

# The Growth Hormone/Insulin-Like Growth Factor-I Axis in Exercise and Sport

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The syndrome of adult GH deficiency and the effects of GH replacement therapy provide a useful model with which to study the effects of the GH/IGF-I axis on exercise physiology. Measures of exercise performance including maximal oxygen uptake and ventilatory threshold are impaired in adult GH deficiency and improved by GH replacement, probably through some combination of increased oxygen delivery to exercising muscle, increased fatty acid availability with glycogen sparing, increased muscle strength, improved body composition, and improved thermoregulation. In normal subjects, in addition to the long-term effects of GH/IGF-I status, there is evidence that the acute GH response to exercise is important in regulating substrate metabolism after exercise. Administration of supraphysiological

cal doses of GH to athletes increases fatty acid availability and reduces oxidative protein loss, particularly during exercise, and increases lean body mass. Despite a lack of evidence that these metabolic effects translate to improved performance, GH abuse by athletes is widespread. Tests to detect GH abuse have been developed based on measurement in serum of 1) indirect markers of GH action, and 2) the relative proportions of the two major naturally occurring isoforms (20 and 22kDa) of GH. There is evidence that exercise performance and strength are improved by administration of GH and testosterone in combination to elderly subjects. The potential benefits of GH in these situations must be weighed against potential adverse effects. (*Endocrine Reviews* 28: 603–624, 2007)

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## I. Introduction

DEVELOPMENT OF AN assay for human GH (1, 2) was closely followed by the observation that plasma levels of GH increase soon after the beginning of exercise (3). Because of the known anabolic and lipolytic effects of GH and the observation that the exercise-associated increase in GH precedes an increase in circulating free fatty acids (FFAs), it was hypothesized that GH might play an important metabolic role during exercise (4, 5). Further evidence for this notion came from the discovery in the 1980s that exercise capacity and muscle strength are impaired in GH-deficient (GHD) adults and improved by GH replacement (6–9). Although there is now a large body of literature addressing the effects of the GH/IGF-I axis on exercise and the effects of exercise on the GH/IGF-I axis, the contribution of GH to exercise capacity in normal subjects remains unclear.

Reports of the use of GH by athletes as a performance-enhancing agent (10, 11) predate the introduction of recombinant human GH (r-hGH) by at least 5 yr, and there is an increasing body of evidence that GH abuse represents a significant problem in a number of sports including athletics, swimming, and cycling (12, 13). The likelihood that attaining supraphysiological GH levels improves exercise perfor-

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Abbreviations: AO-GHD, Adult onset GHD; CO, cardiac output; DBPCT, double-blind, placebo-controlled trial; EF, ejection fraction; FFA, free fatty acid; GHD, GH deficient or GH deficiency; IGFBP, IGF binding protein; LBM, lean body mass; LV, left ventricular; PIIIP, procollagen type III; r-hGH, recombinant human GH; r-hIGF-I, recombinant human IGF-I; SV, stroke volume; SVR, systemic vascular resistance; TBW, total body water; VeT, ventilatory threshold;  $VO_{2max}$ , maximal oxygen uptake.

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## GHD

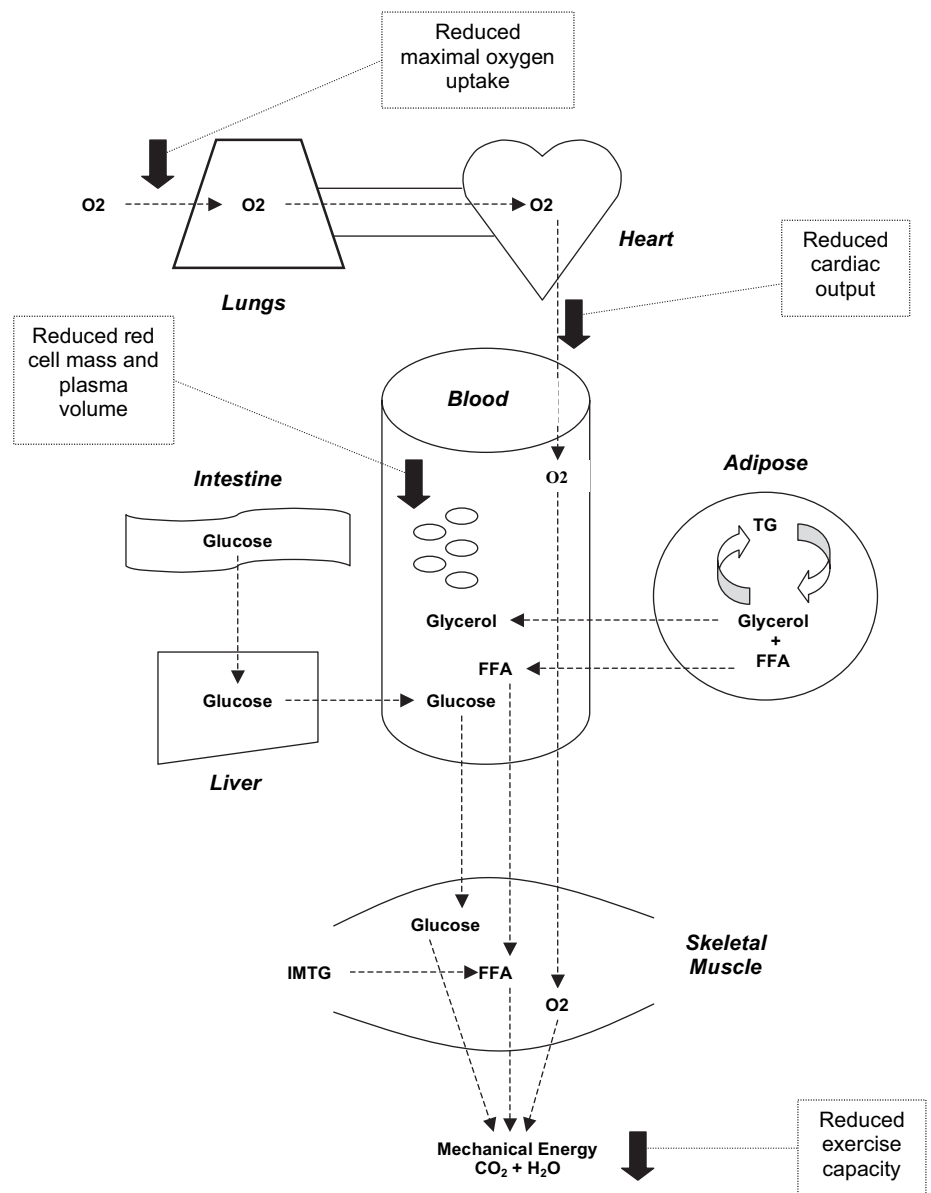


FIG. 1. The effects of GHD (*first panel*) and GH replacement (*second panel*) in GHD adults on components of the physiological response to exercise. TG, Triglyceride; IMTG, intramuscular TG.

mance should be considered in the context that although GH is clearly anabolic, there is no evidence that exercise capacity is enhanced by administration of GH to normal subjects (12–14), and in patients with long-standing endogenous GH excess (acromegaly), muscle strength is usually reduced (15). However, recent metabolic studies provide a plausible mechanistic explanation through which supraphysiological GH administration could lead to short- or medium-term improvements in exercise performance, and regular seizures of GH from athletes demonstrate an ongoing belief in sporting circles that GH is performance enhancing.

The purpose of this review is, using data from GHD and normal subjects, to address the physiological role of the GH-IGF-I axis during exercise. We will also consider whether available evidence supports an effect of supraphysiological GH administration to enhance exercise performance and strength in

athletes, and we will describe recently developed tests to detect GH abuse in sport. Finally, we will review data from studies that have addressed the possibility that administration of supraphysiological doses of GH might improve exercise performance in GH-replete subjects with impaired exercise capacity, including the healthy elderly and the obese.

## II. Lessons from GH-Deficient (GHD) Subjects and Their Response to GH Replacement

### A. The effects of GH deficiency and replacement on exercise performance

In a recent review describing how changes in GH status influence functional capacity and quality of life, the effects of GHD and replacement on exercise performance have been

## GH Replacement

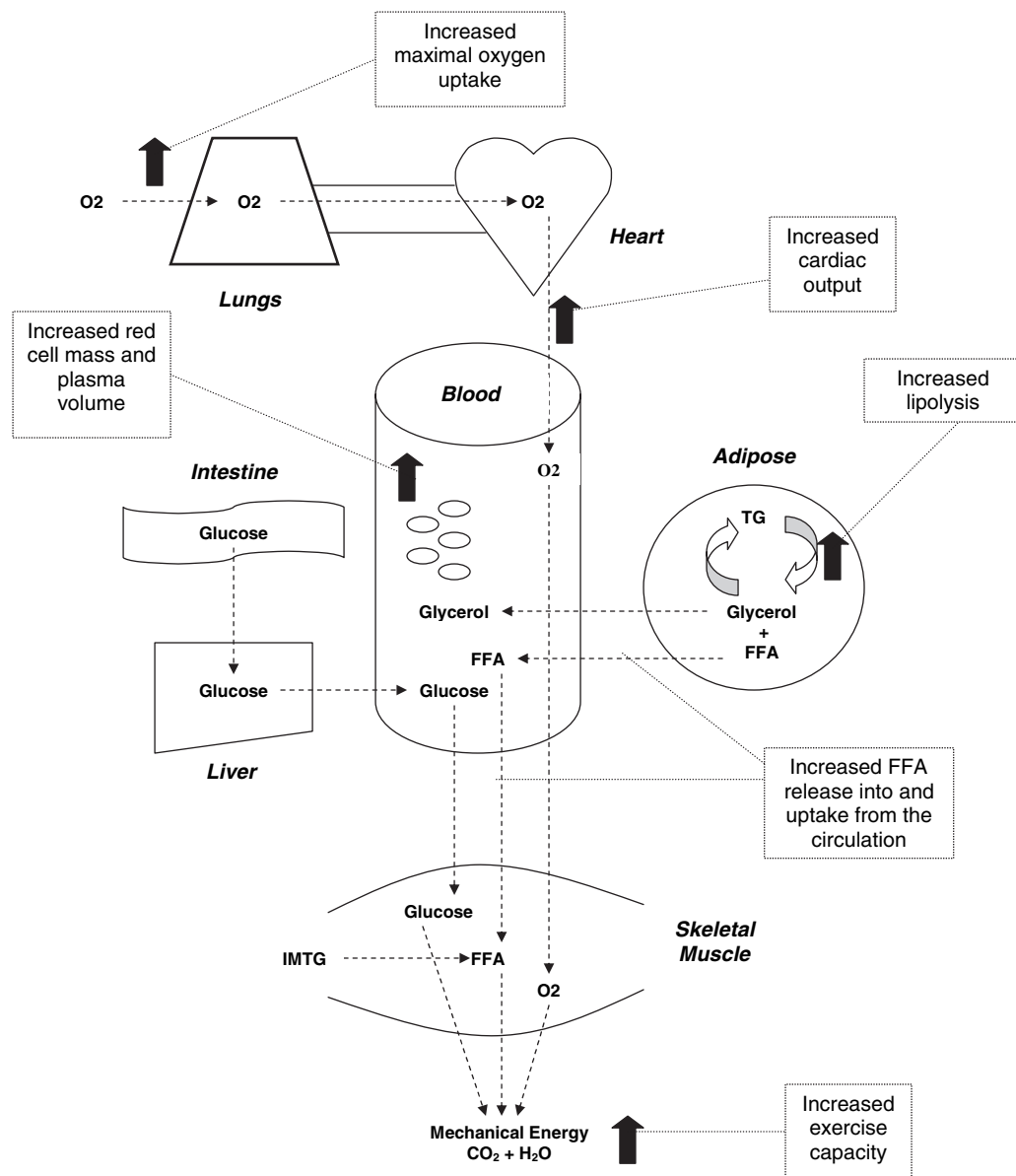


FIG. 1. *Continued*

comprehensively evaluated (16). Briefly, maximal oxygen consumption ( $VO_{2max}$ ; aerobic capacity or the maximum ability to take in and use oxygen) in GHD adults has been consistently shown to be reduced by estimates ranging from 17 to 27% compared with values predicted for age, gender, and height (6, 8, 17). The effect of treatment with GH to improve exercise performance in GHD adults was demonstrated in some of the first trials of GH replacement to be published, although the doses of GH used in those studies are now known to be supraphysiological. Cuneo *et al.* (6) demonstrated increases (and normalization compared with predicted values) in  $VO_{2max}$ , maximal power output, and the ventilatory threshold (VeT; lactate threshold) after 6 months of GH replacement in GHD subjects. Notably, the magnitude of the increase in  $VO_{2max}$  was proportionate to the increase

in lean body mass (LBM), and after adjustment for changes in LBM or thigh muscle area, did not differ from baseline.

Woodhouse *et al.* (9) confirmed the finding that GH replacement increased VeT, demonstrated a reduction in fatigue after GH replacement, and provided a plausible explanation as to the mechanism through which this effect occurred. Before GH replacement, VeT occurred at a high percentage of  $VO_{2max}$  because  $VO_{2max}$  was low. Walking required high oxygen consumption relative to VeT (a mean of 83% at normal speeds and a mean of 120% at fast speeds). This effect is likely to lead to fatigue because, compared with normal subjects, the oxygen consumption necessary to carry out daily activities is more likely to exceed VeT, leading to lactate accumulation and limitation of activity. GH replacement increased VeT and also re-

duced the oxygen cost of walking relative to VeT at normal and fast speeds.

The majority of studies reported to date have demonstrated increased maximum work rate (6, 8, 9, 17–23) and  $VO_{2max}$  (6, 8, 9, 17, 19) after GH replacement in subjects with both childhood- and adult-onset (AO)-GHD, although statistically significant improvements compared with placebo were not demonstrated in all of these studies (8, 18, 19). One study demonstrated no improvement after GH replacement (24), whereas another demonstrated no difference in the improvement in VeT after exercise training in combination with GH replacement compared with after exercise training alone (25). Some of these studies may have been underpowered to detect between-group differences. The largest study to date addressing exercise performance in response to GH replacement included 55 patients with AO-GHD in a placebo-controlled, crossover study in which GH therapy was individually dosed to obtain an IGF-I concentration within the normal range for age and sex (26). A highly significant effect of GH replacement to increase  $VO_{2max}$  by approximately 6% was observed. The overall body of evidence therefore supports an effect of GH to improve maximum work rate,  $VO_{2max}$ , and VeT, with changes in  $VO_{2max}$  apparently accounted for by increased LBM.

### B. Mechanisms by which GH improves exercise performance in GHD adults

The ability to perform exercise requires combustion of metabolic fuels, transforming chemical into kinetic and thermal energy. Glucose is the preferred fuel source for short-term high-intensity activity, whereas FFAs (derived from the circulation or from triglycerides stored in muscle or adipose tissue) become increasingly important during more prolonged activity (27).  $O_2$  delivery to muscles depends upon adequate ventilation and  $O_2$  transport to hemoglobin, circulatory distribution by an adequate cardiac output (CO) and peripheral circulation, dilatation of the muscle capillary network, and extraction of  $O_2$  by the muscle fibers with either storage in myoglobin or immediate combustion. GH could improve exercise performance through increased delivery of substrate and oxygen to exercising muscle, increased fat oxidation with glycogen sparing, increased muscle strength, or a combination of these variables. GH could also improve exercise performance through indirect mechanisms, including changes in body composition or more efficient thermoregulation. These possible effects are demonstrated in Fig. 1.

**1. Cardiorespiratory and hematological effects.** When pulmonary function [which does not appear to be impaired in GHD or improved by GH replacement (6, 8)] is adequate, delivery of  $O_2$  to exercising muscle is dependent on the  $O_2$ -carrying capacity of the blood, CO, and regional blood flow. GH and IGF-I increase erythropoiesis *in vitro* (28, 29), in animal models (30), and in growing children (31). Christ *et al.* (32), using radionuclide dilution studies, demonstrated reduced red cell mass and total blood volume in GHD adults, and normalization after GH replacement. Consistent with other studies, GH replacement also increased plasma volume, which by increasing preload, would be predicted to increase stroke volume (SV) and CO, the product of SV and heart rate.

Independent of effects on preload, GH could also increase cardiac contractility through an anabolic effect on the myocardium, mediated either directly or through increased IGF-I (33). Most (34–36), but not all (37, 38) studies using echocardiography or equilibrium radionuclide angiography have demonstrated reduced left ventricular (LV) mass and LV ejection fraction (EF) in GHD adults compared with normal subjects. Reports of the effects of GH replacement on cardiac structure and function are inconsistent, but a recent meta-analysis (39) of placebo-controlled trials demonstrated a significant effect of GH replacement to increase left ventricular posterior wall thickness and SV. Of particular importance to this review is evidence from studies using radionuclide angiography that GH enhances the ability of LVEF to increase during exercise, which is necessary to provide adequate blood supply to exercising muscle (40, 41).

The effects of GH on SV and CO must be considered in relation to changes in systemic vascular resistance (SVR) and afterload. As described above, GH replacement increases SV, which in the absence of change in heart rate would be expected to increase mean arterial pressure. However, mean arterial pressure does not change or even decreases (42) after GH replacement, and because it represents the product of CO and SVR, this observation can only be explained by a reduction in SVR. A mechanistic explanation for this effect is provided by a study that demonstrated increased production of nitric oxide, the key mediator of endothelial relaxation, after 3 months of GH replacement (43). To date, no reported studies have addressed whether GH also influences the changes in regional blood flow that occur during exercise.

**2. Substrate metabolism.** Hunter *et al.* (5) reported in 1965 that the exercise-induced increase in GH was followed by an increase in fatty acids and suggested that through its lipolytic effect GH could increase availability of fat as substrate during exercise. Under resting conditions, particularly when fasting, fatty acids are the predominant fuel used by skeletal muscle. Fat oxidation increases in relation to the intensity of exercise up to 65% of  $VO_{2max}$  (45), when it accounts for approximately 50% of energy expenditure, but with increasing intensity of exercise, the reliance on glucose as fuel increases, and the relative oxidation of glucose in relation to fat increases (27). Whether fatty acid availability influences partitioning of substrate oxidation during exercise is unclear, some studies demonstrating increased fat oxidation and reduced muscle glycogen depletion when fatty acid availability is greater (46–49), and others demonstrating no effect (46–51).

GH directly stimulates lipolysis through activation of adenyl cyclase followed by activation of cAMP-dependent protein kinase and phosphorylation and activation of hormone-sensitive lipase (52). Studies in fat cells (53–55) and in animal models have shown that in addition to its direct lipolytic effect on adipose tissue (demonstrated by stimulation of basal lipolysis), GH also increases lipolysis indirectly by altering the effect of adipocytes to respond to lipolytic factors such as catecholamines.

Raben and Hollenberg (56) in 1959 demonstrated that GH increased plasma FFA in human subjects, and Rabinowitz *et al.* (57) in 1965 demonstrated that administration of GH en-

TABLE 1. Metabolic effects (under resting conditions) of adult GHD, GH administration to healthy normal subjects, and long-term GH excess in the pathophysiological model of acromegaly

	GHD		Normal Effect of GH administration	Acromegaly	
	Comparison with normal subjects	Effect of treatment		Comparison with normal subjects	Effect of treatment
Insulin sensitivity	↓	↔	↓	↓	↑
Carbohydrate metabolism					
Hepatic glucose production	↔	↓/↔	↔	↑	↓
Glucose uptake	↓/↔	↓	↓	↓	↑
Glucose oxidation	↑/↔	↓	↓/↔	↑/↔	↔
Fat metabolism					
Lipolysis	↓/↔	↑	↑	↑/↔	↔
Fat oxidation	↓	↑	↑	↑/↔	↓/↔
Protein metabolism					
Proteolysis	↓	↑/↔	↑	↑	↓
Oxidative protein loss	↔	↓	↓	↔	↑
Protein synthesis	↓	↑	↑	↑	↓

↑, Increased; ↔, not different/unchanged; ↓, decreased.

hanced forearm muscle uptake and oxidation of FFA and increased the release of FFA from adipose tissue. GH, administered as a bolus or by infusion, increases circulating levels of glycerol and FFA in GHD and normal subjects after a lag time of 2–3 h (58–61). Small pulses of GH designed to mimic physiological pulses have been shown to induce a dose-dependent stimulation of lipid oxidation and increase circulating levels of FFA and glycerol (62). Using microdialysis techniques, it has been shown that a physiological GH pulse stimulates lipolysis in both abdominal and femoral adipose tissue, although to a greater degree in abdominal tissue (62). The metabolic effects of GH under resting conditions are summarized in Table 1.

In normal subjects, the onset of exercise leads to a 3-fold increase in the rate of lipolysis and a rapid increase in uptake of FFAs into skeletal muscle (45). Two recent studies using stable isotope techniques have provided evidence that GH is important in this response. Gibney *et al.* (63) studied lipolysis and fatty acid turnover in GHD subjects during and after discontinuation of long-term GH replacement. Discontinuation of GH was not associated with any change in lipolysis or fatty acid turnover at rest but resulted in a marked reduction in lipolysis and fatty acid release into the circulation during and after exhaustive exercise and in reduction of circulating levels of FFA (Fig. 2). The rate of disappearance of FFA from the circulation, which during exercise is largely into skeletal muscle, was also reduced after GH withdrawal. Kanaley *et al.* (64) carried out exercise studies in GHD adults who were receiving long-term GH replacement on 2 separate days, once with and once without a bolus of GH administered iv at the start of exercise. The protocol resulted in an increment in circulating GH levels during exercise that was indistinguishable from that seen in healthy normal subjects. Under resting conditions, there was no effect of GH, whereas during and after 45 min of exercise at lactate threshold there was a greater increment in fatty acid turnover after GH administration.

GH clearly increases whole-body fat oxidation under resting conditions, and an increase in maximal fat oxidation during exercise has also been demonstrated in GHD adults after 6 and 12 months of GH replacement (65). However, in a recent study using Affymetrix gene chips, GH replacement

significantly reduced the expression in skeletal muscle biopsies of a large group of genes involved in lipid metabolism, including some of the key enzymes that mediate fatty acid  $\beta$ -oxidation (66). These findings suggest that under resting conditions (when the biopsies were taken), increased fat ox-

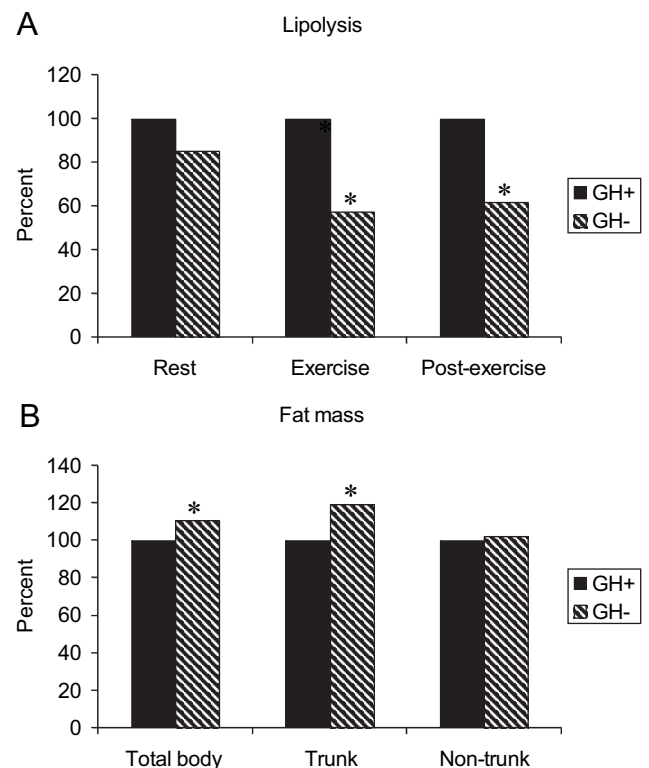


FIG. 2. A, Lipolysis estimated from the rate of appearance of glycerol at rest, during exercise, and 30 min after exercise in GHD adults ( $n = 8$ ) while receiving GH (GH+) and 3 months after discontinuation of GH replacement (GH-). B, Total body, trunk, and nontrunk fat estimated using dual-energy x-ray absorptiometry scanning in GHD adults ( $n = 8$ ) while receiving GH (GH+) and 3 months after discontinuation of GH replacement (GH-). Results are expressed as percentage change from baseline. \* $P < 0.05$  for the change from baseline compared with a matched group of GHD adults who continued on GH replacement (data not shown). [Adapted from Ref. 63 with permission. Copyright 2003, The Endocrine Society.]

idation in response to GH occurs in tissues other than skeletal muscle. It is possible that different effects would occur during exercise.

There is less information available concerning the effects of GHD and GH replacement on glucose kinetics during exercise. Under resting conditions, GH administration results in increased hepatic glucose production, reduced glucose uptake into skeletal muscle, and increased insulin secretion (67–73). There is increasing evidence that this effect may occur secondary to the lipolytic effect of GH (74). In the study of Gibney *et al.* (63), plasma glucose levels were greater under resting and exercise conditions during GH replacement, although in the study of Kanaley *et al.* (64) where a stable isotope glucose tracer was used, there was no discernible effect of GH on the rate of glucose appearance into or disappearance from the circulation. GH replacement did not alter glucose oxidation during exercise in the study of Brandou *et al.* (65).

In summary (Table 2), therefore, there is strong evidence that GH replacement increases lipolysis, FFA availability, and uptake from the circulation more markedly during exercise compared with resting conditions. There is also preliminary evidence that GH replacement increases whole-body fat oxidation during exercise, although it is not known whether this effect occurs in skeletal muscle or in other tissues. The effects of GH replacement on glucose metabolism during exercise appear to be less marked.

**3. Muscle mass and strength.** There is an extensive body of literature from *in vitro* and animal models concerning the cellular mechanisms through which GH and IGF-I exert anabolic effects on skeletal muscle (reviewed in Ref. 16). Recent studies in human subjects have provided further information regarding the immediate and short-term effects on gene transcription through which these processes occur. Jorgensen *et al.* (75) studied the effects on GH signaling in skeletal muscle biopsies in normal subjects before and 30 or 60 min after an iv bolus of GH. GH induced tyrosine phosphorylation (indicating activation) of STAT5, consistent with a direct effect of GH in skeletal muscle, mediated through the Janus kinase/signal transducer and activator of transcription (JAK-STAT) signaling pathway. This finding is consistent with previous observations from regional amino acid balance studies that showed an acute effect of GH to promote protein synthesis in forearm muscle (76). In the study of Sjögren *et*

TABLE 2. Metabolic effects during and after exercise of GH replacement in GHD and GH administration to normal subjects

	GH replacement in GHD adults	GH administration to normal subjects
Carbohydrate metabolism		
Hepatic glucose production	↔	↑↑
Glucose uptake	↔	↑↑
Glucose oxidation	↔	↔
Fat metabolism		
Lipolysis	↑↑	↑↑
Fat oxidation	↑↑	↔
Protein metabolism		
Proteolysis	↔	↑↑
Oxidative protein loss	NK	↓↓
Protein synthesis	NK	↑↑

NK, Not known; ↑, increased; ↔, unchanged; ↓, decreased.

*al.* (66) described in Section II.B.2, 2 wk of GH replacement increased skeletal muscle gene expression of IGF-I and exerted complex potentially anabolic effects on genes involved in protein synthesis and degradation. These results provide preliminary evidence of how GH acts in skeletal muscle, but more studies are clearly required to elucidate these complex effects.

The physiological importance of the anabolic effect of GH is apparent in GHD adults. These effects have been comprehensively documented and reviewed (16, 77, 78) and will not be considered in detail here. Briefly, LBM is reduced in GHD adults by approximately 7–8% compared with age- and gender-matched normal subjects (77–79), representing similar reductions in extracellular water and body cell mass, the metabolically active component of LBM (80). Skeletal muscle comprises the majority of body cell mass, and studies using computed tomography and magnetic resonance imaging scanning have demonstrated a reduction in cross-sectional skeletal muscle area in GHD adults that is proportional to the reduction in LBM estimated by measurement of total body potassium (81, 82). Reduced muscle mass in GHD subjects is associated with reduced isometric muscle strength (81–84), whereas some (19) but not all studies have also demonstrated reduced isokinetic strength (81, 83). It remains uncertain whether reduced strength is entirely accounted for by the reduction in muscle mass or whether there is also intrinsic muscle weakness associated with GHD (for review, see Ref. 16).

In contrast to the protein anabolic effect of GH replacement, which occurs within days to weeks of initiation of treatment, the overall body of evidence suggests that long-term but not short-term GH replacement increases and normalizes muscle strength. Cuneo *et al.* (82) carried out an extensive series of strength tests at the beginning and end of 6 months of GH replacement. Strength increased in most of the nine muscle groups that were studied, but it only reached statistical significance in one of the groups. This study and two other studies of GH replacement, lasting 12 wk and 6 months, respectively (17, 19), may not have been adequately powered to demonstrate a statistically significant effect. However, it is also possible that a detectable increase in muscle strength would require GH replacement of longer duration, and subsequently Johannsson *et al.* (85) demonstrated this in a 2-yr open-label study. In this study at baseline, compared with a reference population of normal subjects, GHD adults exhibited reductions in isometric and isokinetic muscle strength and local muscle endurance. After 2 yr of treatment with a mean daily dose of  $0.62 \pm 0.03$  mg of GH, isometric and isokinetic strength increased into the normal range, although a reduction was seen in muscle endurance. A later study confirmed that these effects persisted after 5 yr of treatment (86). Like many of the clinical features of GHD, the effect of GH replacement was most pronounced in subjects in whom strength was most abnormal at baseline.

**4. Body fat, extracellular water, and thermoregulation.** In addition to reduced muscle mass, other abnormalities of body composition (see Table 3 for summary of effects) and the ability to dissipate excess heat in GHD could contribute to impaired exercise performance. Total body and centrally distributed fat are increased in proportion to the duration of GHD,

TABLE 3. Body composition and the effect of treatment in adults with GHD and acromegaly, and the effect of GH administration in normal subjects

	GHD		Normal subjects	Acromegaly	
	Comparison with normal subjects	Effect of treatment	Effect of GH administration	Comparison with normal subjects	Effect of treatment
LBM	↓	↑	↑	↑	↓
Skeletal muscle	↓	↑	NK	↔	↔
Extracellular water	↓	↑	↑	↑	↓
Total body fat	↑	↓	↔	↓	↑

NK, Not known; ↑, increased; ↔, not different/unchanged; ↓, decreased.

whereas extracellular water is reduced. The ability to carry out weight-bearing exercise is influenced by the quantity of body fat, which represents a mechanical limitation to exercise. The effect of reduced extracellular water on exercise capacity is less clear but might also be important. Sweating is essential for maintenance of body temperature during exercise, and thus impaired thermoregulation during exercise may also contribute to reduced exercise capacity in GHD. Using pilocarpine iontophoresis, it has been demonstrated that the sweat secretion rate is significantly lower in GHD adults than in appropriately matched control subjects and is increased during GH replacement. Juul *et al.* (87) demonstrated impaired thermoregulation during heat exposure and exercise in untreated GHD adults compared with normal control subjects. The same group later compared sweating and body temperature during exercise in hot conditions (35 C) in GHD adults who were receiving long-term (4 to 20 yr) GH replacement and normal subjects (88). Despite GH replacement, sweat secretion rates were reduced, body heat storage was increased, and therefore there was a greater increase in core temperature during exercise in GHD subjects. Interestingly, five of 10 GHD patients stopped exercise prematurely because of subjective discomfort and signs of heat exhaustion.

### C. Limitations of using GHD adults to study the physiological effects of GH

Although GHD adults, studied before and after acute or long-term administration of GH, provide a useful model to study the physiological effects of GH, a number of potentially confounding variables must be considered.

First, studies of exercise physiology in GHD subjects have generally been small and, as detailed in *Section II.A*, did not all demonstrate significant results using rigorous statistical methods. Although this might reflect type 2 statistical error, the possibility of publication bias must also be considered, *i.e.*, trials showing a positive effect of GH are more likely to be published and ultimately included in meta-analysis.

Second, pharmacological GH replacement with a single sc nightly injection poorly reflects physiological GH production. In normal subjects, GH is secreted in a pulsatile manner, with episodic bursts shortly after the onset of sleep, during exercise, and a few hours postprandially (89). Potential effects of the GH/IGF-I axis on exercise physiology include both a long-term effect of GH secretion with changes mediated by both GH and IGF-I, and as described in detail in *Section III.A* a short-term effect mediated by the acute GH response to a given bout of exercise. Most of the studies

reported above have addressed the medium- to long-term effects of GH replacement, but few have included any attempt to replicate the GH response to exercise.

Third, abnormal findings in GHD subjects must be interpreted in the context that the onset of GHD in adult life is usually secondary to significant pathology, most commonly a pituitary tumor (90). Although there is little information concerning the effects of pituitary neoplasia and its treatment on lifestyle and physical fitness, there is extensive evidence that these are impaired in survivors of other neoplastic diseases (91–94).

Finally, most AO-GHD patients have other pituitary hormone deficiencies (90). Interpretation of the effects of GHD and GH replacement in this setting is complicated both by interactions between the GH-IGF-I axis and other endocrine axes and by the inherently unphysiological nature of pituitary hormone replacement. In particular, glucocorticoid excess is characterized by similar features as GHD, including reduced protein synthesis, reduced LBM and muscle mass, increased body fat, and impaired exercise capacity (95–102). Until recently, overreplacement with glucocorticoids was almost universal in glucocorticoid-deficient patients and remains common particularly in patients with hypopituitarism, who are frequently only partially glucocorticoid deficient (103). Studying the effects of GH replacement, while maintaining the same glucocorticoid replacement dose, does not entirely overcome the difficulty of separating the effects of GHD from the effects of glucocorticoid excess because GH replacement, through an effect mediated by IGF-I, inhibits 11 $\beta$ -hydroxysteroid dehydrogenase-1, which catalyzes the conversion of cortisone to cortisol (104, 105) resulting in a shift in cortisol metabolism favoring inactive cortisone (104, 105). Some of the effects of GH replacement therefore might reflect reduced glucocorticoid exposure, particularly in patients receiving cortisone acetate in whom this effect is more marked compared with hydrocortisone (106).

Interactions between the GH/IGF-I axis and thyroid hormones and sex steroids may also be important. Thyroid hormone replacement in the hypopituitary patient cannot be titrated against serum TSH, the most sensitive index of tissue activity of thyroid hormones, and thus subtle degrees of over- and underreplacement with thyroid hormones likely occur in hypopituitarism. GH, through increased 5'-deiodinase activity, increases conversion of T<sub>4</sub> to metabolically active T<sub>3</sub> (7), and it has been suggested that this effect might underlie some of the metabolic changes observed with GH replacement (107, 108). Untreated testosterone deficiency in males is associated with reduced LBM, increased body fat, and reduced exercise capac-

## Study 1

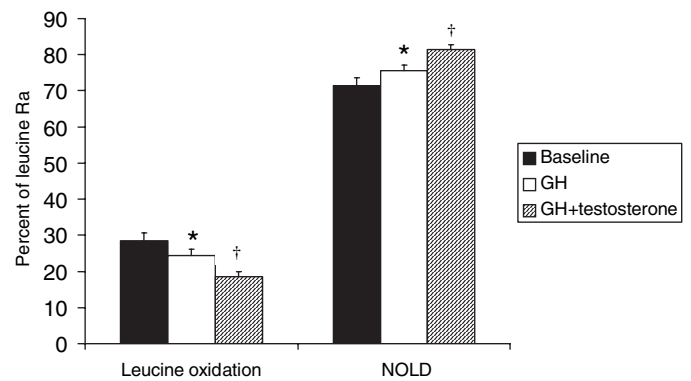
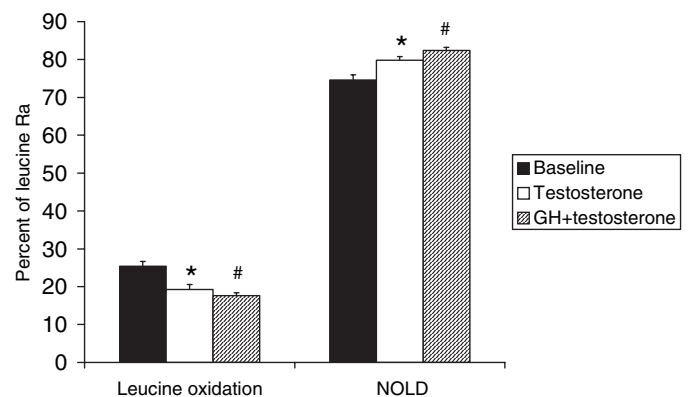


FIG. 3. Percentage leucine oxidation and percentage non-oxidative leucine disposal (NOLD) in hypogonadal GHD subjects at baseline, after treatment with GH alone and GH with testosterone (study 1), and at baseline, after treatment with testosterone alone and GH with testosterone (study 2). \*,  $P < 0.05$  vs. baseline. †,  $P < 0.05$  vs. baseline and vs. GH only. #,  $P < 0.05$  vs. baseline and vs. testosterone only. [Derived from Ref. 111. Adapted from J. Gibney *et al.*: *Am J Physiol Endocrinol Metab* 289:E266-E271, 2005 (112) with permission from The American Physiological Society.]

## Study 2



ity, whereas orally administered estrogen reduces fat oxidation and increases body fat in normal women (109, 110). When administered together, testosterone and GH exert a combined effect on protein anabolism (Fig. 3) and body composition (111, 112), and there is increasing evidence that androgen deficiency might also contribute to the phenotype of hypopituitary women (113).

### III. The GH-IGF-I Axis and Exercise in Normal Subjects

#### A. The acute and long-term effects of exercise on the GH/IGF-I axis

In 1963 Roth *et al.* (3) demonstrated that plasma levels of GH increase during exercise, and it was later shown that exercise is the most potent physiological stimulus to GH release (114). GH levels start to increase 10 to 20 min after the onset of exercise, peak either at the end or shortly after exercise, and remain elevated for up to 2 h after exercise (115–117). The neuroendocrine pathways through which GH secretion is regulated during exercise are complex and poorly understood, but there is evidence that adrenergic, cholinergic, and opioid pathways are involved (89). The magnitude of the GH response to exercise is influenced by age (118–120), gender (121–123), body composition (124–126), physical fitness (118, 120, 127, 128), and the intensity (114, 127, 129–133), nature (134–142), and duration (130, 143–145) of exercise (Table 4). The impact of these variables

has been more clearly defined in a recent series of meticulously carried out studies using ultrasensitive chemiluminescence GH assays and deconvolution analysis of GH secretion. Pritzlaff *et al.* (133) carried out exercise tests at five different exercise intensities normalized to each subject's lactate threshold. A linear dose-response relationship between exercise intensity and the GH secretory response was demonstrated, with escalating GH release across the range (25 to 175% of lactate threshold) of exercise intensities (Fig. 4). Deconvolution analysis revealed that increased GH levels resulted from an increase in the mass of GH secreted per pulse, with no change in pulse frequency or the half-life of elimination. Later studies from the same laboratory demonstrated that GH secretion correlates positively with duration of exercise when intensity is constant (145), is augmented by

TABLE 4. The effect of physiological variables on the GH response to exercise

Variable	Effect
Age	↓
Gender	↔
BMI	↓
Fitness	↑
Exercise intensity	↑
Exercise duration	↑
Repetition of exercise	↑
Time of day	↔
Cold temperature	↓

↑, Increased; ↔, no effect; ↓, decreased.



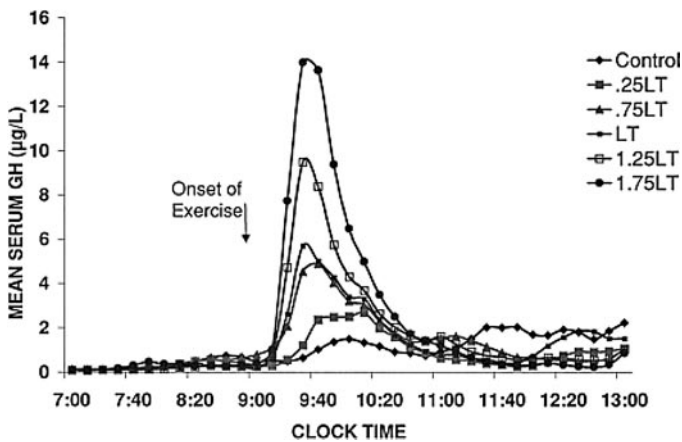


FIG. 4. The response of serum GH concentrations to exercise of different intensities. LT, Lactate threshold; Control, no exercise; 0.25LT, 25% of the difference between  $\text{VO}_2$  achieved at lactate threshold and  $\text{VO}_2$  at rest; 0.75LT, 75% of the difference between  $\text{VO}_2$  achieved at lactate threshold and  $\text{VO}_2$  at rest; 1.25LT, 25% of the difference between  $\text{VO}_2$  achieved at lactate threshold and peak  $\text{VO}_2$ ; 1.75LT, 75% of the difference between  $\text{VO}_2$  achieved at lactate threshold and peak  $\text{VO}_2$ . Values are means  $\pm$  SE;  $n = 10$  subjects. [Reproduced from C. J. Pritzlaff *et al.*: *J Appl Physiol* 87:498–504, 1999 (133) with permission from The American Physiological Society.]

repetitive bouts of exercise (146), but is not influenced by the time of day that exercise was performed (147). Wideman *et al.* (122) compared GH secretion at rest and during exercise in men and women matched for age and physical fitness and demonstrated that GH secretion rates under resting conditions were greater in women; but during exercise, although absolute GH secretion rates were also increased, the increment from baseline was similar in men and women and did not correlate with sex hormones. This finding was confirmed in a later study (123).

The GH response to exercise, like 24-hr GH secretion rates, declines with aging, and it has been demonstrated that even in early middle age (mean age, 42 yr), the GH response to exhaustive exercise is greatly attenuated compared with younger (mean age, 21 yr) subjects (119). It is difficult to separate inherent effects of aging from changes in body composition, because body fat increases with aging and GH secretory rates are reduced in overweight subjects (125, 126). In a study designed to separate out the effects of aging, body composition, and physical fitness, Holt *et al.* (120) compared the GH response to exercise in four groups of male subjects: lean young, overweight young, lean older, and overweight older men. The GH response was found to be determined by age and physical fitness ( $\text{VO}_{2\text{max}}$ ) but not by body fat, implying that maintenance of physical fitness with increased aging is more important in determining GH release than avoidance of increased adiposity. However, training programs that improve physical fitness do not appear to increase the GH response to exercise (119, 124).

The physiological mechanisms through which GH secretion increases during exercise are not known, but changes in body temperature (148), blood lactate levels (130), and pH (149) have all been postulated. Supporting a role of body temperature is the observation that the GH response to exercise is greatly attenuated during exercise in cold conditions

(148) and is proportional to core temperature (150). Against an effect of lactate are the observations that infusion of sodium L-lactate does not increase GH secretion (127) (although this experimental model differs significantly from an exercise-induced metabolic acidosis), and as described above there is a linear increase in GH secretion with increased exercise intensity that can be observed before the lactate threshold is reached (133). However, lactate production occurs very early in exercise although it does not increase substantially in blood until the Cori cycle is overwhelmed, and therefore an effect on GH secretion cannot be completely ruled out. There are little data concerning the effect of pH, although one study has demonstrated reduced GH secretion in response to exercise after alkali infusion (149).

Exercise exerts acute effects on other components of the GH/IGF-I axis. GH-binding protein, total IGF-I, IGF binding protein (IGFBP)-3, and acid-labile subunit increase slightly during exercise, whereas IGFBP-1 increases after exercise (151–156), and free IGF-I does not appear to change during or after exercise (156). These observations are not altered after adjustment for changes in hydration status during exercise (156). IGF-I, IGFBP-3, and acid-labile subunit circulate as a ternary complex, and the observation that all three components increase in parallel with no change in free IGF-I suggests that these effects occur due to mobilization of preformed intact complexes. Consistent with this, IGFBP-3 proteolysis has been shown not to increase during or after strenuous rowing exercise (157). The physiological relevance of these effects is not known, but it has been postulated that the modest increase in IGF-I might enhance postexercise reparative processes, or that increased IGFBP-1 might protect against delayed onset hypoglycemia. There is currently no evidence to support or refute these possibilities.

#### B. The relevance to exercise performance of the GH-IGF-I axis in normal subjects

The strongest supporting evidence that an intact GH/IGF-I axis exerts a long-term effect on exercise performance comes from studies of exercise physiology in GHD subjects and their response to GH replacement. The findings of these studies and the limitations inherent in their interpretation are discussed in detail under *Section II*. Whether the acute increase in GH secretion that occurs in normal subjects in response to exercise is also physiologically relevant is not known. In the study of Kanaley *et al.* (64), acute elevation of GH levels in a pattern similar to the physiological response to exercise increased fatty acid availability during and after exercise at 65% of  $\text{VO}_{2\text{max}}$ . It is possible that this increase in fatty acid availability would result in glycogen sparing and increased exercise duration. However, because GH does not usually begin to increase until at least 10 min of exercise has elapsed and because, under resting conditions, the maximal lipolytic response to a GH infusion does not occur until approximately 120 min after the infusion has started (60), it is physiologically more likely that GH would exert an effect either during more prolonged low-intensity exercise or in the recovery phase after moderate to high intensity exercise. Consistent with this, Wee *et al.* (158) demonstrated an increase in lipolysis that reached maximal levels more than 2 h

after 20 min of exercise at 70% of  $VO_{2max}$  in healthy subjects, and the magnitude of which correlated with the peak GH response to exercise. In the same study, a similar effect was reproduced under resting conditions using an infusion of GH calculated to mimic the GH response to exercise.

Two alternative approaches to determine the acute effects of GH in normal subjects are to administer an agent that suppresses GH secretion or GH effect, or to correlate the GH response to exercise in normal subjects with metabolic changes during exercise. Chalmers *et al.* (159), under control conditions and during an octreotide infusion to suppress endogenous GH release, measured plasma metabolites including glucose, glycerol, and FFA during 30 min of exercise at 70% of  $VO_{2max}$  and 90 min of recovery. No significant effect of GH suppression was observed. This study is important because it is the only one to date to use this approach to study the effects of GH/IGF-I on exercise, but a number of limitations must be considered. First, only six subjects were studied. Second, because no tracers were used, no conclusions can be drawn regarding rates of appearance into and disappearance from the circulation. Notably, in the study of Kanaley *et al.* (64), no statistically significant effects of GH were observed on plasma levels of FFA, despite marked effects on FFA turnover. Finally, results might have been confounded by other metabolic effects of octreotide (160). A similar study using GH receptor antagonists (161), which would be more specific for the effect of GH, and tracer techniques would now be possible and would provide invaluable information.

Pritzlaff *et al.* (162), in recreationally trained men, studied the response of GH and catecholamines during and after exercise of varying intensity and related these responses to changes in circulating metabolites and substrate oxidation. During exercise, neither glucose oxidation, which was directly proportional to exercise intensity, nor fat oxidation, which remained constant, was influenced by hormonal responses. Fat oxidation after exercise was related to exercise intensity, and although it correlated independently with both the peak GH and peak epinephrine response, using multiple regression analysis, only the peak GH response was

found to be an independent predictor. There is evidence, therefore, that endogenous GH secretion exerts an immediate and a delayed effect to increase fatty acid availability after exercise (Fig. 5).

### C. A potential role for GH in adaptation to training

Habitual exercise results in increased LBM and reduced body fat, as well as metabolic effects that can be demonstrated before these changes in body composition are detectable. Repeated GH pulses in response to exercise and/or the increment in GH secretion rates that occurs in response to training could potentially contribute to these effects.

Endurance training over 4 months increases muscle protein synthesis (163), and recently an increase in mixed muscle protein synthesis immediately after endurance exercise has been demonstrated (164). GH secreted in response to exercise could contribute to this postexercise protein anabolic effect either directly or indirectly through increased lipolysis. Studies using animal models have demonstrated that increasing fatty acid availability reduces leucine oxidation (165), and in untrained human subjects, fat oxidation has been shown to correlate negatively with oxidative protein loss (166). Further support for modulation of the anabolic effects of GH through its lipolytic effect comes from a recent study in which an effect of GH to conserve protein during fasting was abolished by administration of the antilipolytic agent, acipimox (167). Administration of acipimox has also been used to demonstrate that GH increases skeletal muscle triglyceride content through its effect on insulin resistance (168). The importance of this is unclear because increased skeletal muscle triglyceride is observed, apparently paradoxically, in both insulin-resistant subjects and endurance-trained athletes (169).

Twenty-four-hour GH secretion rates and plasma IGF-I levels correlate positively with  $VO_{2max}$  and leisure time physical activity (170–173), whereas long-term exercise training approximately doubles integrated GH concentrations in

FIG. 5. Schematic representation of the possible association between the GH response to exercise and lipolysis. The shaded area represents the components of the lipolytic response to exercise that are probably augmented by the GH response to exercise. Because increased lipolysis during exercise precedes increased plasma levels of GH and because of the delayed effect of a GH pulse to stimulate lipolysis under resting conditions, it is probable that any effect of the acute GH response to exercise on lipolysis occurs in the postexercise period or during very prolonged exercise.

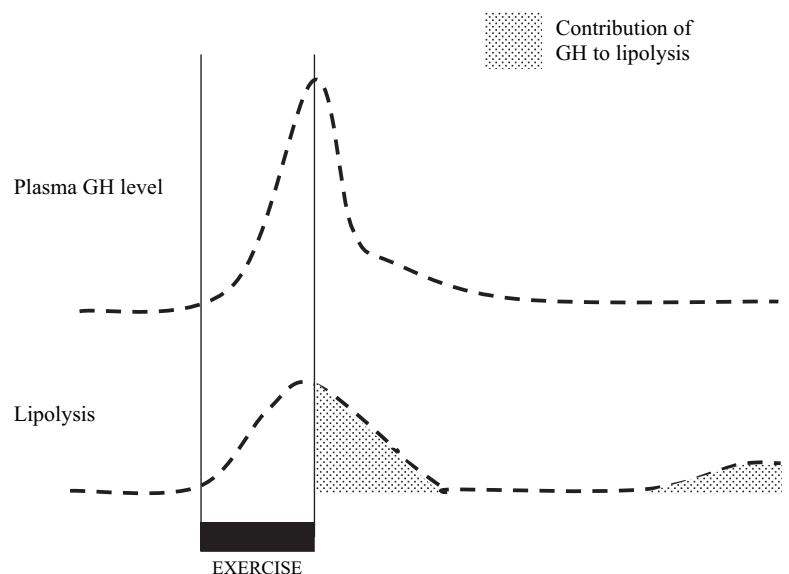


TABLE 5. Studies that have investigated effects on strength or exercise performance of administration of supraphysiological GH to normal or athletically trained subjects

Study	M/F	Design and duration	Daily dose	End-point	Effect
Yarasheski <i>et al.</i> 1992 (186)	7/0	RCT 12 wk (with resistance training)	0.04 mg/kg	Strength	No additional effect of GH on muscle strength
Deyssig <i>et al.</i> 1993 (195)	8/0	DBPCT 6 wk	0.03 mg/kg	Strength	No effect of GH on muscle strength
Lange <i>et al.</i> 2002 (181)	7/0	DBPCT (single-dose crossover)	2.5 mg 4 h preexercise	Metabolic response during and after bicycle exercise	GH increased plasma glucose, glycerol, FFA and lactate during exercise
Healy <i>et al.</i> 2003 (190)	6/0	DBPCT 4 wk	0.067 mg/kg	Protein turnover during and after bicycle exercise	GH reduced oxidative protein loss during and after exercise
Irving <i>et al.</i> 2004 (184)	9/0	RCT – GH × 5 studies/ saline × 1 study	0.01 mg/kg, 0.75–3.75 h preexercise	Power output, indirect calorimetry, metabolic response and perceived exertion during cycling	GH reduced oxygen consumption during exercise with unchanged power output
Hansen <i>et al.</i> 2005 (183)	7/0	RCT – GH/ placebo at rest/ exercise	2.5 mg 4 h preexercise	Indirect calorimetry during 120 min of bicycle exercise	GH did not increase in fat oxidation despite increased FFA availability
Berggren <i>et al.</i> 2005 (212)	10/10	DBPCT 4 wk	0.033 or 0.067 mg/kg	Power output and indirect calorimetry during bicycle exercise	No effect of GH
Healy <i>et al.</i> 2006 (182)	6/0	DBPCT 4 wk	0.067 mg/kg	Glucose and fat metabolism during and after bicycle exercise	GH increased lipolysis and glucose turnover during and after exercise

M/F, Number of male/female subjects who received GH in each study; RCT, randomized controlled trial.

women when measured on nonexercising days (174). Levels of IGFBP-3 and total and free IGF-I increase after training (172, 175), increased IGF-I levels becoming detectable within 2 wk of commencing training (175) and remaining above baseline for at least 6 months (176). These long-term effects of exercise on the GH-IGF-I axis might also contribute to some of the effects of training, including increased muscle mass and increased CO, although evidence for this is currently lacking.

#### IV. Supraphysiological GH and Exercise Performance

##### A. Effects of supraphysiological GH administration on the metabolic response to exercise

Administration of supraphysiological GH to normal subjects under resting conditions increases insulin secretion, lipolysis, fatty acid availability, and fat oxidation, and reduces glucose uptake into skeletal muscle (59, 60, 108, 177–180). More recently, the effects of administration of supraphysiological GH on intermediate metabolism during exercise have also been addressed (Table 5). Lange *et al.* (181) demonstrated that plasma levels of glucose, glycerol, FFA, and lactate were greater during moderate to high-intensity exercise in trained men after administration of a single dose of r-hGH, 2.5 mg sc, 4 h before exercise. Healy *et al.* (182) studied glycerol and glucose turnover using stable isotope techniques in endurance-trained athletes before and during 4 wk of r-hGH (0.06 mg/kg·d) administration. r-hGH increased lipolysis and plasma levels of FFA at rest and during and after submaximal exercise (Fig. 6). r-hGH did not influence glucose turnover at rest but increased rates of glucose production and uptake during and after exercise. The findings of these two studies are consistent, although there were important methodological differences. First, the study of Healy *et al.* addressed the effects of prolonged rather than acute GH administration. Second, the timing of GH administration in the study of Lange *et al.* resulted in increased GH levels during exercise in contrast to the study of Healy *et al.* in which GH levels were lower during exercise. Finally, the study of Healy *et al.* was carried out in the postabsorptive setting, whereas the study of Lange *et al.* was carried out postprandially. Taken together, the findings of these two studies demonstrate that GH enhances lipolysis during exercise under both postabsorptive and postprandial conditions and that the lipolytic effect of GH during and after exercise does not depend on increased circulating levels of GH during exercise. Despite increased fatty acid availability, there was no effect of GH on fat oxidation during or after exercise in either study or in two other studies in which this was also addressed (183, 184), consistent with the effects of GH on gene transcription in skeletal muscle described in Section II.B.2 (66).

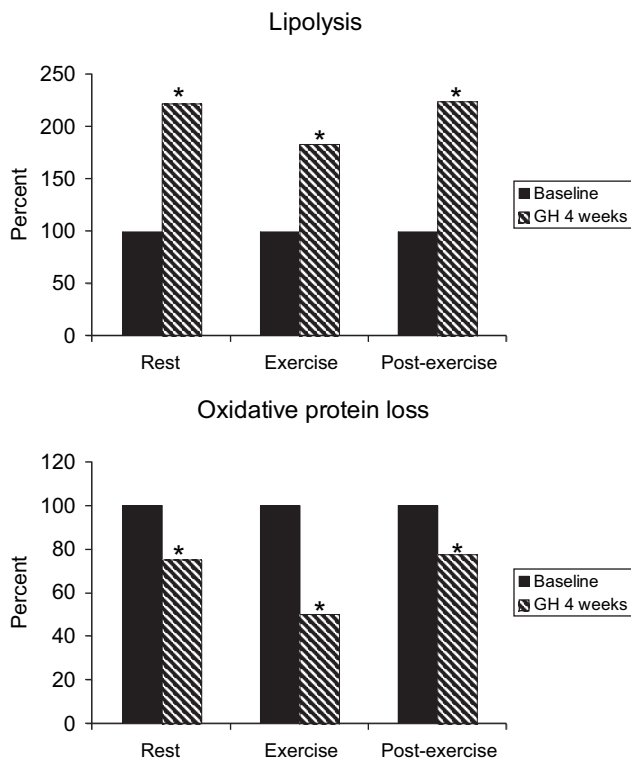


FIG. 6. Lipolysis, estimated from the rate of appearance of glycerol (top panel), and oxidative protein loss, estimated from leucine oxidation (bottom panel) at rest and during and after exercise in endurance-trained athletes ( $n = 6$ ), before and after 4 wk of treatment with GH, 0.066 mg/kg·d. \*,  $P < 0.05$  for the change from baseline. [Adapted from Refs. 182 and 190 with permission. Copyright 2003 and 2006, The Endocrine Society.]

### B. Effects of supraphysiological GH administration on protein metabolism and muscle mass

A number of small studies have addressed the effect of supraphysiological GH administration to normal or trained subjects on protein metabolism with some conflicting findings. Observations vary between studies of athletic and non-athletic subjects, and between those of whole-body protein turnover and muscle protein synthesis. Horber and Haymond (185) demonstrated no change in whole-body protein breakdown but an increase in protein synthesis after administration of 0.1 mg/kg·d of r-hGH to untrained males for 1 wk. Using a lower dose (0.04 mg/kg·d), Yarasheski *et al.* (186) observed an increase in whole-body, but not muscle, protein synthesis in untrained men after 12-wk administration of r-hGH. However, the same group observed no change in whole-body protein synthesis after 14-d administration of the same dose to experienced weight lifters (187). In contrast, Fryburg *et al.* (188) demonstrated that infusion of GH for 8 h to untrained males resulted in increased muscle, but not whole-body protein synthesis. The observation that whole-body protein synthesis did not change in the studies of Fryburg *et al.* possibly reflects a difference between acute and more long-term effects of GH. Notably, the effects of GH on carbohydrate metabolism are known to differ markedly, depending on duration of exposure to GH (71). The observations by Yarasheski *et al.* (186, 187) that GH increased whole-body protein synthesis in normal subjects, but not in weight lifters, may be due to methodological issues or might represent a differential response in resistance-trained subjects. Muscle, which is already hypertrophied, may have less potential to increase further. It is unlikely that the differences between those studies reflect a different period of administration, because measurable effects were clearly demonstrated after 1 wk in the study of Horber and Haymond (185).

Exercise exerts a significant influence on protein metabolism (189). Whole-body and muscle protein breakdown increase during exercise, whereas oxidation of certain amino acids, including leucine, increases during exercise. It is therefore apparent that studies of protein metabolism in the resting state may fail to recognize important changes occurring during or after exercise. Whole-body leucine turnover at rest and during exercise was also reported in the study of supraphysiological GH administration to athletes described under *Section IV.B* (190). At rest, after 1 wk of r-hGH administration, there was a net reduction in leucine oxidation and a net increase in protein synthesis, changes that were accentuated after 4 wk of r-hGH administration. As previously observed (189, 191–193), before r-hGH administration, leucine oxidation increased more than 2-fold during exercise. r-hGH administration reduced leucine oxidation during exercise by more than 50%, compared with a reduction under resting conditions of 29% (Fig. 5).

r-hGH administration has been consistently shown to increase LBM in young normal or trained subjects, but it is not known how much of this increase is secondary to protein accretion and how much to increased total body water (TBW) secondary to the antinatriuretic effect of GH (194). Using measurement of skinfold thicknesses, Deyssig *et al.* (195) demonstrated no change in LBM after 6 wk of treatment with r-hGH, 0.03 mg/kg·d. Using hydrodensitometry and measurement of

TBW with dilution techniques, Yarasheski *et al.* (186) demonstrated an increase in both fat free mass and TBW after 12 wk of treatment with r-hGH, 0.04 mg/kg·d. Crist *et al.* (196), also using hydrodensitometry, demonstrated an increase in fat free mass and a reduction in percentage body fat after 6 wk of treatment with met-hGH. Healy *et al.* (190) demonstrated a mean increase in fat-free soft tissue mass of 3.8 kg using dual-energy x-ray absorptiometry scanning. Although this technique, like hydrodensitometry, does not differentiate metabolically active body cell mass from extracellular water, the observed reduction in resting leucine oxidation data would predict a mean increase in body protein of 0.6 kg over 28 d, representing an increase of approximately 5% based on normative data (197).

There is evidence, therefore, that supraphysiological GH administration to trained subjects results in conservation of protein and that this effect is particularly marked during exercise. As described under *Section III.B*, protein anabolic processes are influenced by fatty acid availability, and therefore it is possible that these effects are secondary to the lipolytic effect of supraphysiological GH. Figure 6 demonstrates the reciprocal relationship between lipolysis and oxidative protein loss demonstrated in the studies of Healy *et al.* (182, 190). Evidence that changes in body composition after administration of supraphysiological GH are functionally important is considered in *Sections V and VI*.

### C. Exercise performance and strength in acromegaly

Patients with acromegaly represent a useful model to study the chronic effect of GH excess, although the potentially confounding influence of duration of disease, recovery from long-term illness, and the effects of other hormone deficiencies and replacement must be considered. Acromegaly is characterized by marked abnormalities in protein (198) and carbohydrate (199–202) metabolism and at least late in the disease process, impairments in strength and exercise performance. Protein remodeling in long-standing acromegaly is abnormal in most organ systems, including skeletal muscle, resulting in tissue disorganization and functional impairment, and in some cases cardiomyopathy. Despite an increase in muscle mass, histological examination of muscle fibers reveals a myopathic process, and physical strength is reduced rather than increased (15). Nagulesparen *et al.* (15) carried out muscle biopsies on 18 acromegalic patients and showed abnormalities in more than half, typically hypertrophy of type 1 fibers and atrophy of type 2 fibers. The degree of abnormality correlated positively with circulating GH levels.

Long-standing acromegaly is also associated with impairment in aerobic exercise capacity and cardiac performance.  $VO_{2max}$  and VeT are reduced in patients with acromegaly, compared with normal subjects, and improve after treatment with octreotide (203). Colao *et al.* (204) using radionuclide angiography studied cardiac performance during exercise in acromegalic subjects and normal controls. The LVEF response to exercise was reduced in acromegalic subjects and correlated inversely with age and duration of acromegaly. The same investigators later reported that normalization of GH and IGF-I levels after 1 yr of treatment with octreotide was associated with

improvement in, but not normalization of, LVEF both at rest and during exercise (205).

Although these findings suggest that long-term GH excess is likely to be detrimental to exercise performance, it should be noted that clinical features of acromegaly are usually present for some years before diagnosis, and that biochemical GH excess precedes the appearance of clinical signs. Although cardiac function is typically found to be impaired in long-standing acromegaly, Fazio *et al.* (206) have demonstrated that in acromegaly of less than 5-yr duration, certain potentially beneficial components of cardiac function including stroke index and cardiac index are increased, and SVR is reduced. Important differences have also been demonstrated in the acute and long-term effects of treatment of acromegaly. Normalization of IGF-I levels in patients with acromegaly results in an increase in oxidative protein loss (representing net protein catabolism) that is not sustained but a reduction in protein remodeling that is sustained (207). Extrapolating these findings to acute and long-term GH excess would imply an initial anabolic phase (evidence for which is described under *Section III.A*) followed by a later phase when body protein mass remains stable but when there is a potentially deleterious effect on protein remodeling. It is therefore possible that there is a window in which the potentially beneficial effects of supraphysiological GH predominate, and indeed one of the authors reports such an occurrence in an elite oarsman (P. H. Sönksen, personal communication). A possible mechanism through which these effects might occur is demonstrated in Fig. 7.

## V. GH Abuse in Sport

### A. GH as a putative performance-enhancing agent

GH was recommended in “The Underground Steroid Handbook” (10) in 1983 as “a new and exciting anabolic agent” approximately 7 yr before any publication suggesting that this effect occurred in adults appeared in the scientific literature. Ben Johnson was disqualified from the gold medal position in the 100 m in the 1988 Olympic Games and subsequently admitted under oath to having self-administered

GH as well as anabolic steroids. Although it is clear that GH abuse by athletes is widespread (208–211), there is no evidence of its efficacy. The most plausible mechanisms by which administration of supraphysiological doses of GH could improve exercise performance are through increased muscle mass and strength and through increased fatty acid availability resulting in glycogen sparing and increased endurance. Only two studies, with seven and eight subjects, respectively, receiving GH, have investigated the effect of GH on strength in young normal or trained subjects (186, 195) (Table 5). Neither demonstrated any significant improvement, although the studies were of short duration and almost certainly lacked statistical power to detect a meaningful difference. There is also no evidence that GH improves endurance. Berggren *et al.* (212) administered supraphysiological GH for 28 d to healthy active normal subjects and found no change in  $VO_{2max}$  or maximal power output during cycling. In the study reported by Lange *et al.* (181), GH administration led to a significant increase in plasma lactate during 90 min of cycling at 65 and 75% of  $VO_{2max}$  during GH administration, and predictably, this was associated with reduced exercise performance in some subjects. It is not known whether GH administration for longer duration might be more effective, but notably changes in strength in GHD adults have proved difficult to convincingly demonstrate in studies of 6-month duration and are more obvious after 2 yr.

However, to put these unimpressive scientific findings into context, anabolic steroids were widely abused for more than 40 yr (14) before they were definitively shown to increase strength (213), and the pattern of GH abuse by athletes may differ considerably from controlled clinical trials. In particular, there is evidence of an additive effect between testosterone and GH (112), and trials of their combined administration to athletes have not yet been reported. Furthermore, the marginal changes that differentiate winning from losing in high-level sport are unlikely to be detected in classical clinical trials, which are usually statistically powered to distinguish much larger differences. Athletes and coaches, who meticulously monitor their own performance, can detect much smaller changes with different interventions that

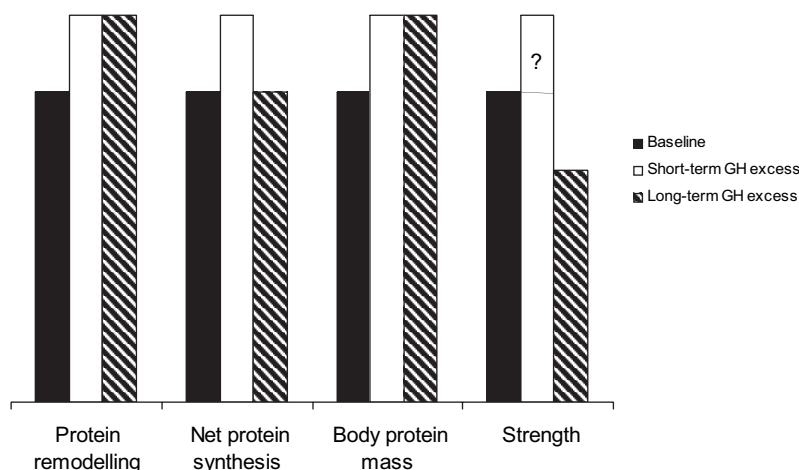


FIG. 7. Schematic representation of the effects of short-term and long-term GH excess. Question mark indicates a possible, but unproven, short-term effect of supraphysiological GH to increase strength.

could not be identified in small or medium-sized clinical trials. This has been demonstrated in secret doctoral theses pertaining to the sports doping program of the German Democratic Republic (214), which became available in the early 1990s after German reunification. In these papers, it is clearly shown that the principal method used by doctors and coaches to evaluate the effects of anabolic steroids was by comparing performance targets in individual athletes when taking and not taking different agents.

### B. Tests to detect GH doping by athletes

It is important to detect abuse of GH in the interest of fair competition and also because, as illustrated by the pathophysiological model of acromegaly, long-standing elevation of GH and IGF-I is detrimental to health (215). However, a number of factors complicate GH detection. Exogenous r-hGH and endogenous GH have identical amino acid sequences, making chemical distinction impossible. GH is secreted in a pulsatile manner; is under the influence of stress, exercise, sleep, and food intake (89); and has a very short half-life in the circulation (216), resulting in serum concentrations that vary widely throughout the day and frequently overlap with measurements obtained after exogenous administration of GH. The concentration of GH (like other proteins) in urine varies markedly with exercise and has been previously demonstrated to be insensitive as a marker of either GH administration or acromegaly (217, 218). It is very likely, therefore, that any useful test for GH abuse will involve blood sampling, which represents a major change from the long-established antidoping methods that are based on postcompetition urine tests.

To date, two approaches to detection of GH administration have shown promise. The first approach involves measurement of serum markers of GH action and has largely been developed

through the work of the GH2000 and GH2004 projects. Serum levels of IGF-I, IGFBP-2, IGFBP-3, and the bone markers bone-specific alkaline phosphatase, carboxy-terminal propeptide of type I procollagen, carboxy-terminal cross-linked telopeptide of type I collagen, and procollagen type III (PIIIP) were identified in a pilot study (156, 219–222) as having characteristics potentially useful in detection of exogenous GH administration. These included a clear response to exogenous GH administration, a much smaller response to acute exercise, day-to-day stability within subjects, clear separation between GH and placebo-treated subjects, and persistence of elevated concentrations for many days after the last GH injection. A subsequent double-blind, placebo-controlled trial (DBPCT) demonstrated that 28 d of self-administration of two doses of GH (0.067 and 0.133 mg/kg-d) predictably altered these markers. Notably, plasma levels of bone and connective tissue turnover remained elevated for significantly longer than components of the IGF-IGFBP axis, up to 8 wk after cessation of GH in the case of osteocalcin and PIIIP (219, 221). Reference data from elite athletes in the postcompetition setting were obtained in a cross-sectional study, in which it was demonstrated that after adjustment for the effects of age there was little or no effect of auxological characteristics or the type of sport performed on any of these variables (223). Interestingly, the age-associated decline of plasma IGF-I observed in that study was at least as marked as that previously observed in normal sedentary populations (224–226), which is highly suggestive that the decline in GH-IGF-I activity is an inexorable feature of the aging process and is not attenuated by maintaining physical fitness (Fig. 8).

From the studies described above, equations using multiple markers (which have improved sensitivity and specificity compared with single markers) were derived, and the most useful test based on these studies appears to be a gender-specific

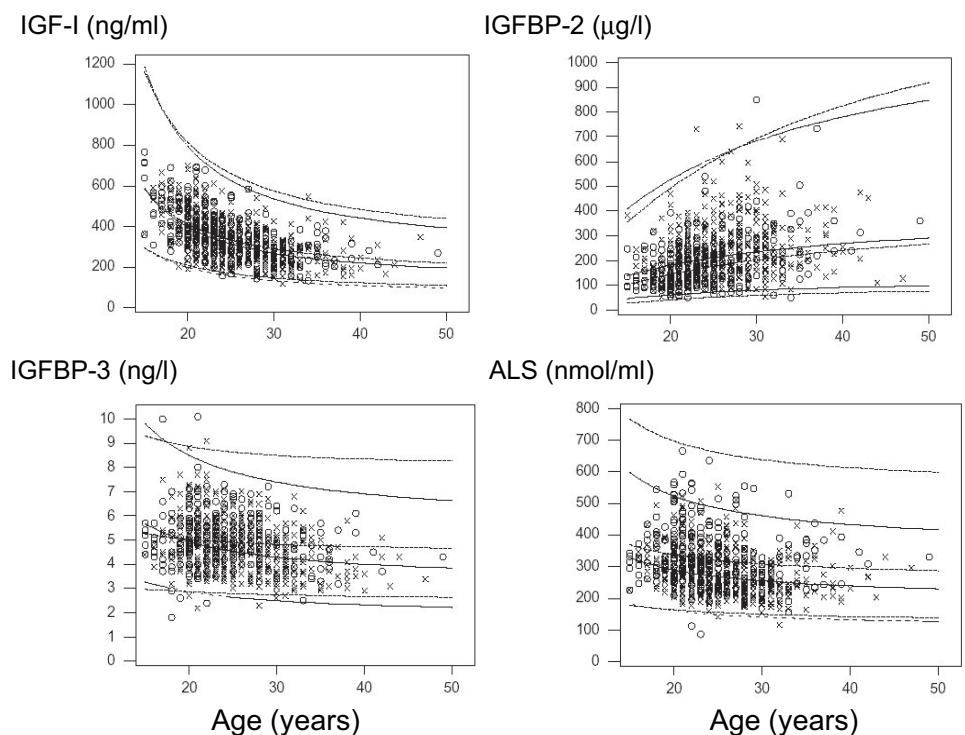


FIG. 8. Age-dependent change in components of the IGF/IGFBP system in 537 elite male (×) and 276 elite female (○) athletes. Reference ranges for male (solid lines) and female (dashed lines) athletes are shown. [Reproduced from Ref. 223 with permission. Copyright 2006, The Endocrine Society].

discriminant function that includes IGF-I and PIIIP and is adjusted for age (227). Some outstanding issues remain however before these formulae can be generally applied. First, more data are required from athletes of ethnic groups other than Caucasians. In this regard, it was interesting that in the cross-sectional study described above (223), plasma levels of IGFBP-2 and IGFBP-3 differed in black subjects, an observation that clearly requires further exploration. Second, it is important to know the effect of concurrent administration of androgenic or estrogenic agents, both of which can exert effects on the GH/IGF-I axis. Finally, the effect of injury, particularly on markers of bone and connective tissue, must be excluded as a potentially confounding variable.

The second potentially useful approach to developing a test for GH abuse involves simultaneous RIA of the natural isoforms and fragments of GH, the two most commonly occurring being 22-kDa GH and 20-kDa GH. Exogenous administration of supraphysiological doses of r-hGH, which consists exclusively of 22-kDa GH, suppresses endogenous GH secretion and therefore increases the ratio in plasma of 22-kDa to 20-kDa GH (228). Preliminary studies evaluating this approach have shown promise (229, 230), although in view of the short half-life of GH in the circulation, this test is only likely to be effective if sampling is carried out within 24 h of the last GH injection. Furthermore, there is a more marked increment in circulating 22-kDa GH compared with 20-kDa GH levels in response to exercise (229), and therefore the sensitivity of the test could be reduced in the postcompetition setting. Pituitary-derived GH consisting of multiple isoforms and fragments is still in circulation, and its use will not be detected. Finally, it must be considered that recombinant 20-kDa GH has also been synthesized, and therefore appropriate combinations of 20- and 22-kDa r-hGH could potentially confound this test. Of note, this test was introduced in the Olympic Games in 2004 and the Winter Olympics in 2006, but no positive tests were recorded.

It must also be considered that in addition to self-administration of GH, other technologies to manipulate the GH/IGF-I axis are emerging. These include gene doping, GH secretagogues, recombinant human IGF-I (r-hIGF-I) and r-hIGF-I/recombinant IGFBP-3 complex. In animals, injection of a recombinant adenoassociated virus genetically manipulated to induce myocyte overexpression of IGF-I induced a 15% increase in muscle mass and a 14% increase in muscle strength without inducing a systemic increase in IGF-I (231). There are few data concerning the effects of r-hIGF-I administration on exercise performance, although one paper demonstrated that a single r-hIGF-I injection to healthy male volunteers 2–4 h before exercise increased SV, CO, and EF, but did not influence exercise duration or  $VO_{2max}$  (232). However, because the effects of GH on these variables appear to be at least partially mediated through increased muscle mass, it is not surprising that a short-term effect would not be detectable.

## VI. Therapeutic Possibilities Related to Exercise Performance of Supraphysiological GH Administration

In contrast to athletes, in whom GH secretory rates are normal or increased, elderly and obese subjects secrete less GH compared with young subjects with normal body mass

index and therefore might be more likely to benefit from GH administration. The first major study to explore the possibility that GH might ameliorate some of the changes in body composition and functional ability that occur with aging was reported by Rudman *et al.* (233), who demonstrated increased LBM, skin thickness, and bone mineral density, and reduced total body fat after administration of GH for 6 months to older men. However, despite confirming these potentially beneficial changes in body composition, subsequent studies demonstrated little or no improvement in strength or functional ability increase after administration of GH alone (233–235) or in combination with exercise training (236, 237) to elderly subjects. These disappointing findings might reflect difficulties in determining the most appropriate dosing regime because side effects related to overdosage were common, or alternatively that because production of both GH and testosterone declines with age and because these two anabolic hormones exert an additive effect treatment with either hormone in isolation might be ineffective.

Three recent well-designed studies have addressed the possibility that GH and testosterone in combination might be more efficacious than either hormone alone. In a 26-wk DB-PCT, small increases in muscle strength and  $VO_{2max}$  that correlated with increases in LBM were demonstrated in men who were treated with combined GH and testosterone (238). Notably, deterioration in glucose tolerance occurred in a significant number of subjects. A small crossover study compared the effect of administration of testosterone, GH, and combined testosterone and GH in doses chosen to approximate physiological production rates for 1 month each to elderly men (85). Small improvements were seen in some indices of physical function, including walking and climbing stairs, after administration of either hormone alone or in combination, and improvement in balance was seen after treatment with GH alone. The effects of administration of GH and testosterone alone and in combination for 6 months to healthy elderly men were studied in a more recent well-powered DBPCT (239). The dose of GH was titrated to achieve plasma IGF-I levels in the upper half of the normal range, and a transdermal preparation of testosterone was administered daily that resulted in plasma testosterone levels within the normal range. LBM increased with GH alone, whereas there was an increase in muscle mass and a reduction in total body fat after combined treatment.  $VO_{2max}$  also increased significantly in patients who received combined treatment compared with those who received placebo and those who received either treatment alone. Overall, the combined effect of the two hormones was additive rather than synergistic. Of note, all of these studies have been relatively short-term and as described under *Section II.B*, improvements in strength in GHD adults have only been clearly identified after 2 yr of treatment.

Fewer studies have addressed the effects of GH on physical performance in overweight or obese normal subjects. No additional effect on muscle strength or  $VO_{2max}$  was observed after addition of either GH or IGF-I or a combination of both to a 12-wk program of exercise and weight loss in overweight women, despite increased fat-free mass and reduced total body fat with GH alone or in combination (240). No additional effect of GH on muscle strength or anaerobic power

output during jumping was observed in 3-wk study that compared the effect of weight reduction and strength training alone or with the addition of GH (44).

## VII. Summary and Conclusions

Studies in GHD adults have provided evidence to support the postulate, first made by Hunter and associates more than 40 yr ago, that the metabolic effects of GH might be important in exercise performance. Adult GHD is associated with a decrease in  $VO_{2\max}$  that is proportional to the well-documented reduction in skeletal muscle mass, and a decrease in VeT that reflects a reduction in the intensity of exercise that can be carried out aerobically and potentially explains reduced energy levels. DBPCTs have, in general, demonstrated that GH replacement improves exercise performance, probably through a combination of increased delivery of oxygen to exercising muscle, increased FFA availability and fat oxidation, increased muscle mass and strength, reduced body fat and improved thermoregulation. Despite potentially confounding variables including the unphysiological nature of GH replacement, the long-term effects of recovery from serious illness and interactions with other hormonal axes, these observations provide evidence that an intact GH-IGF-I axis is important in maintaining normal exercise capacity.

There is also evidence that the acute GH response to exercise in concert with reduced circulating insulin levels is important in regulating fatty acid availability in the postexercise setting, and it is possible that this effect contributes to the changes in body composition and exercise performance that occur as a result of training. It is also possible that the acute GH response also contributes to the protein anabolic effect of exercise, either directly or through increased fatty acid availability, although this remains unproven.

The effects of administration of supraphysiological doses of GH to subjects with an intact GH/IGF-I axis potentially differ between athletically trained subjects, in whom production of GH and IGF-I is normal or increased, and elderly or obese subjects in whom GH secretion rates are decreased. Administration of supraphysiological doses of GH to athletes increases fatty acid availability and reduces oxidative protein loss at rest and during and after exercise and exerts potentially beneficial effects on body composition. Although there is little scientific evidence that these effects translate to improved performance, GH abuse has been widespread among athletes for more than 20 yr. The two most promising approaches to detection of GH abuse involve measurement of serum markers of GH action and measurement of the relative proportions in serum of the naturally occurring isoforms of GH.

There is preliminary evidence that GH treatment is useful in improving body composition and exercise performance in elderly subjects particularly when used in association with testosterone. In contrast, there is no evidence that GH improves physical performance in obese subjects, although there have been a few studies with small numbers of patients carried out over short duration. It will be important, when considering the role of GH treatment in these or any other subject groups, to balance potential gains with the safety

concerns associated with maintaining supraphysiological GH levels.

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