. However, GH does increase anaerobic exercise capacity when administered alone and to a greater extent when combined with testosterone. Thus, despite the wide abuse of GH by athletes, there is little support of performance benefit except for an effect on anaerobic exercise capacity. It is not known how an improvement in Wingate performance translates to performance in the sporting field. It is conceivable that the approximately 4% increase in measure of sprint capacity that we observed could translate to an improvement of 0.4 s in a 10 s sprint over 100 m [53].

## Potential benefits of GH in elite athletes

Although there is no evidence from randomized placebo-controlled studies for significant effects of GH on physical performance in healthy adults, other than the data on anaerobic exercise capacity, the possibility remains that there still are potential benefits of GH in athletes.

Anecdotal evidence suggest that during early stages of acromegaly, GH excess might initially improve physical performance, increasing tolerance for hard training and shortening recovery time after exercise [61]. There is also evidence that GH can be beneficial in accelerating recovery from soft-tissue injury. This is based on the known effects of GH on connective tissue formation, as indicated by an increase in collagen synthesis markers [4,62]. Animal studies show that tendons heal faster after treatment with IGF-I, which increases following GH administration [63]. Evidence from human studies has been provided by the recent demonstration of increased matrix collagen synthesis in skeletal muscle and tendon by up to sixfold in a placebo-controlled study of 14 d of GH administration in healthy young men [52]. The increased synthesis in muscle and tendon collagen suggests that GH could be important in strengthening the supporting connective tissue of muscle.

Finally, there could also be a psychological effect of substance administration, namely the placebo effect. A positive effect of placebo treatment has been found in many conditions, such as pain and movement disorders, and in depression [64]. Placebo treatment can modulate pain pathways, increase endogenous opioids, and influence the neuroendocrine and immune systems [64,65]. In addition, placebo has been show to increase physical performance and pain endurance, and reduce muscle-fatigue perception [65–67]. In our recent study of GH administration [53], athletes in the placebo group who believed they were on active treatment not only had a perceived improvement on performance but also in some actual measures of physical performance [68]. The results suggest that, for some people, the placebo effect could be responsible, at least in part, for the perceived athletic benefit of doping with GH.

## Adverse effects of GH

Although the evidence for increase in physical performance is poor, there are adverse effects associated with GH use (Figure 1). The side-effects from GH arise from its anti-natriuretic, metabolic and growth-promoting properties. Most of the acute side-effects reported in healthy adults arise from fluid retention. These include edema, 'pins and needles', carpal tunnel syndrome and arthralgias [4,43,55]. Other side-effects including sweating, fatigue and dizziness have been reported after GH administration in healthy subjects [43,69]. However serious side-effects, including diabetes, could arise from its anti-insulin properties, especially with high doses of GH [70]. The severity of these adverse effects could be worsened by concurrent abuse of anabolic steroids, which could have synergistic effects with GH, such as effects on fluid retention [71] and on the myocardium [72,73]. High doses of GH negatively affect cardiac function, accompanied by an increase in left ventricular wall thickness [74]. Concomitant administration of anabolic androgenic steroids with GH results in a significant increase in left ventricular mass associated with concentric remodeling [72].

The high doses of GH abused by athletes are potentially devastating, as evidence shows from studies of patients with acromegaly. Prolonged excess of GH in acromegaly causes myopathy with hypertrophic but functionally weaker muscles [75,76]. Acromegaly often presents with hypertension [77], cardiac [78,79], metabolic and articular complications [80,81], with increased risk of diabetes [77,82] and malignant neoplasms [83–85]. The incidence of cardiovascular and cerebrovascular mortality is increased [84]. In acromegaly, overall standardized mortality rates are approximately twofold higher than in the general population, relating to an average reduction in life expectancy of around 10 yr [84].

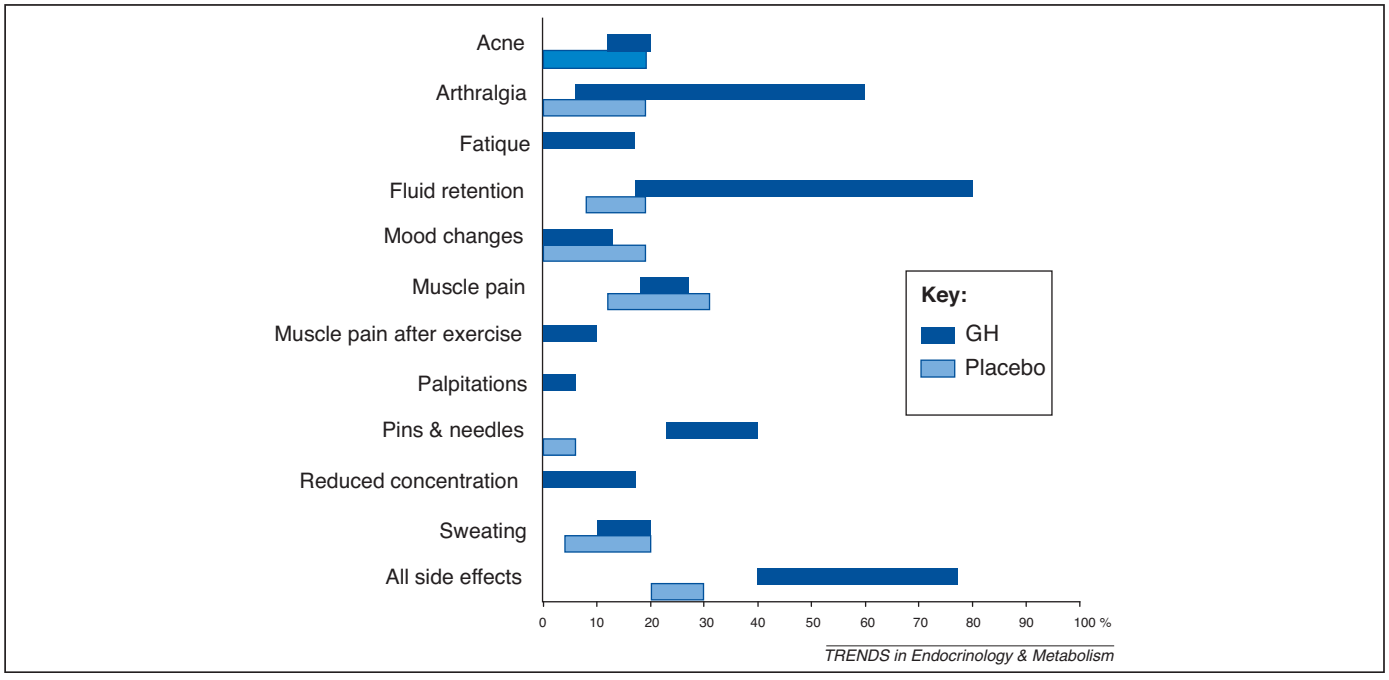


**Figure 1.** Summary of side-effects reported in double-blind placebo-controlled studies in healthy subjects of GH administration for 4–12 wk with median GH dose of 40 μg/kg/d [42,50,53,55,60,62,74]. Data are presented as a range of percent of the subjects reporting side-effects during GH and placebo administration.

The abuse of GH carries a significant health risk which could be even greater when taken as a cocktail with other substances. It is not possible to quantify the degree of harm because of the covert nature of drug-abuse culture and the ethical difficulties of undertaking research in this area. Educational programs highlighting the dangers of drug abuse have been established by organizational and governance bodies and is an approach strongly endorsed by the World Anti-Doping Agency.

## Concluding remarks

In healthy adults, GH treatment reduces fat mass and increases lean body mass; however, it seems that fluid retention accounts for most of the increase in lean body mass. Contrary to improvements in exercise capacity by GH replacement in GH-deficient adults, the evidence suggests that, in healthy adults, muscle strength, power, and aerobic exercise capacity are not enhanced by GH administration. Recent data indicate that GH might improve a selective aspect of performance, the anaerobic exercise capacity. There could be other potential benefits for athletes such as accelerating recovery from injury.

The anaerobic energy system has been a neglected area of fitness research which has focused heavily on aerobic capacity. The discovery that GH improves sprint capacity provides evidence justifying its prohibition in sports. However the physiological significance could extend beyond the sporting arena. The anaerobic energy system is an essential component of survival and function, underpinning all physical activities of daily living. The initiation of all movement and the sustainability of muscle power are dependent on the anaerobic energy system. Fatigue after a short duration of physical activity (e.g. stair climb, lifting objects) is a hallmark of anaerobic incapacity. It is conceivable that GH might play a role in improving physical rehabilitation or physical function and independence in the frail based on its positive effects on the anaerobic energy system.

### Acknowledgments

V.B. was supported by the National Health and Medical Research Council of Australia. A.E.N. was supported by the World Anti-Doping Agency and by the Australian Government through the Anti-Doping Research Program and the Department of Communications, Information Technology and the Arts.

### References

1 Holt, R.I. and Sonksen, P.H. (2008) Growth hormone IGF-I and insulin and their abuse in sport. *Br. J. Pharmacol.* 154, 542–556
2 Wu, Z. *et al.* (1999) Detection of doping with human growth hormone. *Lancet* 353, 895
3 Powrie, J.K. *et al.* (2007) Detection of growth hormone abuse in sport. *Growth Horm. IGF Res.* 17, 220–226
4 Nelson, A.E. *et al.* (2008) Pharmacodynamics of growth hormone abuse biomarkers and the influence of gender and testosterone: a randomized double-blind placebo-controlled study in young recreational athletes. *J. Clin. Endocrinol. Metab.* 93, 2213–2222
5 Rickert, V.I. *et al.* (1992) Human growth hormone: a new substance of abuse among adolescents? *Clin. Pediatr. (Phila.)* 31, 723–726
6 Parkinson, A.B. and Evans, N.A. (2006) Anabolic androgenic steroids: a survey of 500 users. *Med. Sci. Sports Exerc.* 38, 644–651
7 Saugy, M. *et al.* (2006) Human growth hormone doping in sport. *Br. J. Sports Med.* 40 (Suppl. 1), i35–i39
8 Holt, R.I. *et al.* (2009) The history of doping and growth hormone abuse in sport. *Growth Horm. IGF Res.* 19, 320–326
9 Carroll, P.V. *et al.* (1998) Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review Growth Hormone Research Society Scientific Committee. *J. Clin. Endocrinol. Metab.* 83, 382–395
10 Gibney, J. *et al.* (2007) The growth hormone/insulin-like growth factor-I axis in exercise and sport. *Endocr. Rev.* 28, 603–624
11 Gibney, J. *et al.* (1999) The effects of 10 years of recombinant human growth hormone (GH) in adult GH-deficient patients. *J. Clin. Endocrinol. Metab.* 84, 2596–2602
12 Rodriguez-Arnao, J. *et al.* (1999) Effects of growth hormone replacement on physical performance and body composition in GH deficient adults. *Clin. Endocrinol. (Oxf.)* 51, 53–60
13 Gotherstrom, G. *et al.* (2001) A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. *J. Clin. Endocrinol. Metab.* 86, 4657–4665
14 Attanasio, A.F. *et al.* (2002) Human growth hormone replacement in adult hypopituitary patients: long-term effects on body composition and lipid status – 3-year results from the HypoCCS Database. *J. Clin. Endocrinol. Metab.* 87, 1600–1606
15 Burt, M.G. *et al.* (2008) Relationship between GH-induced metabolic changes and changes in body composition: a dose and time course study in GH-deficient adults. *Growth Horm. IGF Res.* 18, 55–64
16 Wolthers, T. *et al.* (2001) Oral estrogen antagonizes the metabolic actions of growth hormone in growth hormone-deficient women. *Am. J. Physiol. Endocrinol. Metab.* 281, E1191–1196
17 Hoffman, D.M. *et al.* (1998) How is whole body protein turnover perturbed in growth hormone-deficient adults? *J. Clin. Endocrinol. Metab.* 83, 4344–4349
18 Russell-Jones, D.L. *et al.* (1993) The effects of growth hormone on protein metabolism in adult growth hormone deficient patients. *Clin. Endocrinol. (Oxf.)* 38, 427–431
19 Russell-Jones, D.L. *et al.* (1998) Effect of growth hormone treatment on postprandial protein metabolism in growth hormone-deficient adults. *Am. J. Physiol.* 274, E1050–1056
20 Shi, J. *et al.* (2003) Short- and long-term effects of growth hormone (GH) replacement on protein metabolism in GH-deficient adults. *J. Clin. Endocrinol. Metab.* 88, 5827–5833
21 Woodhouse, L.J. *et al.* (2006) The influence of growth hormone status on physical impairments, functional limitations, and health-related quality of life in adults. *Endocr. Rev.* 27, 287–317
22 Sartorio, A. and Narici, M.V. (1994) Growth hormone (GH) treatment in GH-deficient adults: effects on muscle size, strength and neural activation. *Clin. Physiol.* 14, 527–537
23 Cuneo, R.C. *et al.* (1990) Skeletal muscle performance in adults with growth hormone deficiency. *Horm. Res.* 33 (Suppl. 4), 55–60
24 Cuneo, R.C. *et al.* (1991) Growth hormone treatment in growth hormone-deficient adults I. Effects on muscle mass and strength. *J. Appl. Physiol.* 70, 688–694
25 Woodhouse, L.J. *et al.* (1999) Measures of submaximal aerobic performance evaluate and predict functional response to growth hormone (GH) treatment in GH-deficient adults. *J. Clin. Endocrinol. Metab.* 84, 4570–4577
26 Widdowson, W.M. and Gibney, J. (2010) The effect of growth hormone (GH) replacement on muscle strength in patients with GH-deficiency: a meta-analysis. *Clin Endocrinol. (Oxf.)* 72, 787–792
27 Jorgensen, J.O. *et al.* (1991) Long-term growth hormone treatment in growth hormone deficient adults. *Acta Endocrinol. (Copenh.)* 125, 449–453
28 Jorgensen, J.O. *et al.* (1994) Three years of growth hormone treatment in growth hormone-deficient adults: near normalization of body composition and physical performance. *Eur. J. Endocrinol.* 130, 224–228
29 Svensson, J. *et al.* (2003) Five years of growth hormone replacement therapy in adults: age- and gender-related changes in isometric and isokinetic muscle strength. *J. Clin. Endocrinol. Metab.* 88, 2061–2069
30 Nass, R. *et al.* (1995) Effect of growth hormone (hGH) replacement therapy on physical work capacity and cardiac and pulmonary function in patients with hGH deficiency acquired in adulthood. *J. Clin. Endocrinol. Metab.* 80, 552–557
31 Cuneo, R.C. *et al.* (1991) Growth hormone treatment in growth hormone-deficient adults II. Effects on exercise performance. *J. Appl. Physiol.* 70, 695–700

32 Cenci, M.C. *et al.* (2009) Effects of 5 years of growth hormone (GH) replacement therapy on cardiac parameters and physical performance in adults with GH deficiency. *Pituitary* 12, 322–329
33 Widdowson, W.M. and Gibney, J. (2008) The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: a metaanalysis. *J. Clin. Endocrinol. Metab.* 93, 4413–4417
34 Merola, B. *et al.* (1996) Lung volumes and respiratory muscle strength in adult patients with childhood- or adult-onset growth hormone deficiency: effect of 12 months' growth hormone replacement therapy. *Eur. J. Endocrinol.* 135, 553–558
35 Colao, A. *et al.* (2004) The severity of growth hormone deficiency correlates with the severity of cardiac impairment in 100 adult patients with hypopituitarism: an observational, case–control study. *J. Clin. Endocrinol. Metab.* 89, 5998–6004
36 Moller, J. *et al.* (1996) Decreased plasma and extracellular volume in growth hormone deficient adults and the acute and prolonged effects of GH administration: a controlled experimental study. *Clin. Endocrinol. (Oxf.)* 44, 533–539
37 El-Sayed, M.S. *et al.* (2005) Haemorheology in exercise and training. *Sports Med.* 35, 649–670
38 Giannoulis, M.G. *et al.* (2005) Gender differences in growth hormone response to exercise before and after rhGH administration and the effect of rhGH on the hormone profile of fit normal adults. *Clin. Endocrinol. (Oxf.)* 62, 315–322
39 Ehrnborg, C. *et al.* (2003) The growth hormone/insulin-like growth factor-I axis hormones and bone markers in elite athletes in response to a maximum exercise test. *J. Clin. Endocrinol. Metab.* 88, 394–401
40 Wallace, J.D. *et al.* (1999) Responses of the growth hormone (GH) and insulin-like growth factor axis to exercise GH administration, and GH withdrawal in trained adult males: a potential test for GH abuse in sport. *J. Clin. Endocrinol. Metab.* 84, 3591–3601
41 Wallace, J.D. *et al.* (2001) The response of molecular isoforms of growth hormone to acute exercise in trained adult males. *J. Clin. Endocrinol. Metab.* 86, 200–206
42 Yarasheski, K.E. *et al.* (1992) Effect of growth hormone and resistance exercise on muscle growth in young men. *Am. J. Physiol.* 262, E261–E267
43 Liu, H. *et al.* (2008) Systematic review: the effects of growth hormone on athletic performance. *Ann. Intern. Med.* 148, 747–758
44 Moller, N. *et al.* (1991) Effects of growth hormone on glucose metabolism. *Horm. Res.* 36 (Suppl. 1), 32–35
45 Ghanaat, F. and Tayek, J.A. (2005) Growth hormone administration increases glucose production by preventing the expected decrease in glycogenolysis seen with fasting in healthy volunteers. *Metabolism* 54, 604–609
46 Sjogren, K. *et al.* (2007) Growth hormone regulation of metabolic gene expression in muscle: a microarray study in hypopituitary men. *Am. J. Physiol. Endocrinol. Metab.* 293, E364–E371
47 Lange, K.H. *et al.* (2002) Acute growth hormone administration causes exaggerated increases in plasma lactate and glycerol during moderate to high intensity bicycling in trained young men. *J. Clin. Endocrinol. Metab.* 87, 4966–4975
48 Cairns, S.P. (2006) Lactic acid and exercise performance: culprit or friend? *Sports Med.* 36, 279–291
49 Philp, A. *et al.* (2005) Lactate – a signal coordinating cell and systemic function. *J. Exp. Biol.* 208, 4561–4575
50 Healy, M.L. *et al.* (2003) High dose growth hormone exerts an anabolic effect at rest and during exercise in endurance-trained athletes. *J. Clin. Endocrinol. Metab.* 88, 5221–5226
51 Yarasheski, K.E. *et al.* (1993) Short-term growth hormone treatment does not increase muscle protein synthesis in experienced weight lifters. *J. Appl. Physiol.* 74, 3073–3076
52 Doessing, S. *et al.* (2010) Growth hormone stimulates the collagen synthesis in human tendon and skeletal muscle without affecting myofibrillar protein synthesis. *J. Physiol.* 588, 341–351
53 Meinhardt, U. *et al.* (2010) The effects of growth hormone on body composition and physical performance in recreational athletes: a randomized placebo-controlled trial. *Ann. Intern. Med.* 152, 568–577
54 Moller, J. *et al.* (1991) Expansion of extracellular volume and suppression of atrial natriuretic peptide after growth hormone administration in normal man. *J. Clin. Endocrinol. Metab.* 72, 768–772
55 Ehrnborg, C. *et al.* (2005) Supraphysiological growth hormone: less fat, more extracellular fluid but uncertain effects on muscles in healthy, active young adults. *Clin. Endocrinol. (Oxf.)* 62, 449–457
56 Mauras, N. *et al.* (2003) Synergistic effects of testosterone and growth hormone on protein metabolism and body composition in prepubertal boys. *Metabolism* 52, 964–969
57 Blackman, M.R. *et al.* (2002) Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. *JAMA* 288, 2282–2292
58 Graham, M.R. *et al.* (2008) Physical effects of short-term recombinant human growth hormone administration in abstinent steroid dependency. *Horm. Res.* 69, 343–354
59 Deyssig, R. *et al.* (1993) Effect of growth hormone treatment on hormonal parameters, body composition and strength in athletes. *Acta Endocrinol. (Copenh.)* 128, 313–318
60 Berggren, A. *et al.* (2005) Short-term administration of supraphysiological recombinant human growth hormone (GH) does not increase maximum endurance exercise capacity in healthy, active young men and women with normal GH-insulin-like growth factor I axes. *J. Clin. Endocrinol. Metab.* 90, 3268–3273
61 Sharp, R.J. (2009) Land of the giants. *Growth Horm. IGF Res.* 19, 291–293
62 Longobardi, S. *et al.* (2000) Growth hormone (GH) effects on bone and collagen turnover in healthy adults and its potential as a marker of GH abuse in sports: a double blind, placebo-controlled study The GH-2000 Study Group. *J. Clin. Endocrinol. Metab.* 85, 1505–1512
63 Kurtz, C.A. *et al.* (1999) Insulin-like growth factor I accelerates functional recovery from Achilles tendon injury in a rat model. *Am. J. Sports Med.* 27, 363–369
64 Price, D.D. *et al.* (2008) A comprehensive review of the placebo effect: recent advances and current thought. *Annu. Rev. Psychol.* 59, 565–590
65 Pollo, A. *et al.* (2008) The top-down influence of ergogenic placebos on muscle work and fatigue. *Eur. J. Neurosci.* 28, 379–388
66 Benedetti, F. *et al.* (2007) Opioid-mediated placebo responses boost pain endurance and physical performance: is it doping in sport competitions? *J. Neurosci.* 27, 11934–11939
67 Beedie, C.J. and Foad, A.J. (2009) The placebo effect in sports performance: a brief review. *Sports Med.* 39, 313–329
68 Hansen, J.L. *et al.* (2008) The power of the mind: an evaluation of the placebo effect in a study of GH on physical performance. *Annual Meeting of the Endocrine Society* San Francisco, P3-750
69 Keller, A. *et al.* (2007) Pharmacokinetics and pharmacodynamics of GH: dependence on route and dosage of administration. *Eur. J. Endocrinol.* 156, 647–653
70 Young, J. and Anwar, A. (2007) Strong diabetes. *Br. J. Sports Med.* 41, 335–336 discussion 336
71 Gibney, J. *et al.* (2005) Comparison of the metabolic effects of raloxifene and oral estrogen in postmenopausal and growth hormone-deficient women. *J. Clin. Endocrinol. Metab.* 90, 3897–3903
72 Karila, T.A. *et al.* (2003) Anabolic androgenic steroids produce dose-dependant increase in left ventricular mass in power atheletes, and this effect is potentiated by concomitant use of growth hormone. *Int. J. Sports Med.* 24, 337–343
73 Mark, P.B. *et al.* (2005) Cardiomyopathy induced by performance enhancing drugs in a competitive bodybuilder. *Heart* 91, 888
74 Cittadini, A. *et al.* (2002) Supraphysiological doses of GH induce rapid changes in cardiac morphology and function. *J. Clin. Endocrinol. Metab.* 87, 1654–1659
75 Nagulesparen, M. *et al.* (1976) Muscle changes in acromegaly. *Br. Med. J.* 2, 914–915
76 Brumback, R.A. and Barr, C.E. (1983) Myopathy in acromegaly A case study. *Pathol. Res. Pract.* 177, 41–46
77 Colao, A. *et al.* (2000) Systemic hypertension and impaired glucose tolerance are independently correlated to the severity of the acromegalic cardiomyopathy. *J. Clin. Endocrinol. Metab.* 85, 193–199
78 Fazio, S. *et al.* (2000) Cardiovascular effects of short-term growth hormone hypersecretion. *J. Clin. Endocrinol. Metab.* 85, 179–182
79 Meyers, D.E. and Cuneo, R.C. (2003) Controversies regarding the effects of growth hormone on the heart. *Mayo Clin. Proc.* 78, 1521–1526
80 Colao, A. *et al.* (2005) The acromegalic arthropathy. *J. Endocrinol. Invest.* 28, 24–31

81 Wassenaar, M.J. *et al.* (2009) High prevalence of arthropathy, according to the definitions of radiological and clinical osteoarthritis, in patients with long-term cure of acromegaly: a case-control study. *Eur. J. Endocrinol.* 160, 357–365
82 Ezzat, S. *et al.* (1994) Acromegaly. Clinical and biochemical features in 500 patients. *Medicine (Baltimore)* 73, 233–240
83 Perry, J.K. *et al.* (2006) The oncogenic potential of growth hormone. *Growth Horm. IGF Res.* 16, 277–289
84 Ayuk, J. and Sheppard, M.C. (2008) Does acromegaly enhance mortality? *Rev. Endocr. Metab. Disord.* 9, 33–39
85 Orme, S.M. *et al.* (1998) Mortality and cancer incidence in acromegaly: a retrospective cohort study, United Kingdom Acromegaly Study Group. *J. Clin. Endocrinol. Metab.* 83, 2730–2734
86 Irving, B.A. *et al.* (2004) The effects of time following acute growth hormone administration on metabolic and power output measures during acute exercise. *J. Clin. Endocrinol. Metab.* 89, 4298–4305