Growth Hormone Administration: Is It Safe and Effective for Athletic Performance

Vita Birzniece, MD, PhD, Anne E. Nelson, PhD,
Ken K.Y. Ho, FRACP, MD*

KEYWORDS

• Growth hormone • Physical performance • Athletes
• Muscle strength • Anaerobic exercise capacity • Side effects

Growth hormone (GH) is listed in the 2008 Prohibited List (http://www.wada-ama.org/rtecontent/document/2008_List_En.pdf) because of its theoretical potential to enhance sports performance, its violation of the spirit of sports, and the health risks that it poses to athletes. Doping with GH is a well-known problem in the world of sports and its abuse has increased since the availability of recombinant GH in the late 1980s. Its increasing popularity stems from its anabolic and lipolytic properties, and the difficulty of detection.[1] There is anecdotal evidence that GH is abused in doses of between 5 to 15 times that of the daily production rate.[2,3] Despite large doses being administered, the evidence of a beneficial effect on performance is weak.

Fitness correlates positively with GH status[4,5] and physical training increases levels of GH and insulin-like growth factor I (IGF-I) in healthy subjects.[6–9] The maximum peak of GH is detected at the end of prolonged exercise[9] with a minor gender difference in the timing of the peak GH response, which occurs earlier in female athletes.[6] The link between GH and exercise suggests a physiologic role of GH in the regulation of physical health.

This article examines effects of GH on physical performance in the state of GH deficiency and in healthy adults, and also examines the health risks posed by long-term abuse.

GROWTH HORMONE DEFICIENCY

Consequences of Growth Hormone Deficiency on Body Composition

The effects of GH replacement in GH-deficient adults provide a useful model to understand its role in adult life. GH deficiency (GHD) results in a reduction of lean body

Pituitary Research Unit, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, New South Wales 2010, Australia
* Corresponding author.
E-mail address: k.ho@garvan.org.au (K.K.Y. Ho).

Endocrinol Metab Clin N Am 39 (2010) 11–23
doi:10.1016/j.ecl.2009.10.007 **endo.theclinics.com**
0889-8529/10/$ – see front matter

mass, muscle atrophy, and an increase in fat mass and central abdominal obesity.[10] GH has a regulatory role in optimizing body composition through its anabolic and lipolytic actions.[11] These effects are demonstrated when patients with GHD are replaced with GH. GH reverses muscle atrophy and reduces central and total body fat mass.[12,13] In adults with GHD, long-term GH replacement reduces fat mass by up to 20% and increases lean body mass (LBM) by about 3% to 7%, depending on the GH dose and the duration of treatment.[13–17]

Consequences of Growth Hormone Deficiency on Muscle Strength

Muscle strength is also reduced in patients with GHD.[18] The reduced muscle mass and strength could be an effect of reduced muscle cross-sectional area in GHD patients.[19] It could also be caused by a reduction in the power generated per muscle area,[20] suggesting that contractile properties and neural activation might be additional factors determining the reduction in muscle strength in adult GHD patients. Most open studies report that GH replacement increases muscle strength in GHD subjects but the effect is not uniform.[18] Some double-blind placebo-controlled studies show that GH replacement increases certain aspects of muscle strength,[21] whereas other studies report no beneficial effect.[22] A recent meta-analysis of nine randomized placebo-controlled studies of mean duration 6.7 months showed that short-term GH replacement does not significantly improve muscle strength in GHD patients.[23] However, Jorgensen and colleagues[24] reported an improvement in isometric knee flexion by 10% and extension by 7% after 12 months of GH treatment. After 3 years of GH replacement, the improvement in muscle strength was maintained but remained only 66% that of healthy subjects.[25] Other studies also show a small although persistent increase in muscle strength.[26] Therefore, with long-term GH replacement a certain degree of improvement in muscle strength can be expected.

Consequences of Growth Hormone Deficiency on Exercise Capacity

In addition to reduced muscle strength, aerobic exercise capacity is impaired in GH-deficient adults. Aerobic exercise capacity is typically measured by assessing maximal oxygen consumption while exercising at maximum capacity (VO_2max). VO_2max is reduced in GHD patients by about 20% compared with predicted VO_2max for age, gender, and height.[18] Cuneo and colleagues[27] in 1991 reported a 17% increase in VO_2max after 6 months of GH replacement compared with only 6% increase in the placebo group. After 5 years of GH replacement, VO_2max was maintained at the level close to that of expected VO_2max for age and gender.[28] Nass and colleagues[29] have shown in a double-blind placebo-controlled 6-month study that GH replacement in GHD adults increased VO_2max, maximal power output, and exercise time compared with placebo-treated patients. However, when VO_2max was expressed per kilogram lean body mass, there were no effects of GH compared with placebo, suggesting that increase in VO_2max may depend on changes in muscle mass from the GH supplementation.[29] A meta-analysis by Widdowson and Gibney[30] of 11 randomized placebo-controlled studies shows that GH replacement improves VO_2max and maximal power output in GH-deficient subjects independent of GH dose.

Several factors may contribute to the reduced exercise capacity in GHD. Respiratory muscle weakness[31] and a reduction in cardiac function, such as left ventricular ejection fraction and diastolic filling at rest, have been reported in patients with GH deficiency.[32] In addition, GHD is associated with an increase in plasma viscosity and a reduction in plasma volume that may affect oxygen delivery and availability to the tissues, rendering reduction in aerobic exercise capacity.[33,34] Central effects, such as reduction in general well-being, may also contribute to the reduced exercise

capacity in GH-deficient patients.[18] Thus, following GH replacement, upon improvement of cardiorespiratory function and quality of life, exercise capacity may improve as well.

In summary, replacement of GH in GH deficiency improves some aspects of exercise capacity but causes no further increase in muscle mass or strength, beyond that expected for healthy adults of the same age and gender.

HEALTHY ADULTS

Protein Metabolism

There is unequivocal evidence that GH induces a protein anabolic effect in healthy adults. This is supported by tracer studies at the tissue and the whole body levels. An increase in whole body protein synthesis upon treatment with GH is clearly demonstrated in untrained men.[35] In a placebo-controlled study, Healy and colleagues[36] reported that GH treatment significantly reduced whole body protein oxidation, thus reducing irreversible protein loss, and increased protein synthesis rate in trained men. A program of resistance exercise also increased protein synthesis in muscle[35] and, in a further study, the effect of resistance training was shown to be maintained for up to 24 hours after exercise.[37] On a whole body level, protein oxidation is also stimulated during exercise.[36] When GH was administered for 4 weeks, it resulted in a smaller increase in protein oxidation compared with that induced by 30 minutes of exercise alone, with concurrent stimulation of protein synthesis.[36] Thus, GH may conserve protein during exercise. However, administration of GH for 12 weeks in combination with training did not have an additional effect on muscle protein metabolism when compared with placebo treatment.[35] Thus, there is little evidence that supra-physiologic doses of GH administration confer an additional protein anabolic effect over and above that induced by exercise in healthy adults.

Although GH induces whole body protein synthesis in untrained men, this effect appears to be lost in highly trained athletes. When Yarasheski and colleagues[38] administered high-dose GH (40 μg/kg/d for 14 days) to experienced athletes during weight-training routines, they found no change in whole body protein synthesis. This finding suggests that GH administration modifies protein metabolism in untrained individuals but is unlikely to induce a major anabolic stimulus to skeletal muscle in highly trained athletes despite substantial increase in IGF-I levels.

Body Composition

There is good evidence that GH supplementation increases LBM in athletes. The LBM is heterogeneous, comprising an inert compartment of extracellular water (ECW) and a functional cellular compartment of mostly muscle, the body cell mass. Most methods for evaluation of LBM, such as dual-energy x-ray absorptiometry (DXA), do not distinguish lean solid tissue from fluid. Therefore, change in LBM measured by DXA alone does not distinguish between changes in muscle mass and ECW. ECW can be quantified separately using techniques such as bromide dilution[39] and when subtracted from the LBM, can be used to provide an estimate of body cell mass.

In a systematic review on the effects of GH recently undertaken by Liu and colleagues,[40] GH increased LBM by an average of 2.1 kg by meta-analysis of nine studies involving an average treatment duration of 4 weeks. What is not clear is whether increase in LBM reflects an increase in muscle mass or increase in fluid retention. Moller and colleagues[41] have reported that 2 weeks of GH treatment in healthy men increased ECW, but not intracellular water, a measure of body cell mass. Another study showed that GH treatment for 1 month reduced body fat by 7% and increased ECW by 10%.[42] As no significant increase in intracellular water was found, the

increase in lean body mass by 5% is likely accounted for by an increase in ECW volume. In a double-blind placebo-controlled study from our group, growth hormone for 8 weeks significantly increased LBM as estimated by DXA by about 2.5 kg.[43] However, there was a concomitant expansion of the ECW volume by 2 L as estimated by concurrent bromide dilution. The data provide strong evidence that fluid retention accounts for most of the increase of LBM induced by GH.

EFFECTS OF GROWTH HORMONE ON PHYSICAL PERFORMANCE IN HEALTHY ADULTS

The effect of GH on physical performance in healthy adults has not been studied rigorously. Most of the studies available have evaluated GH effects in small groups of subjects and almost exclusively in men (**Table 1**). Liu and colleagues[40] have also undertaken a systematic review of the effects of GH on various measures of athletic performance, such as muscle strength and endurance. Twenty-seven studies comprising a total number of 303 physically fit participants with mean age of 27 years and mean body mass index (BMI) of 24 kg/m^2 were considered suitable for analyses. Participants from 7 studies received GH as only one injection but 20 of the studies used GH treatment for an average of 20 days with average daily dose of 36 μg/kg. Change in strength was evaluated in two studies and exercise capacity outcomes were measured in six studies. The authors concluded that claims that GH enhances physical performance are not supported by the scientific literature.[40] However, they stressed that more research is required to conclusively determine the effect of GH on athletic performance. Recently, 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.[48]

Here we review double-blind placebo-controlled studies evaluating the effect of GH on physical performance in healthy subjects including that of a large double-blind placebo-controlled study from our center. The information is summarized in **Table 1**. Effects of GH in this section are discussed according to different measures of physical performance, namely muscle strength and power, and aerobic and anaerobic exercise capacity.

Effects on Muscle Strength

There is little information on the effects of GH on muscle strength in healthy adults. Only three studies have appropriately evaluated muscle strength and none showed any improvement after GH treatment (see **Table 1**).[35,43,44] In one study involving eight athletes, 6 weeks of GH treatment revealed no positive effect on maximal voluntary strength of biceps and quadriceps muscles.[44] Similarly, in a large group of recreational athletes, our group has recently reported that both muscle strength, assessed by dead lift dynamometer, and muscle power, assessed by jump height, were not affected by GH treatment.[43] Athletes often administer a cocktail of performance-enhancing drugs, which contains androgens and GH. However, we showed in healthy trained men, that co-administration of testosterone with GH in pharmacologic doses for 8 weeks also failed to improve muscle strength or power.[43]

Exercise is the most potent stimulant for improving muscle strength. Exercise has been shown to increase GH secretion; however, it is not known whether GH may add to the beneficial effect of exercise on muscle strength. It can be postulated that when GH administration is combined with exercise, it may increase muscle strength more than 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

Table 1
GH effect on physical performance in healthy subjects

Study	Study Type	Subjects	GH Dose	Treatment Duration	Outcome Measures
Yarasheski et al, 1992[35]	Double-blind placebo-controlled parallel study	18 untrained men	40 μg/kg/d for 5 d/wk + resistance exercise	12 weeks	Muscle strength improved with exercise, but similar in placebo and GH groups
Deyssig et al, 1993[44]	Double-blind placebo-controlled parallel study	22 lean men (power athletes)	30 μg/kg/d	6 weeks	No effect on biceps and quadriceps strength
Lange et al, 2002[45]	Double-blind placebo-controlled cross-over study	7 highly trained men	2.5 mg	4 hours pre-exercise	Bicycling speed did not change, but GH prevented 2 subjects from completing the exercise protocol; VO_2max did not change
Irving et al, 2004[46]	Randomized within-subject design of 5 GH and 1 placebo studies	9 fit lean men	10 μg/kg	0.75 to 3.75 hours pre-exercise	VO_2max reduced without a drop-off in power output
Berggren et al, 2005[47]	Double-blind placebo-controlled parallel study	30 active volunteers (15 men, 15 women)	33 μg/kg/d 67 μg/kg/d	4 weeks	VO_2max, power output, muscle mass did not change
Meinhardt et al, in press[43]	Double-blind placebo-controlled parallel study	96 recreational athletes (63 men, 33 women)	2 mg/d	8 weeks	VO_2max, muscle strength, power did not change; anaerobic sprint capacity increased

12 weeks did not further improve muscle strength compared with that achieved by training alone.[35] Taken together, these studies show that in healthy subjects, muscle strength and power do not improve after administration of GH in supraphysiological doses.

Effects on Aerobic Exercise Capacity

Aerobic exercise capacity is assessed by measuring VO_2max, which 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_2max in healthy adults, as reviewed by Liu and colleagues.[40]

In a study involving 30 healthy young men and women, Berggren and colleagues[47] found no significant effect on VO_2max or on maximum achieved power output during exercise after 4 weeks of GH treatment at two different doses, approximately 5 to 10 times daily production rate. There was no relationship between changes in IGF-I and changes in oxygen uptake or maximum achieved power output.[47] This negative finding has been confirmed by our recent large study in 96 recreationally trained athletes (see **Table 1**). GH administration for 8 weeks did not significantly change VO_2max in either men or women, and co-administration of testosterone also failed to increase VO_2max in men.[43]

It has been shown that acute GH administration may be detrimental. Irving and colleagues[46] reported that acute administration of GH reduced oxygen uptake during exercise but did not affect total work and ratings of perceived exertion. In addition, administration of GH 4 hours before exercise reduced performance in well-trained young adults.[45] Two subjects were unable to complete the 90-minute moderate- to high-intensity exercise after receiving the GH treatment.[45]

These findings differ from the beneficial effects of GH replacement in enhancing exercise capacity in GHD subjects. The duration of GH administration in studies in athletes may have been too short, and treatment for months or years may be required to show beneficial effect on physical performance, however observations in acromegaly suggest this is unlikely. Prolonged excess of GH in acromegaly causes myopathy with hypertrophic, but functionally weaker muscles,[49,50] and significantly lower VO_2max is observed in acromegaly patients, to that predicted for healthy sedentary adults of the same age, gender, and height.[51] Importantly, reduction in IGF-I following treatment of acromegaly correlates with improvement in exercise capacity.[51]

Thus, GH administration in healthy adults does not induce a stimulation of aerobic exercise capacity.

Effects on Anaerobic Exercise Capacity

There is little published evidence on assessment of GH effects on anaerobic capacity. Anaerobic capacity assesses the ability to generate a relatively high power output of brief duration and represents capacity to exercise using predominately anaerobic sources of energy, derived from phosphocreatinine degradation and glycogenolysis. It is usually measured by the Wingate test, which is a 30-second all-out sprint capacity test.

We have recently shown a novel enhancing effect of GH on muscle performance that is dependent on the anaerobic metabolism.[43] This is the first study assessing the effect of GH on anaerobic capacity in healthy men and women. Eight weeks of GH improved sprint capacity by about 6%. The effect was slightly greater in men when co-administered with testosterone, with the increase approaching 9%. This study provides the first evidence that growth hormone enhances anaerobic exercise capacity.[43]

In summary, there is no evidence from double-blind placebo-controlled studies that GH enhances muscle strength or aerobic capacity in trained adult athletes despite evidence for an anabolic effect of GH in GH-deficient patients (see **Table 1**). However, there is evidence from a recent study that GH improves anaerobic exercise capacity.

POTENTIAL BENEFITS OF GROWTH HORMONE ADMINISTRATION IN ELITE ATHLETES

There are no published studies on the effects of GH treatment in elite athletes and it is unlikely that these studies will ever be conducted for ethical reasons. Even if these studies were undertaken, it is unlikely they could be sufficiently powered to detect differences of 0.5% to 1.0% in physical performance, the small differences that separate Olympic champions from other finishing positions (http://en.beijing2008.cn/). Another factor that may influence performance relates to the potential psychological effect of any 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 depression.[52] Placebo treatment may modulate pain pathways, increase endogenous opioids and neurotransmitters, and influence the neuroendocrine and immune systems.[52,53] In addition, placebo has been shown to increase physical performance and pain endurance, and reduce muscle fatigue perception.[53–55]

Finally, there is the possibility that GH may 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 turnover markers.[56,57] Animal studies show that tendons heal faster after treatment with IGF-I.[58] Thus, the increase in IGF-I, which parallels GH treatment, may have potential beneficial effects on recovery from injury in athletes, although evidence from human studies are lacking.

GROWTH HORMONE SIDE EFFECTS

Saugy and colleagues[3] have reported that athletes may be using GH in dosages ranging from approximately 10 to 25 IU per day three to four times a week. These doses are approximately 5 to 10 times the daily production rate, and are higher than dosages used in most studies of GH administration. There are side effects from GH that arise from its antinatriuretic, metabolic, and growth-promoting properties. Most of the acute side effects reported in trials in healthy adults arise from fluid retention (**Fig. 1**). These include edema, ''pins and needles,'' carpal tunnel syndrome, and arthralgias.[40,42,57] Other side effects, including sweating, fatigue, and dizziness, have been reported after GH administration in healthy subjects.[40,60] However, serious side effects, including diabetes, may arise from its anti-insulin properties, especially with high doses.[61] The severity of these adverse effects may be worsened by concurrent abuse of anabolic steroids, which could have synergistic effects with GH, such as effects on fluid retention[62] and on the myocardium.[63,64]

Excess levels of GH negatively affect cardiac function. The effects of two doses (0.03 or 0.06 mg/kg/d) of GH on cardiac output and morphology were examined in a group of 30 young healthy men and 30 women treated for 4 weeks.[59] Although the lower dose of GH did not significantly affect echocardiographic parameters, the higher dose increased cardiac output and left ventricular mass index. The accompanying increase in left ventricular wall thickness indicates that GH induces concentric left ventricular remodeling.[59] The effect of massive doses of anabolic androgenic steroids without or with GH on left ventricular mass was studied by Karila and colleagues[63] in 20 male power athletes. They found a significant association between androgenic steroids dose and left ventricular mass increase. Concomitant treatment

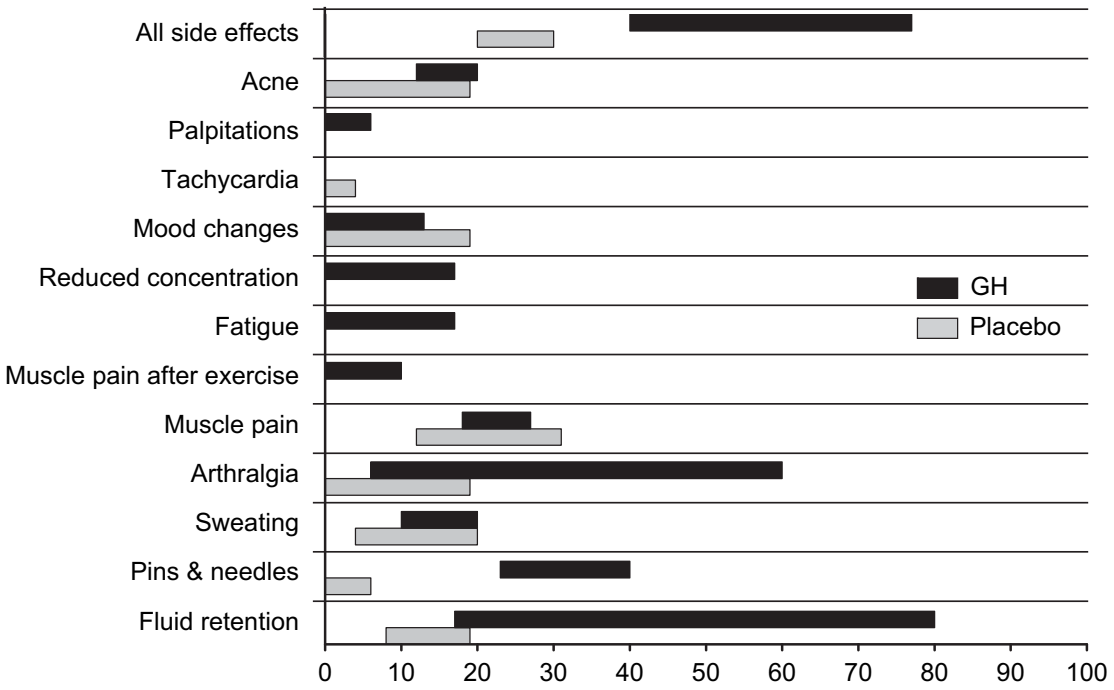

Fig. 1. Summary of side effects reported in seven double-blind placebo-controlled trials in healthy subjects of GH administration for 4 to 12 weeks with median GH dose of 40 μg/kg/day.[35,36,42,43,47,56,59] Data are presented as a range of percent of the subjects reporting side effects after treatment with GH (*black bars*) and placebo (*gray bars*).

with GH further increased left ventricular mass and was associated with concentric remodeling.[63]

The potential health risks of chronic abuse of GH can be gleaned from acromegaly, which presents with cardiac, metabolic, and articular complications with increased risk of malignant neoplasms and shortened life expectancy. Systolic and diastolic functions are impaired in acromegaly.[65] Morphologic studies of the heart in acromegaly report ventricular hypertrophy with increased fibrosis and extracellular collagen, which coexists with myofibrillar derangement, myocyte necrosis, and lymphomononuclear infiltration, resembling a pattern of myocarditis.[5,65] The incidence of hypertension,[66] as well as cardiovascular and cerebrovascular mortality is increased in acromegaly.[67]

GH impairs insulin action and hepatic and peripheral insulin sensitivity.[68–70] Therefore, prolonged and sustained use of GH conveys a state of insulin resistance, predisposing to the development of diabetes. Indeed, diabetes is found in up to 40% of patients with untreated acromegaly.[4,66] There is also some evidence that prolonged use of GH may be associated with increased risk of neoplasms.[67,71] The incidence of colon polyps, thyroid nodules, and prostate hypertrophy is increased in acromegaly. Whether this translates into increase in cancer risk is not clear.[72] However, the mortality rate of colon cancer is significantly increased in patients with acromegaly compared with the control population,[72] suggesting that a milieu of GH excess accelerates the growth of malignancy.

GH excess induces dysregulated growth of cartilage, causing arthralgia.[73] These changes in articular cartilage are irreversible. This is exemplified by a study in a group of patients cured of acromegaly, in whom the authors reported radiological evidence of osteoarthritis in 99% and clinical osteoarthritis in 63%.[74]

Life expectancy is reduced in acromegaly, which is normalized by achieving disease control. Overall standardized mortality rates are approximately two times higher than in the general population, relating to an average reduction in life expectancy of approximately 10 years.[67]

In summary, many of the acute side effects of GH arise from fluid retention. The features of the acromegaly indicate the potential health risks of chronic abuse of GH, which include cardiac complications, arthralgia, insulin resistance, and increased risk of diabetes and malignancy. Finally, a potential risk is that of abusers acquiring fatal Creutzfelt-Jakob disease from the use of cadaveric pituitary-derived GH that is still available on the black market because of the high cost of recombinant human GH (rhGH).[75]

SUMMARY

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 may improve a selective aspect of performance, that of anaerobic exercise capacity. There are, however, serious adverse effects of long-term abuse of GH, including fluid retention, carpal tunnel syndrome, arthralgias, myalgias, insulin resistance, and increased risk of diabetes, cardiomyopathy, and malignancy. Thus, there are serious health risks and potential increase in mortality rate from prolonged use of GH in healthy adults.

ACKNOWLEDGMENTS

Dr Vita Birzniece was supported by the National Health and Medical Research Council of Australia. Dr Anne E. Nelson 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 RI, Sonksen PH. Growth hormone, IGF-I and insulin and their abuse in sport. Br J Pharmacol 2008;154:542.
2. Holt RI, Erotokritou-Mulligan I, Sonksen PH. The history of doping and growth hormone abuse in sport. Growth Horm IGF Res 2009;19(4):320–6.
3. Saugy M, Robinson N, Saudan C, et al. Human growth hormone doping in sport. Br J Sports Med 2006;40(Suppl 1):i35.
4. Ezzat S, Forster MJ, Berchtold P, et al. Acromegaly. Clinical and biochemical features in 500 patients. Medicine (Baltimore) 1994;73:233.
5. Fazio S, Cittadini A, Biondi B, et al. Cardiovascular effects of short-term growth hormone hypersecretion. J Clin Endocrinol Metab 2000;85:179.
6. Ehrnborg C, Lange KH, Dall R, et al. 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 2003;88:394.
7. Giannoulis MG, Boroujerdi MA, Powrie J, et al. 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) 2005;62:315.
8. Wallace JD, Cuneo RC, Baxter R, et al. 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 1999;84:3591.

9. Wallace JD, Cuneo RC, Bidlingmaier M, et al. The response of molecular isoforms of growth hormone to acute exercise in trained adult males. J Clin Endocrinol Metab 2001;86:200.
10. Carroll PV, Christ ER, Bengtsson BA, et al. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. J Clin Endocrinol Metab 1998;83:382.
11. Gibney J, Healy ML, Sonksen PH. The growth hormone/insulin-like growth factor-I axis in exercise and sport. Endocr Rev 2007;28:603.
12. Gibney J, Wallace JD, Spinks T, et al. The effects of 10 years of recombinant human growth hormone (GH) in adult GH-deficient patients. J Clin Endocrinol Metab 1999;84:2596.
13. Rodriguez-Arnao J, Jabbar A, Fulcher K, et al. Effects of growth hormone replacement on physical performance and body composition in GH deficient adults. Clin Endocrinol (Oxf) 1999;51:53.
14. Attanasio AF, Bates PC, Ho KK, et al. 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 2002;87:1600.
15. Burt MG, Gibney J, Hoffman DM, et al. 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 2008;18:55.
16. Gotherstrom G, Svensson J, Koranyi J, et al. 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 2001;86:4657.
17. Wolthers T, Hoffman DM, Nugent AG, et al. Oral estrogen antagonizes the metabolic actions of growth hormone in growth hormone-deficient women. Am J Physiol Endocrinol Metab 2001;281:E1191.
18. Woodhouse LJ, Mukherjee A, Shalet SM, et al. The influence of growth hormone status on physical impairments, functional limitations, and health-related quality of life in adults. Endocr Rev 2006;27:287.
19. Sartorio A, Narici MV. Growth hormone (GH) treatment in GH-deficient adults: effects on muscle size, strength and neural activation. Clin Physiol 1994;14:527.
20. Cuneo RC, Salomon F, Wiles CM, et al. Skeletal muscle performance in adults with growth hormone deficiency. Horm Res 1990;33(Suppl 4):55.
21. Cuneo RC, Salomon F, Wiles CM, et al. Growth hormone treatment in growth hormone-deficient adults. I. Effects on muscle mass and strength. J Appl Physiol 1991;70:688.
22. Woodhouse LJ, Asa SL, Thomas SG, et al. Measures of submaximal aerobic performance evaluate and predict functional response to growth hormone (GH) treatment in GH-deficient adults. J Clin Endocrinol Metab 1999;84:4570.
23. Widdowson MW, Gibney J. The effect of growth hormone (GH) replacement on muscle strength in patients with GH-deficiency: a meta-analysis. Clin Endocrinol (Oxf) 2009, in press.
24. Jorgensen JO, Pedersen SA, Thuesen L, et al. Long-term growth hormone treatment in growth hormone deficient adults. Acta Endocrinol (Copenh) 1991;125:449.
25. Jorgensen JO, Thuesen L, Muller J, et al. Three years of growth hormone treatment in growth hormone-deficient adults: near normalization of body composition and physical performance. Eur J Endocrinol 1994;130:224.
26. Svensson J, Sunnerhagen KS, Johannsson G. Five years of growth hormone replacement therapy in adults: age- and gender-related changes in isometric and isokinetic muscle strength. J Clin Endocrinol Metab 2003;88:2061.

27. Cuneo RC, Salomon F, Wiles CM, et al. Growth hormone treatment in growth hormone-deficient adults. II. Effects on exercise performance. J Appl Physiol 1991;70:695.
28. Cenci MC, Soares DV, Spina LD, et al. Effects of 5 years of growth hormone (GH) replacement therapy on cardiac parameters and physical performance in adults with GH deficiency. Pituitary 2009;12(4):322–9.
29. Nass R, Huber RM, Klauss V, et al. 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 1995;80:552.
30. Widdowson WM, Gibney J. The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: a metaanalysis. J Clin Endocrinol Metab 2008;93:4413.
31. Merola B, Longobardi S, Sofia M, et al. 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 1996;135:553.
32. Colao A, Di Somma C, Cuocolo A, et al. 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 2004;89:5998.
33. El-Sayed MS, Ali N, El-Sayed Ali Z. Haemorheology in exercise and training. Sports Med 2005;35:649.
34. Moller J, Frandsen E, Fisker S, et al. 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) 1996; 44:533.
35. Yarasheski KE, Campbell JA, Smith K, et al. Effect of growth hormone and resistance exercise on muscle growth in young men. Am J Physiol 1992;262:E261.
36. Healy ML, Gibney J, Russell-Jones DL, et al. High dose growth hormone exerts an anabolic effect at rest and during exercise in endurance-trained athletes. J Clin Endocrinol Metab 2003;88:5221.
37. Chesley A, MacDougall JD, Tarnopolsky MA, et al. Changes in human muscle protein synthesis after resistance exercise. J Appl Physiol 1992;73:1383.
38. Yarasheski KE, Zachweija JJ, Angelopoulos TJ, et al. Short-term growth hormone treatment does not increase muscle protein synthesis in experienced weight lifters. J Appl Physiol 1993;74:3073.
39. Miller ME, Cosgriff JM, Forbes GB. Bromide space determination using anion-exchange chromatography for measurement of bromide. Am J Clin Nutr 1989; 50:168.
40. Liu H, Bravata DM, Olkin I, et al. Systematic review: the effects of growth hormone on athletic performance. Ann Intern Med 2008;148:747.
41. Moller J, Jorgensen JO, Moller N, et al. Expansion of extracellular volume and suppression of atrial natriuretic peptide after growth hormone administration in normal man. J Clin Endocrinol Metab 1991;72:768.
42. Ehrnborg C, Ellegard L, Bosaeus I, et al. Supraphysiological growth hormone: less fat, more extracellular fluid but uncertain effects on muscles in healthy, active young adults. Clin Endocrinol (Oxf) 2005;62:449.
43. Meinhardt U, Nelson AE, Hansen JL, et al. The effects of growth hormone on body composition and physical performance in recreational athletes: a randomized placebo-controlled trial. Ann Intern Med, in press.

44. Deyssig R, Frisch H, Blum WF, et al. Effect of growth hormone treatment on hormonal parameters, body composition and strength in athletes. Acta Endocrinol (Copenh) 1993;128:313.
45. Lange KH, Larsson B, Flyvbjerg A, et al. 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 2002; 87:4966.
46. Irving BA, Patrie JT, Anderson SM, et al. The effects of time following acute growth hormone administration on metabolic and power output measures during acute exercise. J Clin Endocrinol Metab 2004;89:4298.
47. Berggren A, Ehrnborg C, Rosen T, et al. 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 2005;90:3268.
48. Graham MR, Baker JS, Evans P, et al. Physical effects of short-term recombinant human growth hormone administration in abstinent steroid dependency. Horm Res 2008;69:343.
49. Brumback RA, Barr CE. Myopathy in acromegaly. A case study. Pathol Res Pract 1983;177:41.
50. Nagulesparen M, Trickey R, Davies MJ, et al. Muscle changes in acromegaly. Br Med J 1976;2:914.
51. Thomas SG, Woodhouse LJ, Pagura SM, et al. Ventilation threshold as a measure of impaired physical performance in adults with growth hormone excess. Clin Endocrinol (Oxf) 2002;56:351.
52. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. Annu Rev Psychol 2008;59:565.
53. Pollo A, Carlino E, Benedetti F. The top-down influence of ergogenic placebos on muscle work and fatigue. Eur J Neurosci 2008;28:379.
54. Beedie CJ, Foad AJ. The placebo effect in sports performance: a brief review. Sports Med 2009;39:313.
55. Benedetti F, Pollo A, Colloca L. Opioid-mediated placebo responses boost pain endurance and physical performance: is it doping in sport competitions? J Neurosci 2007;27:11934.
56. Longobardi S, Keay N, Ehrnborg C, et al. 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 2000;85:1505.
57. Nelson AE, Meinhardt U, Hansen JL, et al. 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 2008;93:2213.
58. Kurtz CA, Loebig TG, Anderson DD, et al. Insulin-like growth factor I accelerates functional recovery from Achilles tendon injury in a rat model. Am J Sports Med 1999;27:363.
59. Cittadini A, Berggren A, Longobardi S, et al. Supraphysiological doses of GH induce rapid changes in cardiac morphology and function. J Clin Endocrinol Metab 2002;87:1654.
60. Keller A, Wu Z, Kratzsch J, et al. Pharmacokinetics and pharmacodynamics of GH: dependence on route and dosage of administration. Eur J Endocrinol 2007;156:647.
61. Young J, Anwar A. Strong diabetes. Br J Sports Med 2007;41:335.

62. Johannsson G, Gibney J, Wolthers T, et al. Independent and combined effects of testosterone and growth hormone on extracellular water in hypopituitary men. J Clin Endocrinol Metab 2005;90:3989.
63. Karila TA, Karjalainen JE, Mantysaari MJ, et al. Anabolic androgenic steroids produce dose-dependant increase in left ventricular mass in power athletes, and this effect is potentiated by concomitant use of growth hormone. Int J Sports Med 2003;24:337.
64. Mark PB, Watkins S, Dargie HJ. Cardiomyopathy induced by performance enhancing drugs in a competitive bodybuilder. Heart 2005;91:888.
65. Meyers DE, Cuneo RC. Controversies regarding the effects of growth hormone on the heart. Mayo Clin Proc 2003;78:1521.
66. Colao A, Baldelli R, Marzullo P, et al. Systemic hypertension and impaired glucose tolerance are independently correlated to the severity of the acromegalic cardiomyopathy. J Clin Endocrinol Metab 2000;85:193.
67. Ayuk J, Sheppard MC. Does acromegaly enhance mortality? Rev Endocr Metab Disord 2008;9:33.
68. Bratusch-Marrain PR, Smith D, DeFronzo RA. The effect of growth hormone on glucose metabolism and insulin secretion in man. J Clin Endocrinol Metab 1982;55:973.
69. Fowelin J, Attvall S, von Schenck H, et al. Characterization of the insulin-antagonistic effect of growth hormone in man. Diabetologia 1991;34:500.
70. Rizza RA, Mandarino LJ, Gerich JE. Effects of growth hormone on insulin action in man. Mechanisms of insulin resistance, impaired suppression of glucose production, and impaired stimulation of glucose utilization. Diabetes 1982;31:663.
71. Perry JK, Emerald BS, Mertani HC, et al. The oncogenic potential of growth hormone. Growth Horm IGF Res 2006;16:277.
72. Orme SM, McNally RJ, Cartwright RA, et al. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab 1998;83:2730.
73. Colao A, Pivonello R, Scarpa R, et al. The acromegalic arthropathy. J Endocrinol Invest 2005;28:24.
74. Wassenaar MJ, Biermasz NR, van Duinen N, et al. 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 2009;160:357.
75. Brown P, Preece M, Brandel JP, et al. Iatrogenic Creutzfeldt-Jakob disease at the millennium. Neurology 2000;55:1075.