0163-769X/07/$20.00/0
Printed in U.S.A.

Endocrine Reviews 28(6):603–624

doi: 10.1210/er.2006-0052

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

James Gibney, Marie-Louise Healy, and Peter H. Sönksen

Department of Endocrinology and Diabetes (J.G.), Adelaide and Meath Hospital, Tallaght, Dublin 24, Ireland; Department of Endocrinology and Diabetes (M.-L.H.), St. James's Hospital, Dublin 8, Ireland; and Endocrinology and Metabolism Subdivision (P.H.S.), Developmental Origins of Adult Health and Disease Division, School of Medicine, University of Southampton, Southampton, United Kingdom

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 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)

First Published Online September 4, 2007

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.

***Endocrine Reviews* is published by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

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-

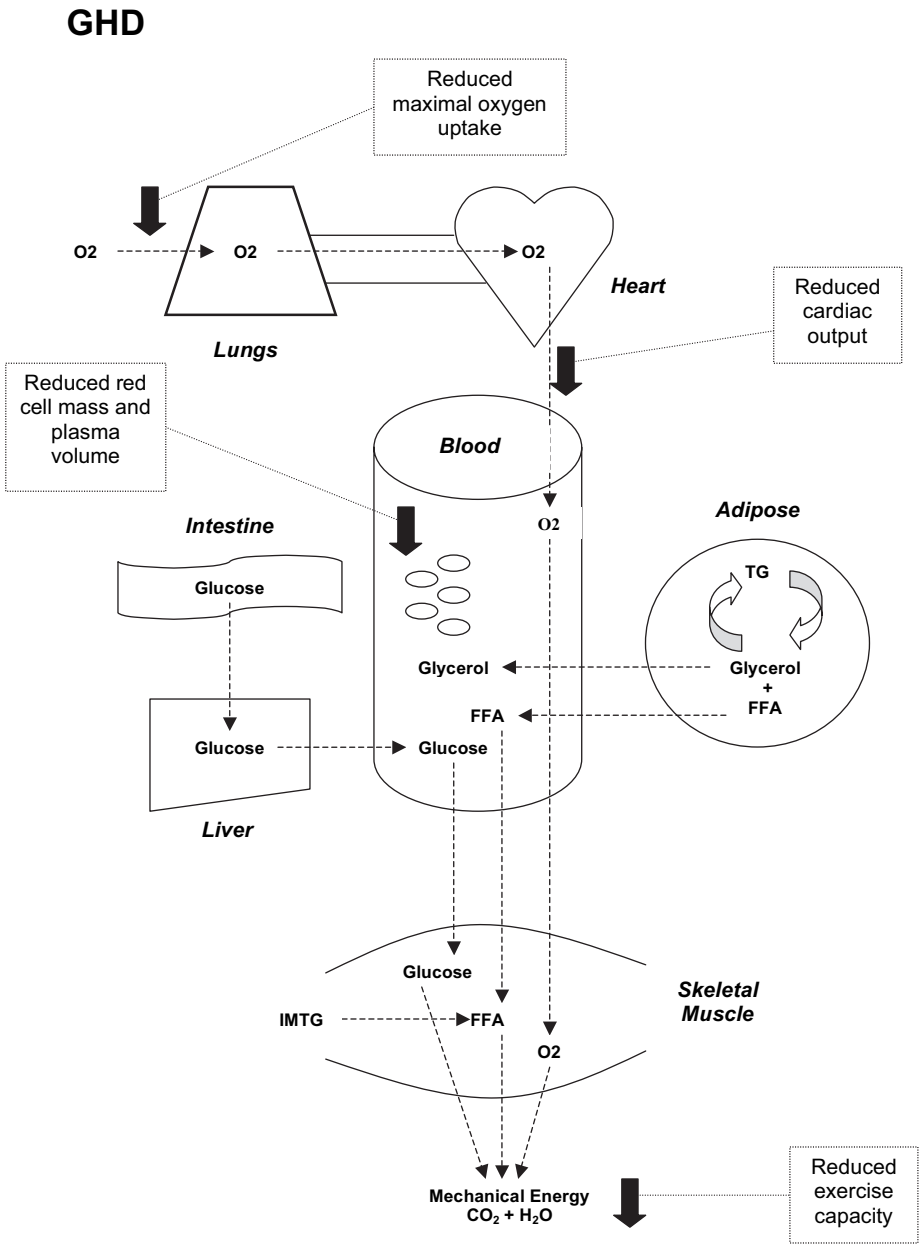

FIG. 1. The effects of GHD (*first panel*) and GH replacement (*second panel*) in GHD adults on components of the physiological response to exercise. TG, Triglyceride; IMTG, intramuscular TG.

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

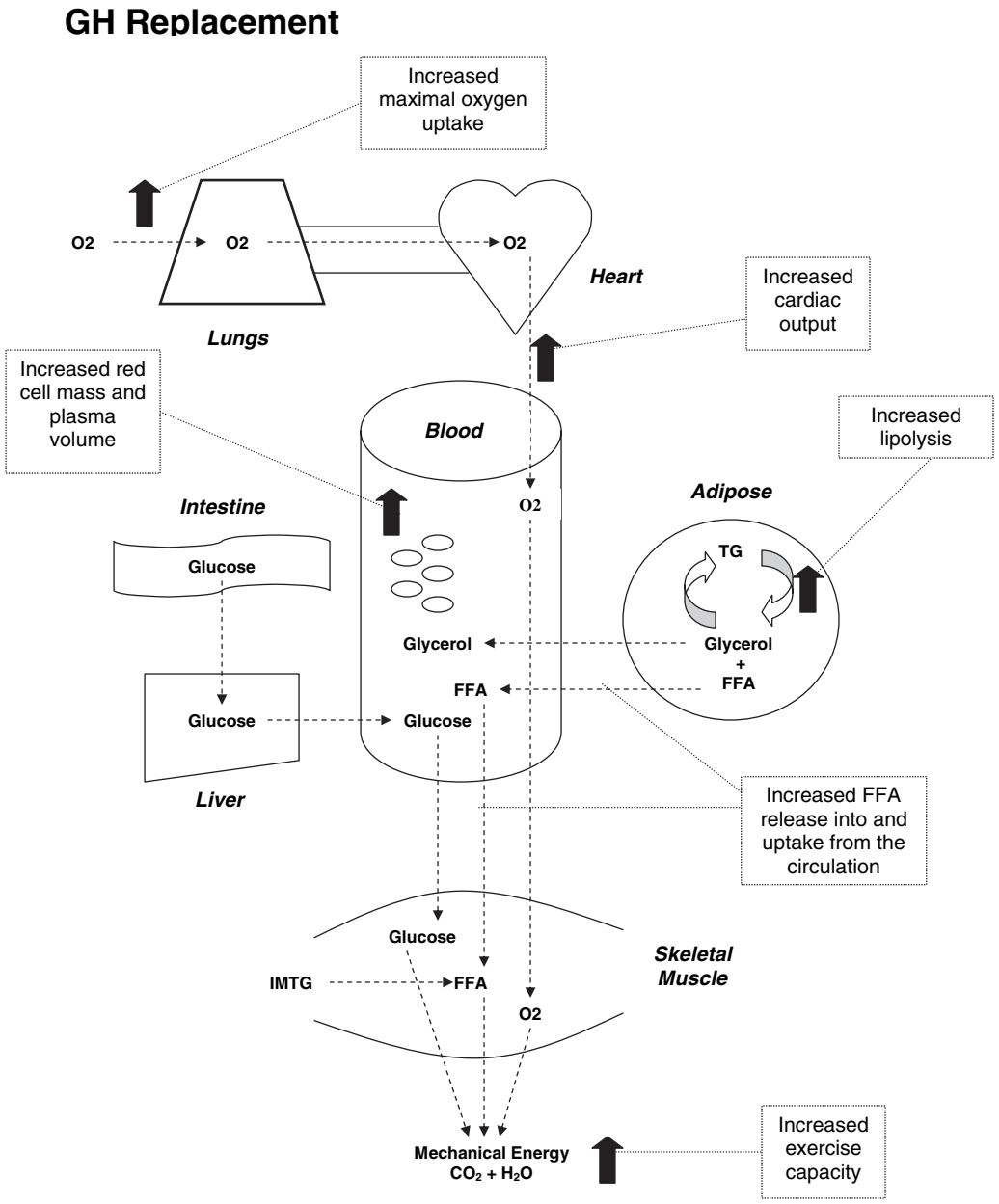

FIG. 1. *Continued*

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 radionucleide 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 radionucleide 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 radionucleide 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 adenylyl 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	Acromegaly	
	Comparison with normal subjects	Effect of treatment	Effect of GH administration	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 β-oxidation (66). These findings suggest that under resting conditions (when the biopsies were taken), increased fat ox-

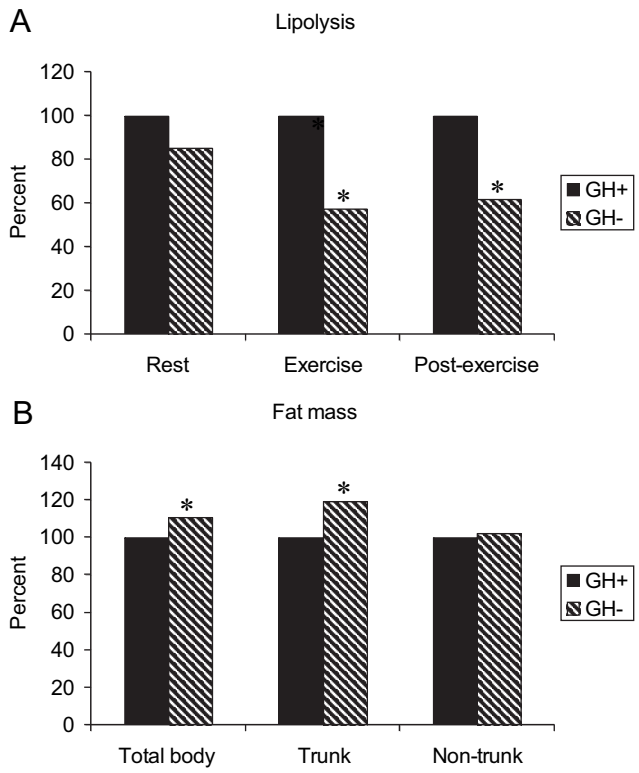

FIG. 2. A, Lipolysis estimated from the rate of appearance of glycerol at rest, during exercise, and 30 min after exercise in GHD adults (n = 8) while receiving GH (GH+) and 3 months after discontinuation of GH replacement (GH−). B, Total body, trunk, and nontrunk fat estimated using dual-energy x-ray 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 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.

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.

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 ± 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 11β-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_4 to metabolically active T_3 (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-

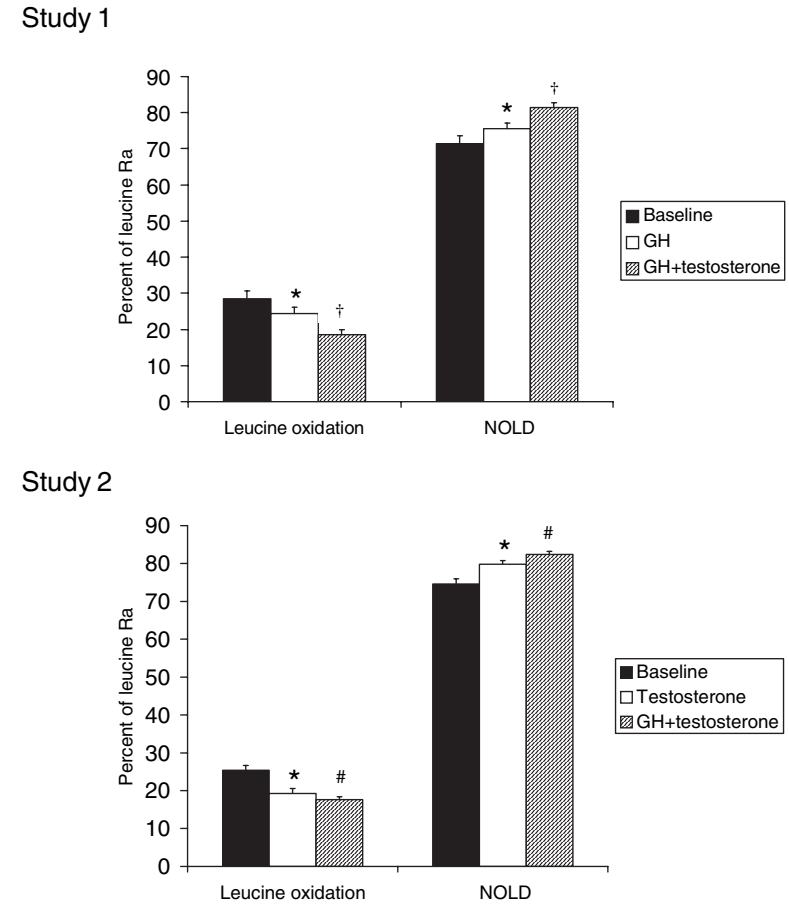

FIG. 3. Percentage leucine oxidation and percentage nonoxidative leucine disposal (NOLD) in hypogonadal GHD subjects at baseline, after treatment with GH alone and GH with testosterone (study 1), and at baseline, after treatment with testosterone alone and GH with testosterone (study 2). *, $P < 0.05$ *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.]

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.

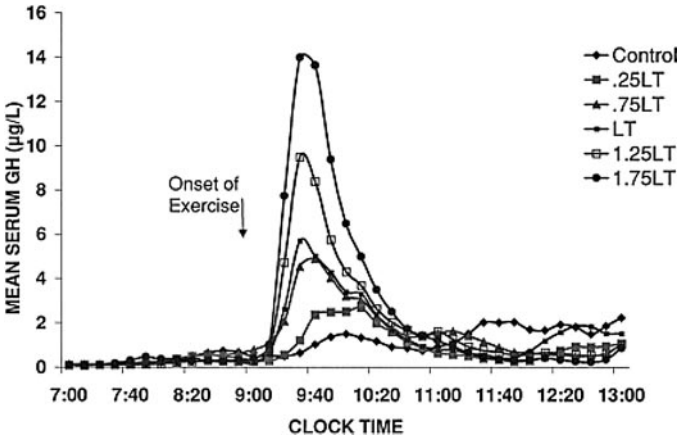

FIG. 4. The response of serum GH concentrations to exercise of different intensities. LT, Lactate threshold; Control, no exercise; 0.25LT, 25% of the difference between VO_2 achieved at lactate threshold and VO_2 at rest; 0.75LT, 75% of the difference between VO_2 achieved at lactate threshold and VO_2 at rest; 1.25LT, 25% of the difference between VO_2 achieved at lactate threshold and peak VO_2; 1.75LT, 75% of the difference between VO_2 achieved at lactate threshold and peak VO_2. Values are means ± 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 (VO_{2max}) 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 VO_{2max}. 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

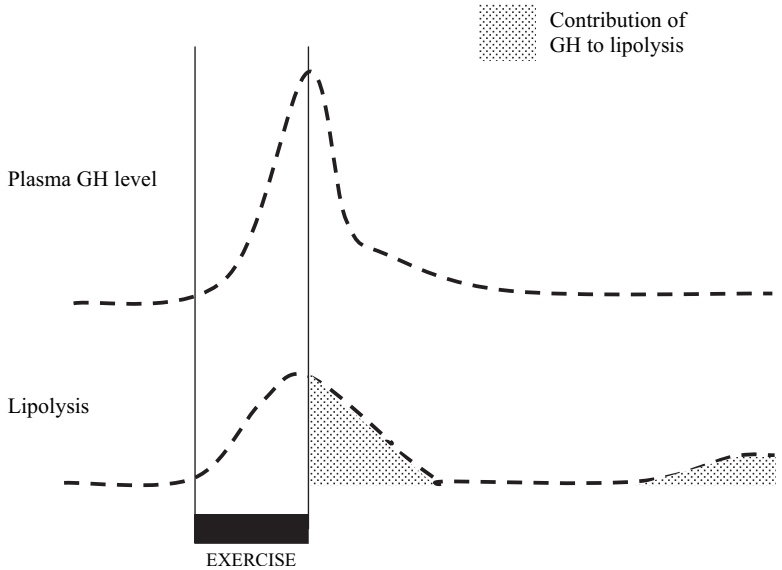

FIG. 5. Schematic representation of the possible association between the GH response to exercise and lipolysis. The *shaded area* represents the components of the lipolytic response to exercise that are probably augmented by the GH response to exercise. Because increased lipolysis during exercise precedes 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 *et al.* 1992 (186)	7/0	RCT 12 wk (with resistance training)	0.04 mg/kg	Strength	No additional effect of GH on muscle strength
Deyssig *et al.* 1993 (195)	8/0	DBPCT 6 wk	0.03 mg/kg	Strength	No effect of GH on muscle strength
Lange *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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 *et al.* 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.

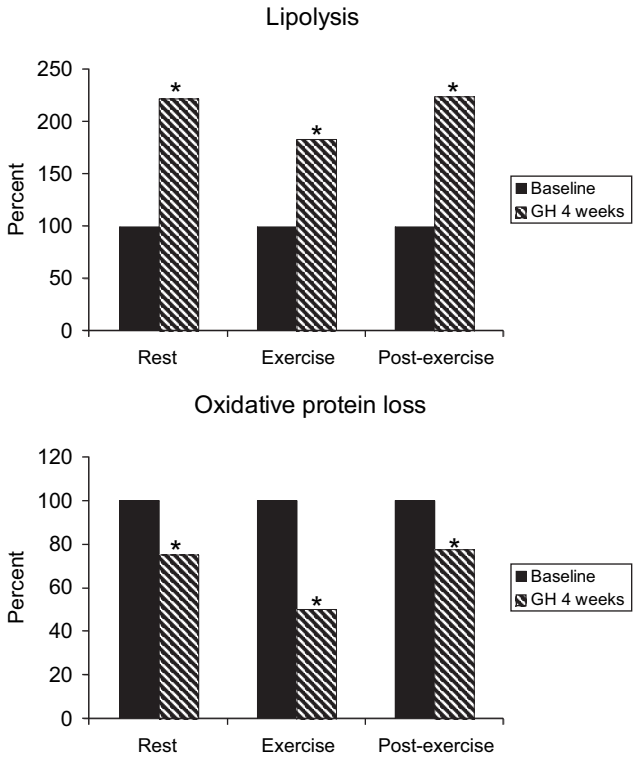

FIG. 6. Lipolysis, estimated from the rate of appearance of glycerol (*top panel*), and oxidative protein loss, estimated from leucine oxidation (*bottom panel*) at rest and during and after exercise in endurance-trained athletes (n = 6), before and after 4 wk of treatment with GH, 0.066 mg/kg·d. *,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

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).

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 nonathletic 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 radionucleide 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 exiting 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

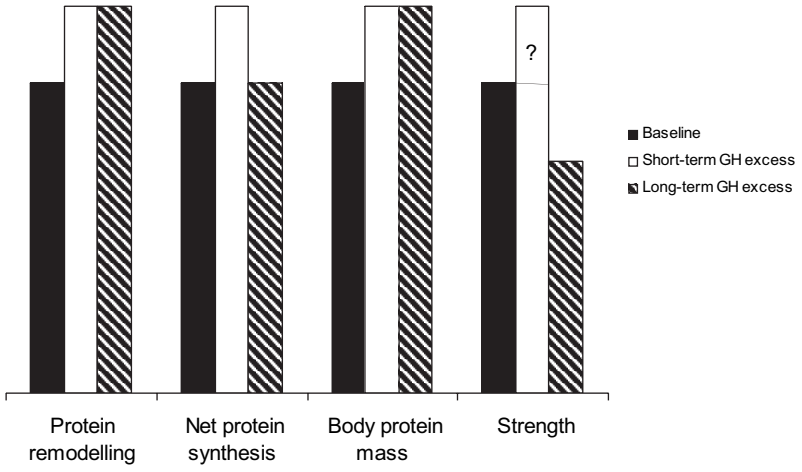

FIG. 7. Schematic representation of the effects of short-term and long-term GH excess. *Question mark* indicates a possible, but unproven, short-term effect of supraphysiological GH to increase strength.

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

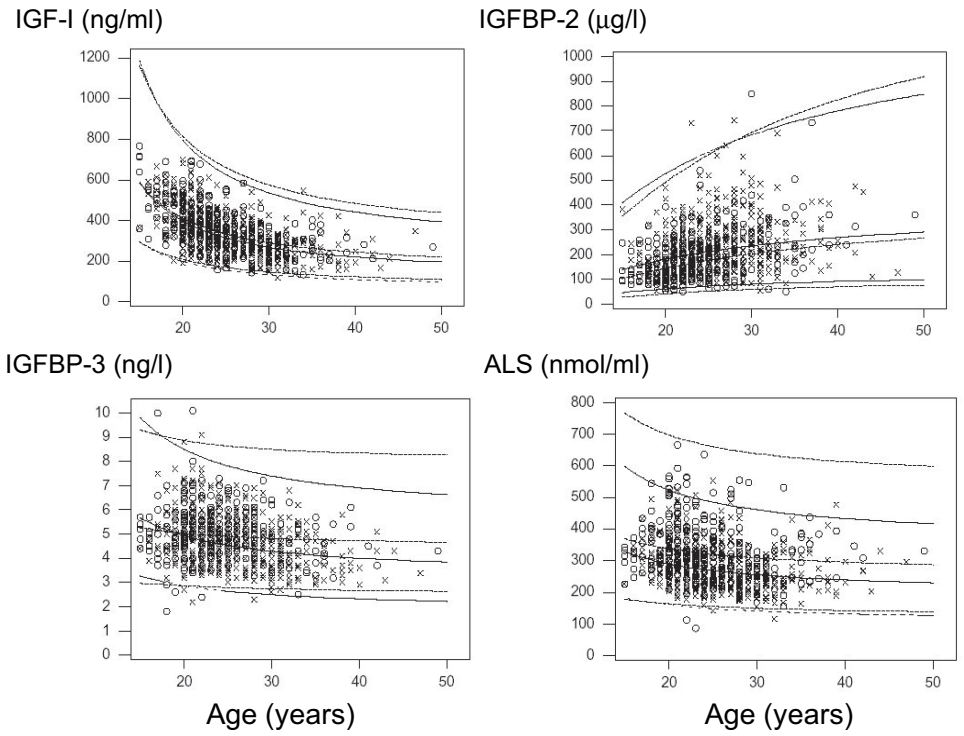

FIG. 8. Age-dependent change in components of the IGF/IGFBP system in 537 elite male (×) and 276 elite female (○) athletes. Reference ranges for male (*solid lines*) and female (*dashed lines*) athletes are shown. [Reproduced from Ref. 223 with permission. Copyright 2006, The Endocrine Society].

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 DBPCT, 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_{2max} 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.

Acknowledgments

Address all correspondence and requests for reprints to: Peter Sönksen, East Wing Preshaw House, Preshaw, Upham, Hants SO32 1HP, United Kingdom. E-mail: PHSonksen@aol.com

Disclosure Statement: The authors have nothing to declare.

References

1. **Glick SM, Roth J, Yalow RS, Berson SA** 1963 Immunoassay of human growth hormone in plasma. Nature 199:784–787
2. **Hunter WM, Greenwood FC** 1962 A radio-immunoelectrophoretic assay for human growth hormone. Biochem J 85:39
3. **Roth J, Glick SM, Yalow RS, Berson SA** 1963 Secretion of human growth hormone: physiologic and experimental modification. Metabolism 12:577–579
4. **Hunter WM, Fonseka CC, Passmore R** 1965 The role of growth hormone in the mobilization of fuel for muscular exercise. Q J Exp Physiol Cogn Med Sci 50:406–416
5. **Hunter WM, Fonseka CC, Passmore R** 1965 Growth hormone: important role in muscular exercise in adults. Science 150:1051–1053
6. **Cuneo RC, Salomon F, Wiles CM, Hesp R, Sonksen PH** 1991 Growth hormone treatment in growth hormone-deficient adults. II. Effects on exercise performance. J Appl Physiol 70:695–700
7. **Jorgensen JO, Pedersen SA, Laurberg P, Weeke J, Skakkebaek NE, Christiansen JS** 1989 Effects of growth hormone therapy on thyroid function of growth hormone-deficient adults with and without concomitant thyroxine-substituted central hypothyroidism. J Clin Endocrinol Metab 69:1127–1132
8. **Nass R, Huber RM, Klauss V, Muller OA, Schopohl J, Strasburger CJ** 1995 Effect of growth hormone (hGH) replacement therapy on physical work capacity and cardiac and pulmonary function in patients with hGH deficiency acquired in adulthood. J Clin Endocrinol Metab 80:552–557
9. **Woodhouse LJ, Asa SL, Thomas SG, Ezzat S** 1999 Measures of submaximal aerobic performance evaluate and predict functional response to growth hormone (GH) treatment in GH-deficient adults. J Clin Endocrinol Metab 84:4570–4577
10. **Duchaine D** 1983 Underground steroid handbook. 1 ed. Venice, CA: HLR Technical Books
11. **Todd T** October 15, 1984 The use of human growth hormone poses a grave dilemma for sport. Sports Illustrated; 8–12
12. **Jenkins PJ** 1999 Growth hormone and exercise. Clin Endocrinol (Oxf) 50:683–689
13. **Healy ML, Russell-Jones D** 1997 Growth hormone and sport: abuse, potential benefits, and difficulties in detection. Br J Sports Med 31:267–268
14. **Noakes TD** 2004 Tainted glory: doping and athletic performance. N Engl J Med 351:847–849
15. **Nagulesparen M, Trickey R, Davies MJ, Jenkins JS** 1976 Muscle changes in acromegaly. Br Med J 2:914–915
16. **Woodhouse LJ, Mukherjee A, Shalet SM, Ezzat S** 2006 The influence of growth hormone status on physical impairments, functional limitations, and health-related quality of life in adults. Endocr Rev 27:287–317
17. **Whitehead HM, Boreman C, McIlrath EM, Sheridan B, Kennedy L, Atkinson AB, Hadden DR** 1992 Growth hormone treatment of adults with growth hormone deficiency: results of a 13-month placebo controlled cross-over study. Clin Endocrinol (Oxf) 36:45–52
18. **Beshyah SA, Freemantie C, Shahi M, Anyaoku V, Merson S, Lynch S, Skinner E, Sharp P, Foale R, Johnston DG** 1995 Replacement treatment with biosynthetic human growth hormone in growth hormone-deficient hypopituitary adults. Clin Endocrinol (Oxf) 42:73–84
19. **Degerblad M, Almkvist O, Grunditz R, Hall K, Kaijser L, Knutsson E, Ringertz H, Thorén M** 1990 Physical and psycholog-

ical capabilities during substitution therapy with recombinant growth hormone in adults with growth hormone deficiency. Acta Endocrinol (Copenh) 123:185–193
20. **Jørgensen JOL, Pedersen SA, Thuesen L, Jorgensen J, Ingemann-Hansen T, Skakkebaek NE, Christiansen JS** 1989 Beneficial effect of growth hormone treatment in GH-deficient adults. Lancet 1:1221–1225
21. **Jørgensen JOL, Pedersen SA, Thuesen L, Jorgensen J, Moller J, Muller J, Skakkebaek NE, Christiansen JS** 1991 Long-term growth hormone treatment in growth hormone deficient adults. Acta Endocrinol 125:449–453
22. **Jørgensen JOL, Vahl N, Hansen TB, Thuesen L, Hagen C, Christiansen JS** 1996 Growth hormone versus placebo treatment for one year in growth hormone-deficient adults: increase in exercise capacity and normalisation of body composition. Clin Endocrinol (Oxf) 45:681–688
23. **Vahl N, Jørgensen JO, Hansen TB, Klausen IB, Jurik AG, Hagen C, Christiansen JS** 1998 The favourable effects of growth hormone (GH) substitution on hypercholesterolaemia in GH-deficient adults are not associated with concomitant reductions in adiposity. A 12 month placebo-controlled study. Int J Obes Relat Metab Disord 22:529–536
24. **Rodriguez-Arnao J, Jabbar A, Fulcher K, Besser GM, Ross RJ** 1999 Effects of growth hormone replacement on physical performance and body composition in GH-deficient adults. Clin Endocrinol (Oxf) 51:53–60
25. **Thomas SG, Esposito JG, Ezzat S** 2003 Exercise training benefits growth hormone (GH)-deficient adults in the absence or presence of GH treatment. J Clin Endocrinol Metab 88:5734–5738
26. **Bollerslev J, Hallen J, Fougner KJ, Jørgensen AP, Kristo C, Fagertun H, Gudmundsen O, Burman P, Schreiner T** 2005 Low-dose GH improves exercise capacity in adults with GH deficiency: effects of a 22-month placebo-controlled, crossover trial. Eur J Endocrinol 153:379–387
27. **Jeukendrup AE** 2002 Regulation of fat metabolism in skeletal muscle. Ann NY Acad Sci 967:217–235
28. **Golde DW, Bersch N, Li CH** 1977 Growth hormone: species-specific stimulation of erythropoiesis in vitro. Science 196:1112–1113
29. **Claustres M, Chatelain P, Sultan C** 1987 Insulin-like growth factor I stimulates human erythroid colony formation *in vitro*. J Clin Endocrinol Metab 65:78–82
30. **Kurtz A, Zapf J, Eckardt KU, Clemons G, Froesch ER, Bauer C** 1988 Insulin-like growth factor I stimulates erythropoiesis in hypophysectomized rats. Proc Natl Acad Sci USA 85:7825–7829
31. **Vihervuori E, Virtanen M, Koistinen H, Koistinen R, Seppala M, Siimes MA** 1996 Hemoglobin level is linked to growth hormone-dependent proteins in short children. Blood 87:2075–2081
32. **Christ ER, Cummings MH, Westwood NB, Sawyer BM, Pearson TC, Sönksen PH, Russell-Jones DL** 1997 The importance of growth hormone in the regulation of erythropoiesis, red cell mass, and plasma volume in adults with growth hormone deficiency. J Clin Endocrinol Metab 82:2985–2990
33. **Saccà L, Cittadini A, Fazio S** 1994 Growth hormone and the heart. Endocr Rev 15:555–573
34. **Amato G, Carella C, Fazio S, La Montagna G, Cittadini A, Sabatini D, Marciano-Mone C, Sacca L, Bellastella A** 1993 Body composition, bone metabolism, and heart structure and function in growth hormone(GH)-deficient adults before and after GH replacement therapy at low doses. J Clin Endocrinol Metab 77:1671–1676
35. **Merola B, Cittadini A, Colao A, Longobardi S, Fazio S, Sabatini D, Sacca L, Lombardi G** 1993 Cardiac structural and functional abnormalities in adult patients with growth hormone deficiency. J Clin Endocrinol Metab 77:1658–1661
36. **Sartorio A, Ferrero S, Conti A, Bragato R, Malfatto G, Leonetti G, Faglia G** 1997 Adults with childhood-onset growth hormone deficiency: effects of growth hormone treatment on cardiac structure. J Intern Med 241:515–520
37. **Shahi M, Beshyah SA, Hacket D, Sharp PS, Johnston DG, Foale RA** 1992 Myocardial dysfunction in treated adult hypopituitarism: a possible explanation for increased cardiovascular mortality. Br Heart J 67:92–96
38. **Thuesen L, Jørgensen JOL, Müller JR, Kristensen BO, Skakkebaek NE, Vahl N, Christiansen JS** 1994 Short and long-term cardiovascular effects of growth hormone therapy in growth hormone deficient adults. Clin Endocrinol (Oxf) 41:615–620
39. **Maison P, Chanson P** 2003 Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. Circulation 108:2648–2652
40. **Colao A, di Somma C, Cuocolo A, Spinelli L, Tedesco N, Pivonello R, Bonaduce D, Salvatore M, Lombardi G** 2001 Improved cardiovascular risk factors and cardiac performance after 12 months of growth hormone (GH) replacement in young adult patients with GH deficiency. J Clin Endocrinol Metab 86:1874–1881
41. **Colao A, Di Somma C, Cuocolo A, Filippella M, Rota F, Acampa W, Savastano S, Salvatore M, Lombardi G** 2004 The severity of growth hormone deficiency correlates with the severity of cardiac impairment in 100 adult patients with hypopituitarism: an observational, case-control study. J Clin Endocrinol Metab 89:5998–6004
42. **Johannsson G, Sverrisdottir YB, Ellegard L, Lundberg PA, Herlitz H** 2002 GH increases extracellular volume by stimulating sodium reabsorption in the distal nephron and preventing pressure natriuresis. J Clin Endocrinol Metab 87:1743–1749
43. **Boger RH, Skamira C, Bode-Boger SM, Brabant G, von zur Muhlen A, Frolich JC** 1996 Nitric oxide may mediate the hemodynamic effects of recombinant growth hormone in patients with acquired growth hormone deficiency. A double-blind, placebo-controlled study. J Clin Invest 98:2706–2713
44. **Sartorio A, Maffiuletti NA, Agosti F, Marinone PG, Ottolini S, Lafortuna CL** 2004 Body mass reduction markedly improves muscle performance and body composition in obese females aged 61–75 years: comparison between the effects exerted by energy-restricted diet plus moderate aerobic-strength training alone or associated with rGH or nandrolone undecanoate. Eur J Endocrinol 150:511–515
45. **Wolfe RR, Klein S, Carraro F, Weber JM** 1990 Role of triglyceride-fatty acid cycle in controlling fat metabolism in humans during and after exercise. Am J Physiol 258:E382–E389
46. **Costill DL, Coyle E, Dalsky G, Evans W, Fink W, Hoopes D** 1977 Effects of elevated plasma FFA and insulin on muscle glycogen usage during exercise. J Appl Physiol 43:695–699
47. **Dyck DJ, Putman CT, Heigenhauser GJ, Hultman E, Spriet LL** 1993 Regulation of fat-carbohydrate interaction in skeletal muscle during intense aerobic cycling. Am J Physiol 265:E852–E859
48. **Matzinger O, Schneiter P, Tappy L** 2002 Effects of fatty acids on exercise plus insulin-induced glucose utilization in trained and sedentary subjects. Am J Physiol Endocrinol Metab 282:E125–E131
49. **Vukovich MD, Costill DL, Hickey MS, Trappe SW, Cole KJ, Fink WJ** 1993 Effect of fat emulsion infusion and fat feeding on muscle glycogen utilization during cycle exercise. J Appl Physiol 75:1513–1518
50. **Hargreaves M, Kiens B, Richter EA** 1991 Effect of increased plasma free fatty acid concentrations on muscle metabolism in exercising men. J Appl Physiol 70:194–201
51. **Kanaley JA, Cryer PE, Jensen MD** 1993 Fatty acid kinetic responses to exercise. Effects of obesity, body fat distribution, and energy-restricted diet. J Clin Invest 92:255–261
52. **Yip RG, Goodman HM** 1999 Growth hormone and dexamethasone stimulate lipolysis and activate adenylyl cyclase in rat adipocytes by selectively shifting Gi α2 to lower density membrane fractions. Endocrinology 140:1219–1227
53. **Marcus C, Bolme P, Micha-Johansson G, Margery V, Bronnegard M** 1994 Growth hormone increases the lipolytic sensitivity for catecholamines in adipocytes from healthy adults. Life Sci 54:1335–1341
54. **Beauville M, Harant I, Crampes F, Riviere D, Tauber MT, Tauber JP, Garrigues M** 1992 Effect of long-term rhGH administration in GH-deficient adults on fat cell epinephrine response. Am J Physiol 263:E467–E472
55. **Harant I, Beauville M, Crampes F, Riviere D, Tauber MT, Tauber JP, Garrigues M** 1994 Response of fat cells to growth hormone (GH): effect of long term treatment with recombinant human GH in GH-deficient adults. J Clin Endocrinol Metab 78:1392–1395
56. **Raben MS, Hollenberg CH** 1959 Effect of growth hormone on plasma fatty acids. J Clin Invest 38:484–488
57. **Rabinowitz D, Klassen GA, Zierler KL** 1965 Effects of human

growth hormone on muscle and adipose tissue metabolism in the forearm of man. J Clin Invest 44:51–61
58. **Fineberg SE, Merimee TJ** 1974 Acute metabolic effects of human growth hormone. Diabetes 23:499–504
59. **Moller N, Jorgensen JOL, Alberti KGMM, Flyvbjerg A, Schmitz O** 1990 Short-term effects of growth hormone on fuel oxidation and regional substrate metabolism in normal man. J Clin Endocrinol Metab 70:1179–1186
60. **Møller N, Jørgensen JOL, Schmitz O, Møller J, Christiansen J, Alberti KG, Orskov H** 1990 Effects of a growth hormone pulse on total and forearm substrate fluxes in humans. Am J Physiol 258: E86–E91
61. **Laursen T, Jørgensen JOL, Christiansen JS** 1994 Metabolic effects of growth hormone administered subcutaneously once or twice daily to growth hormone deficient adults. Clin Endocrinol (Oxf) 41:337–343
62. **Gravholt CH, Schmitz O, Simonsen L, Bulow J, Christiansen JS, Moller N** 1999 Effects of a physiological GH pulse on interstitial glycerol in abdominal and femoral adipose tissue. Am J Physiol 277:E848–854
63. **Gibney J, Healy ML, Stolinski M, Bowes SB, Pentecost C, Breen L, McMillan C, Russell-Jones DL, Sonksen PH, Umpleby AM** 2003 Effect of growth hormone (GH) on glycerol and free fatty acid metabolism during exhaustive exercise in GH-deficient adults. J Clin Endocrinol Metab 88:1792–1797
64. **Kanaley JA, Dall R, Moller N, Nielsen SC, Christiansen JS, Jensen MD, Jorgensen JO** 2004 Acute exposure to GH during exercise stimulates the turnover of free fatty acids in GH-deficient men. J Appl Physiol 96:747–753
65. **Brandou F, Aloulou I, Razimbaud A, Facdou C, Mercier J, Brun JF** 2006 Lower ability to oxidize lipids in adult patients with growth hormone (GH) deficiency: reversal under GH treatment. Clin Endocrinol (Oxf) 65:423–428
66. **Sjögren K, Leung KC, Kaplan W, Gardiner-Garden M, Gibney J, Ho KK** 2007 Growth hormone regulation of metabolic gene expression in muscle: a microarray study in hypopituitary men. Am J Physiol Endocrinol Metab 293:E364–E371
67. **Cheng JS, Kalant N** 1970 Effects of insulin and growth hormone on the flux rates of plasma glucose and plasma free fatty acids in man. J Clin Endocrinol Metab 31:647–653
68. **Metcalfe P, Johnston DG, Nosadini R, Orksov H, Alberti KG** 1981 Metabolic effects of acute and prolonged growth hormone excess in normal and insulin-deficient man. Diabetologia 20:123–128
69. **Rizza RA, Mandarino LJ, Gerich JE** 1982 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 31:663–669
70. **Sherwin RS, Schulman GA, Hendler R, Walesky M, Belous A, Tamborlane W** 1983 Effect of growth hormone on oral glucose tolerance and circulating metabolic fuels in man. Diabetologia 24: 155–161
71. **Davidson MB** 1987 Effect of growth hormone on carbohydrate and lipid metabolism. Endocr Rev 8:115–131
72. **Jorgensen JO, Moller N, Lauritzen T, Alberti KG, Orskov H, Christiansen JS** 1990 Evening versus morning injections of growth hormone (GH) in GH- deficient patients: effects on 24-hour patterns of circulating hormones and metabolites. J Clin Endocrinol Metab 70:207–214
73. **Hussain MA, Schmitz O, Mengel A, Glatz Y, Christiansen JS, Zapf J, Froesch ER** 1994 Comparison of the effects of growth hormone and insulin-like growth factor I on substrate oxidation and on insulin sensitivity in growth hormone-deficient humans. J Clin Invest 94:1126–1133
74. **Bramnert M, Segerlantz M, Laurila E, Daugaard JR, Manhem P, Groop L** 2003 Growth hormone replacement therapy induces insulin resistance by activating the glucose-fatty acid cycle. J Clin Endocrinol Metab 88:1455–1463
75. **Jorgensen JO, Jessen N, Pedersen SB, Vestergaard E, Gormsen L, Lund SA, Billestrup N** 2006 GH receptor signaling in skeletal muscle and adipose tissue in human subjects following exposure to an intravenous GH bolus. Am J Physiol Endocrinol Metab 291: E899–E905
76. **Fryburg DA, Gelfand RA, Barrett EJ** 1991 Growth hormone acutely stimulates forearm muscle protein synthesis in normal humans. Am J Physiol 260:E499–E504
77. **Carroll PV, Christ ER, Bengtsson BA, Carlsson L, Christiansen JS, Clemmons D, Hintz R, Ho K, Laron Z, Sizonenko P, Sönksen PH, Tanaka T, Thorne M** 1998 Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. J Clin Endocrinol Metab 83:382–395
78. **de Boer H, Blok G-J, van der Veen EA** 1995 Clinical aspects of growth hormone deficiency in adults. Endocr Rev 16:63–86
79. **Salomon F, Cuneo RC, Hesp R, Sonksen PH** 1989 The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. N Engl J Med 321:1797–1803
80. **Hoffman DM, O'Sullivan AJ, Freund J, Ho KK** 1995 Adults with growth hormone deficiency have abnormal body composition but normal energy metabolism. J Clin Endocrinol Metab 80:72–77
81. **Janssen YJ, Doornbos J, Roelfsema F** 1999 Changes in muscle volume, strength, and bioenergetics during recombinant human growth hormone (GH) therapy in adults with GH deficiency. J Clin Endocrinol Metab 84:279–284
82. **Cuneo RC, Salomon F, Wiles CM, Hesp R, Sonksen PH** 1991 Growth hormone treatment in growth hormone-deficient adults. I. Effects on muscle mass and strength. J Appl Physiol 70:688–694
83. **Johannsson G, Grimby G, Sunnerhagen KS, Bengtsson BA** 1997 Two years of growth hormone (GH) treatment increase isometric and isokinetic muscle strength in GH-deficient adults. J Clin Endocrinol Metab 82:2877–2884
84. **Rutherford OM, Beshyah SA, Schott J, Watkins Y, Johnston DG** 1995 Contractile properties of the quadriceps muscle in growth hormone-deficient hypopituitary adults. Clin Sci (Lond) 88:67–71
85. **Brill KT, Weltman AL, Gentili A, Patrie JT, Fryburg DA, Hanks JB, Urban RJ, Veldhuis JD** 2002 Single and combined effects of growth hormone and testosterone administration on measures of body composition, physical performance, mood, sexual function, bone turnover, and muscle gene expression in healthy older men. J Clin Endocrinol Metab 87:5649–5657
86. **Svensson J, Sunnerhagen KS, Johannsson G** 2003 Five years of growth hormone replacement therapy in adults: age- and gender-related changes in isometric and isokinetic muscle strength. J Clin Endocrinol Metab 88:2061–2069
87. **Juul A, Behrenscheer A, Tims T, Nielsen B, Halkjær-Kristensen J, Skakkebæk NE** 1993 Impaired thermoregulation in adults with growth hormone deficiency during heat exposure and exercise. Clin Endocrinol (Oxf) 38:237–244
88. **Juul A, Hjortskov N, Jepsen LT, Nielsen B, Halkjaer-Kristensen J, Vahl N, Jorgensen JO, Christiansen JS, Skakkebaek NE** 1995 Growth hormone deficiency and hyperthermia during exercise: a controlled study of sixteen GH-deficient patients. J Clin Endocrinol Metab 80:3335–3340
89. **Giustina A, Veldhuis JD** 1998 Pathophysiology of the neororegulation of growth hormone secretion in experimental animals and the human. Endocr Rev 19:717–797
90. **Bengtsson B-Å, Abs R, Bennmarker H, Monson JP, Feldt-Rasmussen U, Hernberg-Stahl E, Westberg B, Wilton P, Wuster C** 1999 The effects of treatment and the individual responsiveness to growth hormone (GH) replacement therapy in 665 GH-deficient adults. KIMS Study Group and the KIMS International Board. J Clin Endocrinol Metab 84:3929–3935
91. **De Caro E, Fioredda F, Calevo MG, Smeraldi A, Saitta M, Hanau G, Faraci M, Grisolia F, Dini G, Pongiglione G, Haupt R** 2006 Exercise capacity in apparently healthy survivors of cancer. Arch Dis Child 91:47–51
92. **McTiernan A** 2004 Physical activity after cancer: physiologic outcomes. Cancer Invest 22:68–81
93. **Ness KK, Baker KS, Dengel DR, Youngren N, Sibley S, Mertens AC, Gurney JG**, Body composition, muscle strength deficits and mobility limitations in adult survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2006 Nov 7 [Epub ahead of print]
94. **Schmitz KH, Holtzman J, Courneya KS, Masse LC, Duval S, Kane R** 2005 Controlled physical activity trials in cancer survivors: a

systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 14:1588–1595
95. **Burt MG, Gibney J, Ho KK** 2006 Characterization of the metabolic phenotypes of Cushing's syndrome and growth hormone deficiency: a study of body composition and energy metabolism. Clin Endocrinol (Oxf) 64:436–443
96. **Rockall AG, Sohaib SA, Evans D, Kaltsas G, Isidori AM, Monson JP, Besser GM, Grossman AB, Reznek RH** 2003 Computed tomography assessment of fat distribution in male and female patients with Cushing's syndrome. Eur J Endocrinol 149:561–567
97. **Pirlich M, Biering H, Gerl H, Ventz M, Schmidt B, Ertl S, Lochs H** 2002 Loss of body cell mass in Cushing's syndrome: effect of treatment. J Clin Endocrinol Metab 87:1078–1084
98. **Garrapa GG, Pantanetti P, Arnaldi G, Mantero F, Faloia E** 2001 Body composition and metabolic features in women with adrenal incidentaloma or Cushing's syndrome. J Clin Endocrinol Metab 86:5301–5306
99. **Wajchenberg BL, Bosco A, Marone MM, Levin S, Rocha M, Lerário AC, Nery M, Goldman J, Liberman B** 1995 Estimation of body fat and lean tissue distribution by dual energy x-ray absorptiometry and abdominal body fat evaluation by computed tomography in Cushing's disease. J Clin Endocrinol Metab 80:2791–2794
100. **Lamberts SW, Birkenhager JC** 1976 Body composition in Cushing's disease. J Clin Endocrinol Metab 42:864–868
101. **Aloia JF, Roginsky M, Ellis K, Shukla K, Cohn S** 1974 Skeletal metabolism and body composition in Cushing's syndrome. J Clin Endocrinol Metab 39:981–985
102. **Burt MG, Gibney J, Ho KK** 2007 Protein metabolism in glucocorticoid excess: study in Cushing's syndrome and the effect of treatment. Am J Physiol Endocrinol Metab 292:E1426–E1432
103. **Agha A, Liew A, Finucane F, Baker L, O'Kelly P, Tormey W, Thompson CJ** 2004 Conventional glucocorticoid replacement overtreats adult hypopituitary patients with partial ACTH deficiency. Clin Endocrinol (Oxf) 60:688–693
104. **Toogood AA, Taylor NF, Shalet SM, Monson JP** 2000 Modulation of cortisol metabolism by low-dose growth hormone replacement in elderly hypopituitary patients. J Clin Endocrinol Metab 85:1727–1730
105. **Moore JS, Monson JP, Kaltsas G, Putignano P, Wood PJ, Sheppard MC, Besser GM, Taylor NF, Stewart PM** 1999 Modulation of 11β-hydroxysteroid dehydrogenase isozymes by growth hormone and insulin-like growth factor: *in vivo* and *in vitro* studies. J Clin Endocrinol Metab 84:4172–4177
106. **Swords FM, Carroll PV, Kisalu J, Wood PJ, Taylor NF, Monson JP** 2003 The effects of growth hormone deficiency and replacement on glucocorticoid exposure in hypopituitary patients on cortisone acetate and hydrocortisone replacement. Clin Endocrinol (Oxf) 59:613–620
107. **Jorgensen JO, Moller J, Skakkebaek NE, Weeke J, Christiansen JS** 1992 Thyroid function during growth hormone therapy. Horm Res 38:63–67
108. **Moller J, Jorgensen JO, Moller N, Christiansen JS, Weeke J** 1992 Effects of growth hormone administration on fuel oxidation and thyroid function in normal man. Metabolism 41:728–731
109. **Gibney J, Johannsson G, Leung KC, Ho KK** 2005 Comparison of the metabolic effects of raloxifene and oral estrogen in postmenopausal and growth hormone-deficient women. J Clin Endocrinol Metab 90:3897–3903
110. **O'Sullivan AJ, Crampton L, Freund J, Ho KKY** 1998 Route of estrogen replacement confers divergent effects of energy metabolism and body composition in postmenopausal women. J Clin Invest 102:1035–1040
111. **Johannsson G, Gibney J, Wolthers T, Leung KC, Ho KK** 2005 Independent and combined effects of testosterone and growth hormone on extracellular water in hypopituitary men. J Clin Endocrinol Metab 90:3989–3994
112. **Gibney J, Wolthers T, Johannsson G, Umpleby AM, Ho KK** 2005 Growth hormone and testosterone interact positively to enhance protein and energy metabolism in hypopituitary men. Am J Physiol Endocrinol Metab 289:E266–E271
113. **Johannsson G, Burman P, Wiren L, Engström BE, Nilsson AG, Ottosson M, Jonsson B, Bengtsson BA, Karlsson FA** 2002 Low dose dehydroepiandrosterone affects behavior in hypopituitary androgen-deficient women: a placebo-controlled trial. J Clin Endocrinol Metab 87:2046–2052
114. **Sutton J, Lazarus L** 1976 Growth hormone in exercise: comparison of physiological and pharmacological stimuli. J Appl Physiol 41:523–527
115. **Lassarre C, Girard F, Durand J, Raynaud J** 1974 Kinetics of human growth hormone during submaximal exercise. J Appl Physiol 37:826–830
116. **Raynaud J, Drouet L, Martineaud JP, Bordachar J, Coudert J, Durand J** 1981 Time course of plasma growth hormone during exercise in humans at altitude. J Appl Physiol 50:229–233
117. **Viru A, Karelson K, Smirnova T** 1992 Stability and variability in hormonal responses to prolonged exercise. Int J Sports Med 13:230–235
118. **Hagberg JM, Seals DR, Yerg JE, Gavin J, Gingerich R, Premachandra B, Holloszy JO** 1988 Metabolic responses to exercise in young and older athletes and sedentary men. J Appl Physiol 65:900–908
119. **Zaccaria M, Varnier M, Piazza P, Noventa D, Ermolao A** 1999 Blunted growth hormone response to maximal exercise in middle-aged versus young subjects and no effect of endurance training. J Clin Endocrinol Metab 84:2303–2307
120. **Holt RI, Webb E, Pentecost C, Sonksen PH** 2001 Aging and physical fitness are more important than obesity in determining exercise-induced generation of GH. J Clin Endocrinol Metab 86:5715–5720
121. **Bunt JC, Boileau RA, Bahr JM, Nelson RA** 1986 Sex and training differences in human growth hormone levels during prolonged exercise. J Appl Physiol 61:1796–1801
122. **Wideman L, Weltman JY, Shah N, Story S, Veldhuis JD, Weltman A** 1999 Effects of gender on exercise-induced growth hormone release. J Appl Physiol 87:1154–1162
123. **Giannoulis MG, Boroujerdi MA, Powrie J, Giannoulis MG, Boroujerdi MA, Powrie J, Dall R, Napoli R, Ehrnborg C, Pentecost C, Cittadini A, Jørgensen JO, Sonksen PH; GH-2000 Study Group** 2005 Gender differences in growth hormone response to exercise before and after rhGH administration and the effect of rhGH on the hormone profile of fit normal adults. Clin Endocrinol (Oxf) 62:315–322
124. **Kanaley JA, Weatherup-Dentes MM, Jaynes EB, Hartman ML** 1999 Obesity attenuates the growth hormone response to exercise. J Clin Endocrinol Metab 84:3156–3161
125. **Veldhuis JD, Liem AY, South S, Weltman A, Weltman J, Clemmons DA, Abbott R, Mulligan T, Johnson ML, Pincus S** 1995 Differential impact of age, sex steroid hormones, and obesity on basal versus pulsatile growth hormone secretion in men as assessed in an ultrasensitive chemiluminescence assay. J Clin Endocrinol Metab 80:3209–3222
126. **Veldhuis JD, Iranmanesh A, Ho KK, Waters MJ, Johnson ML, Lizarralde G** 1991 Dual defects in pulsatile growth hormone secretion and clearance subserve the hyposomatotropism of obesity in man. J Clin Endocrinol Metab 72:51–59
127. **Luger A, Watschinger B, Deuster P, Svoboda T, Clodi M, Chrousos GP** 1992 Plasma growth hormone and prolactin responses to graded levels of acute exercise and to a lactate infusion. Neuroendocrinology 56:112–117
128. **Sutton JR** 1978 Hormonal and metabolic responses to exercise in subject of high and low work capacities. Med Sci Sports 10:1–6
129. **Farrell PA, Garthwaite TL, Gustafson AB** 1983 Plasma adrenocorticotropin and cortisol responses to submaximal and exhaustive exercise. J Appl Physiol 55:1441–1444
130. **Felsing NE, Brasel JA, Cooper DM** 1992 Effect of low and high intensity exercise on circulating growth hormone in men. J Clin Endocrinol Metab 75:157–162
131. **Naveri H** 1985 Blood hormone and metabolite levels during graded cycle ergometer exercise. Scand J Clin Lab Invest 45:599–603
132. **Naveri H, Kuoppasalmi K, Harkonen M** 1985 Metabolic and hormonal changes in moderate and intense long-term running exercises. Int J Sports Med 6:276–281
133. **Pritzlaff CJ, Wideman L, Weltman JY, Abbott RD, Gutgesell ME, Hartman ML, Veldhuis JD, Weltman A** 1999 Impact of acute exercise intensity on pulsatile growth hormone release in men. J Appl Physiol 87:498–504

134. **Gray AB, Telford RD, Weidemann MJ** 1993 Endocrine response to intense interval exercise. Eur J Appl Physiol Occup Physiol 66:366–371
135. **Hakkinen K, Pakarinen A** 1993 Acute hormonal responses to two different fatiguing heavy-resistance protocols in male athletes. J Appl Physiol 74:882–887
136. **Hakkinen K, Pakarinen A, Alen M, Kauhanen H, Komi PV** 1988 Neuromuscular and hormonal responses in elite athletes to two successive strength training sessions in one day. Eur J Appl Physiol Occup Physiol 57:133–139
137. **Karagiorgos A, Garcia JF, Brooks GA** 1979 Growth hormone response to continuous and intermittent exercise. Med Sci Sports 11:302–307
138. **Kraemer WJ, Fleck SJ, Dziados JE, Harman EA, Marchitelli LJ, Gordon SE, Mello R, Frykman PN, Koziris LP, Triplett NT** 1993 Changes in hormonal concentrations after different heavy-resistance exercise protocols in women. J Appl Physiol 75:594–604
139. **Kraemer WJ, Gordon SE, Fleck SJ, Marchitelli LJ, Mello R, Dziados JE, Friedl K, Harman E, Maresh C, Fry AC** 1991 Endogenous anabolic hormonal and growth factor responses to heavy resistance exercise in males and females. Int J Sports Med 12:228–235
140. **Kraemer WJ, Marchitelli L, Gordon SE, Harman E, Dziados JE, Mello R, Frykman P, McCurry D, Fleck SJ** 1990 Hormonal and growth factor responses to heavy resistance exercise protocols. J Appl Physiol 69:1442–1450
141. **Raynaud J, Capderou A, Martineaud JP, Bordachar J, Durand J** 1983 Intersubject viability in growth hormone time course during different types of work. J Appl Physiol 55:1682–1687
142. **VanHelder WP, Casey K, Goode RC, Radomski WM** 1986 Growth hormone regulation in two types of aerobic exercise of equal oxygen uptake. Eur J Appl Physiol Occup Physiol 55:236–239
143. **Snegovskaya V, Viru A** 1993 Elevation of cortisol and growth hormone levels in the course of further improvement of performance capacity in trained rowers. Int J Sports Med 14:202–206
144. **Hartley LH, Mason JW, Hogan RP, Jones LG, Kotchen TA, Mougey EH, Wherry FE, Pennington LL, Ricketts PT** 1972 Multiple hormonal responses to prolonged exercise in relation to physical training. J Appl Physiol 33:607–610
145. **Wideman L, Consitt L, Patrie J, Swearingin B, Bloomer R, Davis P, Weltman A** 2006 The impact of sex and exercise duration on growth hormone secretion. J Appl Physiol 101:1641–1647
146. **Kanaley JA, Weltman JY, Veldhuis JD, Rogol AD, Hartman ML, Weltman A** 1997 Human growth hormone response to repeated bouts of aerobic exercise. J Appl Physiol 83:1756–1761
147. **Kanaley JA, Weltman JY, Pieper KS, Weltman A, Hartman ML** 2001 Cortisol and growth hormone responses to exercise at different times of day. J Clin Endocrinol Metab 86:2881–2889
148. **Christensen SE, Jorgensen OL, Moller N, Orskov H** 1984 Characterization of growth hormone release in response to external heating. Comparison to exercise induced release. Acta Endocrinol (Copenh) 107:295–301
149. **Elias AN, Wilson AF, Naqvi S, Pandian MR** 1997 Effects of blood pH and blood lactate on growth hormone, prolactin, and gonadotropin release after acute exercise in male volunteers. Proc Soc Exp Biol Med 214:156–160
150. **Wheldon A, Savine RL, Sonksen PH, Holt RI** 2006 Exercising in the cold inhibits growth hormone secretion by reducing the rise in core body temperature. Growth Horm IGF Res 16:125–131
151. **Bang P, Brandt J, Degerblad M, Enberg G, Kaijser L, Thorén M, Hall K** 1990 Exercise-induced changes in insulin-like growth factors and their low molecular weight binding protein in healthy subjects and patients with growth hormone deficiency. Eur J Clin Invest 20:285–292
152. **Cappon J, Brasel JA, Mohan S, Cooper DM** 1994 Effect of brief exercise on circulating insulin-like growth factor I. J Appl Physiol 76:2490–2496
153. **Koistinen H, Koistinen R, Selenius L, Ylikorkala Q, Seppala M** 1996 Effect of marathon run on serum IGF-I and IGF-binding protein 1 and 3 levels. J Appl Physiol 80:760–764
154. **Schwarz AJ, Brasel JA, Hintz RL, Mohan S, Cooper DM** 1996 Acute effect of brief low- and high-intensity exercise on circulating insulin-like growth factor (IGF) I, II, and IGF-binding protein-3 and its proteolysis in young healthy men. J Clin Endocrinol Metab 81:3492–3497
155. **Suikkari AM, Sane T, Seppala M, Yki-Jarvinen H, Karonen SL, Koivisto VA** 1989 Prolonged exercise increases serum insulin-like growth factor-binding protein concentrations. J Clin Endocrinol Metab 68:141–144
156. **Wallace JD, Cuneo RC, Baxter R, Orskov H, Keay N, Pentecost C, Dall R, Rosén T, Jørgensen JO, Cittadini A, Longobardi S, Sacca L, Christiansen JS, Bengtsson BA, Sönksen PH** 1999 Responses of the growth hormone (GH) and insulin-like growth factor axis to exercise, GH administration, and GH withdrawal in trained adult males: a potential test for GH abuse in sport. J Clin Endocrinol Metab 84:3591–3601
157. **Dall R, Lange KH, Kjaer M, Jorgensen JO, Christiansen JS, Orskov H, Flyvbjerg A** 2001 No evidence of insulin-like growth factor-binding protein 3 proteolysis during a maximal exercise test in elite athletes. J Clin Endocrinol Metab 86:669–674
158. **Wee J, Charlton C, Simpson H, Jackson NC, Shojaee-Moradie F, Stolinski M, Pentecost C, Umpleby AM** 2005 GH secretion in acute exercise may result in post-exercise lipolysis. Growth Horm IGF Res 15:397–404
159. **Chalmers RJ, Bloom SR, Duncan G, Johnson RH, Sulaiman WR** 1979 The effect of somatostatin on metabolic and hormonal changes during and after exercise. Clin Endocrinol (Oxf) 10:451–458
160. **Lamberts SW, van der Lely AJ, de Herder WW, Hofland LJ** 1996 Octreotide. N Engl J Med 334:246–254
161. **Veldhuis JD, Bidlingmaier M, Anderson SM, Wu Z, Strasburger CJ** 2001 Lowering total plasma insulin-like growth factor I concentrations by way of a novel, potent, and selective growth hormone (GH) receptor antagonist, pegvisomant (B2036-peg), augments the amplitude of GH secretory bursts and elevates basal/nonpulsatile GH release in healthy women and men. J Clin Endocrinol Metab 86:3304–3310
162. **Pritzlaff CJ, Wideman L, Blumer J, Jensen M, Abbott RD, Gaesser GA, Veldhuis JD, Weltman A** 2000 Catecholamine release, growth hormone secretion, and energy expenditure during exercise vs. recovery in men. J Appl Physiol 89:937–946
163. **Short KR, Vittone JL, Bigelow ML, Proctor DN, Nair KS** 2004 Age and aerobic exercise training effects on whole body and muscle protein metabolism. Am J Physiol Endocrinol Metab 286:E92–E101
164. **Sheffield-Moore M, Yeckel CW, Volpi E, Wolf SE, Morio B, Chinkes DL, Paddon-Jones D, Wolfe RR** 2004 Postexercise protein metabolism in older and younger men following moderate-intensity aerobic exercise. Am J Physiol Endocrinol Metab 287:E513—E522
165. **Tessari P, Nissen SL, Miles JM, Haymond MW** 1986 Inverse relationship of leucine flux and oxidation to free fatty acid availability in vivo. J Clin Invest 77:575–581
166. **Solini A, Bonora E, Bonadonna R, Castellino P, DeFronzo RA** 1997 Protein metabolism in human obesity: relationship with glucose and lipid metabolism and with visceral adipose tissue. J Clin Endocrinol Metab 82:2552–2558
167. **Norrelund H, Nair KS, Nielsen S, Frystyk J, Ivarsen P, Jorgensen JO, Christiansen JS, Moller N** 2003 The decisive role of free fatty acids for protein conservation during fasting in humans with and without growth hormone. J Clin Endocrinol Metab 88:4371–4378
168. **Krag MB, Gormsen LC, Guo Z, Christiansen JS, Jensen MD, Nielsen S, Jørgensen JO** 2007 Growth hormone-induced insulin resistance is associated with increased intramyocellular triglyceride content but unaltered VLDL-triglyceride kinetics. Am J Physiol Endocrinol Metab 292:E920—E927
169. **Goodpaster BH, He J, Watkins S, Kelley DE** 2001 Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes. J Clin Endocrinol Metab 86:5755–5761
170. **Eliakim A, Brasel JA, Mohan S, Barstow TJ, Berman N, Cooper DM** 1996 Physical fitness, endurance training, and the growth hormone-insulin-like growth factor I system in adolescent females. J Clin Endocrinol Metab 81:3986–3992
171. **Kelly PJ, Eisman JA, Stuart MC, Pocock NA, Sambrook PN, Gwinn TH** 1990 Somatomedin-C, physical fitness, and bone density. J Clin Endocrinol Metab 70:718–723
172. **Poehlman ET, Copeland KC** 1990 Influence of physical activity on

insulin-like growth factor-I in healthy younger and older men. J Clin Endocrinol Metab 71:1468–1473
173. **Weltman A, Weltman JY, Hartman ML, Abbott RD, Rogol AD, Evans WS, Veldhuis JD** 1994 Relationship between age, percentage body fat, fitness, and 24-hour growth hormone release in healthy young adults: effects of gender. J Clin Endocrinol Metab 78:543–548
174. **Weltman A, Weltman JY, Schurrer R, Evans WS, Veldhuis JD, Rogol AD** 1992 Endurance training amplifies the pulsatile release of growth hormone: effects of training intensity. J Appl Physiol 72:2188–2196
175. **Roelen CA, de Vries WR, Koppeschaar HP, Vervoorn C, Thijssen JH, Blankenstein MA** 1997 Plasma insulin-like growth factor-I and high affinity growth hormone-binding protein levels increase after two weeks of strenuous physical training. Int J Sports Med 18: 238–241
176. **Koziris LP, Hickson RC, Chatterton Jr RT, Groseth RT, Christie JM, Goldflies DG, Unterman TG** 1999 Serum levels of total and free IGF-I and IGFBP-3 are increased and maintained in long-term training. J Appl Physiol 86:1436–1442
177. **Bak JF, Møller N, Schmitz O** 1991 Effects of growth hormone on fuel utilization and muscle glycogen synthase activity in normal humans. Am J Physiol 260:E736–E742
178. **Copeland KC, Nair KS** 1994 Acute growth hormone effects on amino acid and lipid metabolism. J Clin Endocrinol Metab 78: 1040–1047
179. **Jorgensen JOL, Pedersen SB, Borglum J, Moller N, Schmitz O, Christiansen JS, Richelsen B** 1994 Fuel metabolism, energy expenditure, and thyroid function in growth hormone-treated obese women: a double-blind placebo-controlled study. Metabolism 43: 872–877
180. **Møller N, Møller J, Jørgensen JOL, Ovesen P, Schmitz O, Alberti KG, Christiansen JS** 1993 Impact of 2 weeks growth hormone treatment on basal and insulin stimulated substrate metabolism in humans. Clin Endocrinol (Oxf) 39:577–581
181. **Lange KH, Larsson B, Flyvbjerg A, Dall R, Bennekou M, Rasmussen MH, Orskov H, Kjaer M** 2002 Acute growth hormone administration causes exaggerated increases in plasma lactate and glycerol during moderate to high intensity bicycling in trained young men. J Clin Endocrinol Metab 87:4966–4975
182. **Healy ML, Gibney J, Pentecost C, Croos P, Russell-Jones DL, Sönksen PH, Umpleby AM** 2006 Effects of high-dose growth hormone on glucose and glycerol metabolism at rest and during exercise in endurance-trained athletes. J Clin Endocrinol Metab 91: 320–327
183. **Hansen M, Morthorst R, Larsson B, Dall R, Flyvbjerg A, Rasmussen MH, Orskov H, Kjaer M, Lange KH** 2005 No effect of growth hormone administration on substrate oxidation during exercise in young, lean men. J Physiol 567:1035–1045
184. **Irving BA, Patrie JT, Anderson SM, Watson-Winfield DD, Frick KI, Evans WS, Veldhuis JD, Weltman A** 2004 The effects of time following acute growth hormone administration on metabolic and power output measures during acute exercise. J Clin Endocrinol Metab 89:4298–4305
185. **Horber FF, Haymond MW** 1990 Human growth hormone prevents the catabolic side-effects of prednisone in humans. J Clin Invest 86:265–272
186. **Yarasheski KE, Campbell JA, Smith K, Rennie MJ, Holloszy JO, Bier DM** 1992 Effect of growth hormone and resistance exercise on muscle growth in young men. Am J Physiol 262:E261—E267
187. **Yarasheski KE, Zachweija JJ, Angelopoulos TJ, Bier DM** 1993 Short-term growth hormone treatment does not increase muscle protein synthesis in experienced weight lifters. J Appl Physiol 74:3073–3076
188. **Fryburg DA, Barrett EJ** 1993 Growth hormone acutely stimulates skeletal muscle but not whole-body protein synthesis in humans. Metabolism 42:1223–1227
189. **Rennie MJ, Edwards RH, Krywawych S, Davies CT, Halliday D, Waterlow JC, Millward DJ** 1981 Effect of exercise on protein turnover in man. Clin Sci (Lond) 61:627–639
190. **Healy ML, Gibney J, Russell-Jones DL, Pentecost C, Croos P, Sonksen PH, Umpleby AM** 2003 High dose growth hormone exerts an anabolic effect at rest and during exercise in endurance-trained athletes. J Clin Endocrinol Metab 88:5221–5226
191. **Bowtell JL, Leese GP, Smith K, Watt PW, Nevill A, Rooyackers O, Wagenmakers AJ, Rennie MJ** 2000 Effect of oral glucose on leucine turnover in human subjects at rest and during exercise at two levels of dietary protein. J Physiol 525:271–281
192. **Bowtell JL, Leese GP, Smith K, Watt PW, Nevill A, Rooyackers O, Wagenmakers AJ, Rennie MJ** 1998 Modulation of whole body protein metabolism, during and after exercise, by variation of dietary protein. J Appl Physiol 85:1744–1752
193. **Knapik J, Meredith C, Jones B, Fielding R, Young V, Evans W** 1991 Leucine metabolism during fasting and exercise. J Appl Physiol 70:43–47
194. **Hoffman DM, Crampton L, Sernia C, Nguyen TV, Ho KK** 1996 Short-term growth hormone (GH) treatment of GH-deficient adults increases body sodium and extracellular water, but not blood pressure. J Clin Endocrinol Metab 81:1123–1128
195. **Deyssig R, Frisch H, Blum WF, Waldhor T** 1993 Effect of growth hormone treatment on hormonal parameters, body composition and strength in athletes. Acta Endocrinol (Copenh) 128:313–318
196. **Crist DM, Peake GT, Egan PA, Waters DL** 1988 Body composition response to exogenous GH during training in highly conditioned adults. J Appl Physiol 65:579–584
197. **Smith R, James WPT** 1996 Nutrition. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. Oxford textbook of medicine. 3rd ed. Oxford, UK: Oxford University Press; 1267–1332
198. **Battezzati A, Benedini S, Fattorini A, Losa M, Mortini P, Bertoli S, Lanzi R, Testolin G, Biolo G, Luzi L** 2003 Insulin action on protein metabolism in acromegalic patients. Am J Physiol Endocrinol Metab 284:E823—E829
199. **Sönksen PH, Greenwood FC, Ellis JP, Lowy C, Rutherford A, Nabarro JD** 1967 Changes of carbohydrate tolerance in acromegaly with progress of the disease and in response to treatment. J Clin Endocrinol Metab 27:1418–1430
200. **Moller N, Schmitz O, Jorgensen JO, Astrup J, Bak JF, Christensen SE, Alberti KG, Weeke J** 1992 Basal- and insulin-stimulated substrate metabolism in patients with active acromegaly before and after adenomectomy. J Clin Endocrinol Metab 74:1012–1019
201. **Foss MC, Saad MJ, Paccola GM, Paula FJ, Piccinato CE, Moreira AC** 1991 Peripheral glucose metabolism in acromegaly. J Clin Endocrinol Metab 72:1048–1053
202. **Jap TS, Ho LT** 1990 Insulin secretion and sensitivity in acromegaly. Clin Physiol Biochem 8:64–69
203. **Thomas SG, Woodhouse LJ, Pagura SM, Ezzat S** 2002 Ventilation threshold as a measure of impaired physical performance in adults with growth hormone excess. Clin Endocrinol (Oxf) 56:351–358
204. **Colao A, Cuocolo A, Marzullo P, Nicolai E, Ferone D, Della Morte AM, Petretta M, Salvatore M, Lombardi G** 1999 Impact of patient's age and disease duration on cardiac performance in acromegaly: a radionuclide angiography study. J Clin Endocrinol Metab 84:1518–1523
205. **Colao A, Cuocolo A, Marzullo P, Nicolai E, Ferone D, Florimonte L, Salvatore M, Lombardi G** 1999 Effects of 1-year treatment with octreotide on cardiac performance in patients with acromegaly. J Clin Endocrinol Metab 84:17–23
206. **Fazio S, Cittadini A, Biondi B, Palmieri EA, Riccio G, Bone F, Oliviero U, Sacca L** 2000 Cardiovascular effects of short-term growth hormone hypersecretion. J Clin Endocrinol Metab 85:179–182
207. **Gibney J, Wolthers T, Burt MG, Leung KC, Umpleby AM, Ho KK** 2007 Protein metabolism in acromegaly: differential effects of short- and long-term treatment. J Clin Endocrinol Metab 92:1479–1484
208. **McHugh CM, Park RT, Sonksen PH, Holt RI** 2005 Challenges in detecting the abuse of growth hormone in sport. Clin Chem 51: 1587–1593
209. **Reiterer W** 2000 Positive: an Australian Olympian reveals the inside story of drugs and sport. Sydney, Australia: Pan Macmillan Sydney
210. **Sonksen PH** 2001 Insulin, growth hormone and sport. J Endocrinol 170:13–25
211. **Voet W** 2001 Breaking the chain: drugs and cycling; the true story. Fotheringham W, translator. London: Yellow Jersey
212. **Berggren A, Ehrnborg C, Rosen T, Ellegard L, Bengtsson BA,**

Caidahl K 2005 Short-term administration of supraphysiological recombinant human growth hormone (GH) does not increase maximum endurance exercise capacity in healthy, active young men and women with normal GH-insulin-like growth factor I axes. J Clin Endocrinol Metab 90:3268–3273
213. **Bhasin S, Storer TW, Berman N, Callegari C, Clevenger B, Phillips J, Bunnell TJ, Tricker R, Shirazi A, Casaburi R** 1996 The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 335:1–7
214. **Franke WW, Berendonk B** 1997 Hormonal doping and androgenization of athletes: a secret program of the German Democratic Republic government. Clin Chem 43:1262–1279
215. **Nabarro JD** 1987 Acromegaly. Clin Endocrinol (Oxf) 26:481–512
216. **Refetoff S, Sonksen PH** 1970 Disappearance rate of endogenous and exogenous human growth hormone in man. J Clin Endocrinol Metab 30:386–392
217. **Flanagan DE, Taylor MC, Parfitt V, Mardell R, Wood PJ, Leatherdale BA** 1997 Urinary growth hormone following exercise to assess growth hormone production in adults. Clin Endocrinol (Oxf) 46:425–429
218. **Saugy M, Cardis C, Schweizer C, Veuthey JL, Rivier L** 1996 Detection of human growth hormone doping in urine: out of competition tests are necessary. J Chromatogr B Biomed Appl 687:201–211
219. **Dall R, Longobardi S, Ehrnborg C, Keay N, Rosen T, Jorgensen JO, Cuneo RC, Boroujerdi MA, Cittadini A, Napoli R, Christiansen JS, Bengtsson BA, Sacca L, Baxter RC, Basset EE, Sonksen PH** 2000 The effect of four weeks of supraphysiological growth hormone administration on the insulin-like growth factor axis in women and men. GH-2000 Study Group. J Clin Endocrinol Metab 85:4193–4200
220. **Ehrnborg C, Lange KH, Dall R, Christiansen JS, Lundberg PA, Baxter RC, Boroujerdi MA, Bengtsson BA, Healey ML, Pentecost C, Longobardi S, Napoli R, Rosén T; GH-2000 Study Group** 2003 The growth hormone/insulin-like growth factor-I axis hormones and bone markers in elite athletes in response to a maximum exercise test. J Clin Endocrinol Metab 88:394–401
221. **Longobardi S, Keay N, Ehrnborg C, Cittadini A, Rosen T, Dall R, Boroujerdi MA, Bassett EE, Healy ML, Pentecost C, Wallace JD, Powrie J, Jorgensen JO, Sacca L** 2000 Growth hormone (GH) effects on bone and collagen turnover in healthy adults and its potential as a marker of GH abuse in sports: a double blind, placebo-controlled study. The GH-2000 Study Group. J Clin Endocrinol Metab 85:1505–1512
222. **Wallace JD, Cuneo RC, Lundberg PA, Rosen T, Jorgensen JO, Longobardi S, Keay N, Sacca L, Christiansen JS, Bengtsson BA, Sonksen PH** 2000 Responses of markers of bone and collagen turnover to exercise, growth hormone (GH) administration, and GH withdrawal in trained adult males. J Clin Endocrinol Metab 85:124–133
223. **Healy ML, Dall R, Gibney J, Bassett E, Ehrnborg C, Pentecost C, Rosen T, Cittadini A, Baxter RC, Sönksen PH** 2005 Toward the development of a test for growth hormone abuse: a study of extreme physiological ranges of growth hormone dependent markers in 813 elite athletes in the postcompetition setting. J Clin Endocrinol Metab 90:641–649
224. **O'Connor KG, Tobin JD, Harman SM, Plato CC, Roy TA, Sherman SS, Blackman MR** 1998 Serum levels of insulin-like growth factor-I are related to age and not to body composition in healthy women and men. J Gerontol A Biol Sci Med Sci 53:M176—M182
225. **Yu H, Mistry J, Nicar MJ, Khosravi MJ, Diamandis A, van Doorn J, Juul A** 1999 Insulin-like growth factors (IGF-I, free IGF-I and IGF-II) and insulin-like growth factor binding proteins (IGFBP-2, IGFBP-3, IGFBP-6, and ALS) in blood circulation. J Clin Lab Anal 13:166–172
226. **Landin-Wilhelmsen K, Wilhelmsen L, Lappas G, Rosen T, Lindstedt G, Lundberg PA, Bengtsson BA** 1994 Serum insulin-like growth factor I in a random population sample of men and women: relation to age, sex, smoking habits, coffee consumption and physical activity, blood pressure and concentrations of plasma lipids, fibrinogen, parathyroid hormone and osteocalcin. Clin Endocrinol (Oxf) 41:351–357
227. **Powrie JK, Bassett EE, Rosen T, Jørgensen JO, Napoli R, Sacca L, Christiansen JS, Bengtsson BA, Sönksen PH; on behalf of the GH-2000 Project Study Group** 2007 Detection of growth hormone abuse in sport. Growth Horm IGF Res 17:220–226
228. **Leung KC, Howe C, Gui LY, Trout G, Veldhuis JD, Ho KK** 2002 Physiological and pharmacological regulation of 20-kDa growth hormone. Am J Physiol Endocrinol Metab 283:E836—E843
229. **Wallace JD, Cuneo RC, Bidlingmaier M, Lundberg PA, Carlsson L, Boguszewski CL, Hay J, Healy ML, Napoli R, Dall R, Rosen T, Strasburger CJ** 2001 The response of molecular isoforms of growth hormone to acute exercise in trained adult males. J Clin Endocrinol Metab 86:200–206
230. **Wallace JD, Cuneo RC, Bidlingmaier M, Lundberg PA, Carlsson L, Boguszewski CL, Hay J, Boroujerdi M, Cittadini A, Dall R, Rosen T, Strasburger CJ** 2001 Changes in non-22-kilodalton (kDa) isoforms of growth hormone (GH) after administration of 22-kDa recombinant human GH in trained adult males. J Clin Endocrinol Metab 86:1731–1737
231. **Barton-Davis ER, Shoturma DI, Musaro A, Rosenthal N, Sweeney HL** 1998 Viral mediated expression of insulin-like growth factor I blocks the aging-related loss of skeletal muscle function. Proc Natl Acad Sci USA 95:15603–15607
232. **Donath MY, Jenni R, Brunner HP, Anrig M, Kohli S, Glatz Y, Froesch ER** 1996 Cardiovascular and metabolic effects of insulin-like growth factor I at rest and during exercise in humans. J Clin Endocrinol Metab 81:4089–4094
233. **Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Schlenker RA, Cohn L, Rudman IW, Mattson DE** 1990 Effects of human growth hormone in men over 60 years old. N Engl J Med 323:1–6
234. **Papadakis MA, Grady D, Black D, Tierney MJ, Gooding GA, Schambelan M, Grunfeld C** 1996 Growth hormone replacement in healthy older men improves body composition but not functional ability. Ann Intern Med 124:708–716
235. **Marcus R, Butterfield G, Holloway L, Gilliland L, Baylink DJ, Hintz RL, Sherman BM** 1990 Effects of short-term administration of recombinant human growth hormone to elderly people. J Clin Endocrinol Metab 70:519–527
236. **Taaffe DR, Pruitt L, Reim J, Hintz RL, Butterfield G, Hoffman AR, Marcus R** 1994 Effect of recombinant human growth hormone on the muscle strength response to resistance exercise in elderly men. J Clin Endocrinol Metab 79:1361–1366
237. **Taaffe DR, Jin IH, Vu TH, Hoffman AR, Marcus R** 1996 Lack of effect of recombinant human growth hormone (GH) on muscle morphology and GH-insulin-like growth factor expression in resistance-trained elderly men. J Clin Endocrinol Metab 81:421–425
238. **Blackman MR, Sorkin JD, Munzer T, Bellantoni MF, Busby-Whitehead J, Stevens TE, Jayme J, O'Connor KG, Christmas C, Tobin JD, Stewart KJ, Cottrell E, St Clair C, Pabst KM, Harman SM** 2002 Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. JAMA 288:2282–2292
239. **Giannoulis MG, Sonksen PH, Umpleby M, Breen L, Pentecost C, Whyte M, McMillan CV, Bradley C, Martin FC** 2006 The effects of growth hormone and/or testosterone in healthy elderly men: a randomized controlled trial. J Clin Endocrinol Metab 91:477–484
240. **Thompson JL, Butterfield GE, Gylfadottir UK, Yesavage J, Marcus R, Hintz RL, Pearman A, Hoffman AR** 1998 Effects of human growth hormone, insulin-like growth factor I, and diet and exercise on body composition of obese postmenopausal women. J Clin Endocrinol Metab 83:1477–1484

***Endocrine Reviews* is published by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**