Effects of Growth Hormone on Glucose, Lipid, and Protein Metabolism in Human Subjects

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In evolutionary terms, GH and intracellular STAT 5 signaling is a very old regulatory system. Whereas insulin dominates peripendially, GH may be viewed as the primary anabolic hormone during stress and fasting. GH exerts anabolic effects directly and through stimulation of IGF-I, insulin, and free fatty acids (FFA). When subjects are well nourished, the GH-induced stimulation of IGF-I and insulin is important for anabolic storage and growth of lean body mass (LBM), adipose tissue, and glycogen reserves. During fasting and other catabolic states, GH predominantly stimulates the release and oxidation of FFA, which leads to decreased glucose and protein oxidation and preservation of LBM and glycogen stores.

The most prominent metabolic effect of GH is a marked increase in lipolysis and FFA levels. In the basal state, the effects of GH on protein metabolism are modest and include increased protein synthesis and decreased breakdown at the whole body level and in muscle together with decreased amino acid degradation/oxidation and decreased hepatic urea formation. During fasting and stress, the effects of GH on protein metabolism become more pronounced; lack of GH during fasting increases protein loss and urea production rates by approximately 50%, with a similar increase in muscle protein breakdown. GH is a counterregulatory hormone that antagonizes the hepatic and peripheral effects of insulin on glucose metabolism via mechanisms involving the concomitant increase in FFA flux and uptake. This ability of GH to induce insulin resistance is significant for the defense against hypoglycemia, for the development of “stress” diabetes during fasting and inflammatory illness, and perhaps for the “Dawn” phenomenon (the increase in insulin requirements in the early morning hours). Adult patients with GH deficiency are insulin resistant—probably related to increased adiposity, reduced LBM, and impaired physical performance—which temporarily worsens when GH treatment is initiated. Conversely, despite increased LBM and decreased fat mass, patients with acromegaly are consistently insulin resistant and become more sensitive after appropriate treatment. (Endocrine Reviews 30: 152–177, 2009)

I. Introduction

PHYLOGENETICALLY, GH IS AN ancestral hormone that has been identified in the pituitary of primitive vertebrates, such as the jawless sea lamprey fish (1). In addition signal transducers and activators of transcription (STAT) 5, a principal intracellular mediator of GH signaling, exhibits a very high degree of homology to invertebrate and prevertebrate STATs, reflecting the ancient nature of the GH/STAT signaling system (2). Intriguingly, it also appears that insulin-like peptides, such as IGF-I and proinsulin, have evolved from a common gene and that these peptides are much older than both the pancreas and insulin (3). In line with this phylogenetic hierarchy, it has been shown that GH, together with prolactin and human placental lactogen, stimulates glycogen gene expression, and insulin biosynthesis and secretion (4).

In terms of evolutionary biology, the effects of GH on substrate metabolism in humans are simple: during conditions of energy surplus, GH, in concert with IGF-I and insulin, promotes nitrogen retention, and when food is sparse, GH alters fuel consumption from the use of carbohydrates and protein to the use of lipids, thereby allowing conservation of vital protein stores. Undoubtedly, this master fuel switch from carbohydrate utilization to lipolysis and lipid oxidation has played a major role for survival and will continue to prevail whenever shortage of nutrients again may threaten. Apart from lipid-mediated protein conservation, GH possesses direct and indirect—via IGF-I and insulin—protein anabolic effects as indicated in Fig. 1. This concept of
A central metabolic role of GH emerges from three seminal hypotheses from the early 1960s:

1) The “thrifty genotype” hypothesis by J. V. Neel (5), according to which evolution has favored survival of individuals genetically equipped with a good appetite and the ability to store surplus calories as fat.

2) The “glucose fatty acid cycle” by P. J. Randle et al. (6), according to which free fatty acids (FFA) from fat stores compete with and displace glucose utilization, leading to insulin resistance. Because sustained glucose release is dependent on gluconeogenesis from amino acids, increased fat utilization and diminished glucose utilization also decrease the need for protein breakdown.

3) The “feast and famine cycle” by Rabinowitz and Zierler (7), according to which insulin is the major anabolic hormone storing all fuels during feast and GH is the major anabolic hormone during famine and stress, sparing glucose and protein at the expense of lipids.

As indicated in Fig. 2, these hypotheses imply that during periods of food surplus, predisposed individuals overeat and gain weight. On one side, the ensuing obesity renders the individual susceptible to insulin resistance, diabetes, and cardiovascular disease, and, on the other side, fat depots and high levels of FFA safeguard the individual during famine. It should be underlined that the proposed potential of insulin resistance and hyperinsulinemia to promote protein conservation merely rests on circumstantial evidence that high levels of insulin restrict protein breakdown and increase protein synthesis. Unlike cardiovascular morbidity, which in general affects people at the grand parental stage, famine poses a greater threat to human survival because all age groups are afflicted and reproduction is jeopardized. The cycling between feast and famine is regulated by insulin building up glycogen and fat, insulin and GH building up protein, and GH with low insulin levels triggering fat mobilization and utilization.

Thus, in many ways the metabolic role of GH in humans is best understood in the long perspective of evolutionary fuel economy. In patients with acromegaly and GH deficiency, the metabolic effects of GH lead to distinct clinical features as delineated below.

The present review seeks to outline current knowledge about the affects of GH on lipid, protein, and glucose metabolism in humans. The major focus is on the effects in adults, both healthy subjects and patients with abnormal GH status, whereas the critical importance of GH and IGF-I for statural growth and somatic maturation in childhood and adolescence is beyond the scope of this review.

II. Background

Human GH is a 191-amino acid, 22-kDa polypeptide, that is secreted from the pituitary gland (8, 9). In the circulation,
various molecular forms of GH exist, a majority of which are bound to carrier proteins corresponding to the extracellular domain of the GH receptor (GHR) (10, 11). It has been estimated that free monomeric 22-kDa GH represents only approximately 20% of total immunoreactivity in plasma (10, 11). More recently, a novel assay of free GH has been developed, and implementation of this shows that free GH depends much on prevailing total GH and GH binding protein concentrations (12). In man, GH is secreted episodically from the pituitary gland with a major surge at the onset of slow-wave sleep and less conspicuous secretory episodes a few hours after meals (13–16). A healthy young adult secretes roughly 0.25 mg/m^2 body surface of GH per 24 h (=0.4–0.5 mg/24 h), which mainly occurs as “pulses within pulses” (13). During fasting and certain conditions of physical stress, GH secretion is amplified, whereas excess of fuels such as glucose and lipid intermediates inhibits GH release in healthy man (13, 14, 17, 18). The secretion of GH is maximal at midpuberty, which is accompanied by very high circulating IGF-I levels as previously reviewed (19). Interestingly, there is compelling evidence to suggest that the activated GH/GH-I axis at puberty is causally linked to the comitant increase in insulin resistance (20). Adulthood is associated with a gradual decline in GH secretion and circulating IGF-I levels (21). The degree to which this is related to senescent changes in body composition and organ function remains controversial, but it is noteworthy that accumulation of visceral fat rather than chronological age is the most important predictor of GH status in midlife adults (22).

Circulating IGF-I is predominately stimulated by GH and is produced in the liver in the presence of sufficient nutrient intake and elevated portal insulin levels (23), and IGF-I is critical for promoting the protein anabolic effects of GH (24). Circulating IGF-I concentrations are reduced during fasting, and GH secretion is amplified, whereas infusion of IGF-I suppresses GH secretion (25), strongly suggesting a feedback regulation by IGF-I on GH secretion. This notion is supported by the observation that a single dose of IGF-I in patients with type 1 diabetes mellitus abrogates GH hypersecretion (26). More recent experiments have revealed that liver-specific IGF-I gene-deleted mice exhibit marked reductions in circulating IGF-I and elevated GH levels (27), which again implies a feedback loop between circulating IGF-I and GH release.

These observations suggest that the IGF-I-independent effects of GH are mainly exerted during states of relative fuel shortage, such as fasting or prolonged exercise, and accordingly that these states appear to be important domains for direct actions of GH.

One of the first pieces of evidence showing that GH is involved in the regulation of intermediary metabolism was published in 1936 (28), when the 1946 Nobel laureate B. A. Houssay reported that hypophysectomized dogs are hypersensitive to the actions of insulin and are prone to hypoglycemia. Later, when pituitary human GH extracts became available, it was shown that injection of large amounts of GH in healthy subjects and patients with GH deficiency and diabetes stimulated lipolysis and led to hyperglycemia (29–31). Additionally, classic studies in which pituitary GH was perfused locally through the brachial artery demonstrated that GH acutely inhibited muscle glucose uptake in normal postabsorptive subjects (32–34).

GH has acute and chronic metabolic effects. As outlined below the acute actions include stimulation of lipolysis and increased FFA levels in the blood. More prolonged GH exposure, e.g., repetitive GH pulses in the presence of adequate nutrient supply and subsequent elevations in systemic and portal insulin levels, induces hepatic IGF-I production (23). This is accompanied by suppression of IGF binding protein (IGFBP)-1, which may act to increase free IGF-I. Eventually protein stores, lean body mass (LBMs), and a majority of body organs grow, and body fat mass decreases (Fig. 3). The order and time sequence of events are of importance. GH stimulates lipolysis and causes insulin resistance within 1–2 h, and these effects disappear after approximately 8 h (35, 36). The stimulating effect of GH on IGF-I production and action is a more chronic process, which, as previously discussed, depends on a positive energy balance and ensuing elevations in insulin. Thus, during prolonged severe GH administration, the actions of IGF-I and insulin prevail 8–10 h after each injection. Interestingly, the liver-specific IGF-I gene-deleted mice mentioned previously show normal postnatal growth and development despite low circulating IGF-I levels, which indicates an important role for direct GH effects in target tissues such as adipose tissue, bone, and skeletal muscle, which may involve stimulation of local IGF-I production (27). In support of the importance of GH per se, two very recent studies failed to record any independent effects of GH-induced hyperinsulaemia on whole body and muscle protein metabolism in humans and in a pig model (37, 38).

### III. Growth Hormone Signaling in Human Models

GH signaling is a separate and prolific research field by itself, as recently reviewed (39). This section will focus on recent data obtained in human models.

The GHR belongs to class I of the hematopoietin superfamily of cytokine receptors, which includes more than 30 members, among others prolactin, erythropoietin, leptin, granulocyte stimulating factor, and several IL (e.g., IL-2, IL-3, and IL-6) (40). GHRs have been identified in many tissues including muscle, fat, liver, heart, kidney, brain, and the

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**Fig. 3.** A modified version of the feast-famine cycle including variations in the secretion and action of insulin and GH and the ensuing changes in IGFBP-1 and IGF-I. In the immediate postprandial period, insulin acts alone to promote storage of glucose. In the remote postabsorptive or fasting state, GH acts alone to promote lipolysis. In the intermediate phase, insulin and GH act in synergy to promote IGF-I production and bioactivity and subsequent protein synthesis.
pancreas (41). Activation of receptor-associated Janus kinase (JAK) 2 is considered the critical step in initiating GH signaling. One GH molecule binds to two GHR molecules, and it is believed that preformed, unliganded GHR dimers exist (39). After GH binding, the intracellular domains of the GHR dimer undergo rotation, which is thought to bring together the two intracellular domains, each of which binds one JAK2 molecule. This in turn induces cross-phosphorylation of tyrosine residues in the kinase domain of each JAK2 molecule, followed by tyrosine phosphorylation of the GHR. Phosphorylated residues on GHR and JAK2 form docking sites for different signaling molecules including STAT1, -3, -5a, and -5b, the MAPK pathway, and the phosphatidylinositol 3-kinase (PI 3-kinase) pathway (39). STATs bound to the activated GHR-JAK2 complex are subsequently phosphorylated on a single tyrosine by JAK2, after which they dimerize and translocate to the nucleus, where they bind to DNA and act as transcription factors for targeted genes. A STAT5b binding site has recently been characterized in the IGF-1 gene promoter region, which mediates GH-stimulated IGF-I gene activation (42).

Down-regulation or attenuation of JAK2-associated GH signaling is mediated by a family of cytokine-inducible suppressors of cytokine signaling (SOCS), of which there are eight members: SOCS 1-7, and the cytokine-inducible SH2-domain-containing proteins (43). SOCS proteins bind to phosphorytrosine residues on the GHR or JAK2 and suppress GH signaling by inhibiting JAK2 activity and competing with STATs for binding on the GHR or by inducing proteasomal degradation of the GHR complex.

Data on GH signaling derive mainly from rodent models and experimental cell lines, although GH-induced activation of the JAK2/STAT5b and the MAPK pathways has been recorded in cultured human fibroblasts from normal human subjects (44). STAT5b in human subjects is critical for GH-induced IGF-I expression and statural growth as demonstrated by the identification of mutations in the STAT5b gene of patients presenting with severe GH insensitivity in the presence of normal GHR (45). GHR signaling in human models in vivo has been reported in a study in healthy young male subjects exposed to an iv GH bolus vs. saline (46). In muscle and fat biopsies, significant STAT5b tyrosine phosphorylation was recorded 30–60 min after GH exposure, compared with saline (46) (Fig. 4). Evidence of less intense STAT5b activation associated with small spontaneous GH bursts in the saline study was also observed in several subjects. DNA binding activity by STAT5 assessed by the EMSA was evident in fat but not muscle tissue samples. Likewise, significant GH-dependent IGF-I mRNA expression was only detectable in adipose tissue, whereas SOCS-1 and SOCS-3 mRNA expression tended to increase in muscle and fat, respectively (46). There was no evidence of GH-induced activation of PI 3-kinase, Akt/protein kinase B (PKB), or MAPK in either tissue. The latter observation is noteworthy in relation to the insulin antagonistic effects of GH.

There is animal and in vitro evidence to suggest that insulin and GH share postreceptor signaling pathways (47). Convergence has also been reported at the levels of STAT5 and SOCS3 (48), as well as on protein kinases comprising the major insulin receptor signaling pathway: insulin receptor substrates (IRS) 1 and 2, PI 3-kinase, Akt, and ERK 1 and 2 (49, 50). Studies in rodent models suggest that the insulin-antagonistic effects of GH in adipose and skeletal muscle tissue are PI 3-kinase-dependent through direct up-regulation of the p85α subunit and subsequent decrease in insulin-stimulated PI 3-kinase activity (47, 51). One study assessed the impact of a GH infusion on insulin sensitivity and the activity of PI 3-kinase, as well as PKB/Akt in skeletal muscle, in a controlled design involving healthy young subjects (52). The infusion of GH induced a sustained increase in FFA levels and subsequently insulin resistance as assessed by the euglycemic clamp technique. This was, however, not associated with any changes in the insulin-stimulated increase in either IRS-1-associated PI 3-kinase or PKB/Akt activity (Fig. 5) (52). This finding could be time-dependent because some studies have failed to detect any effects of FFA on proximal insulin signaling (53). Conversely, it was subsequently assessed that insulin had no impact on GH-induced STAT5b activation or SOCS3 mRNA expression either (54).

A. Conclusion

The JAK2/STAT5b signaling pathway is also activated by GH in human models and is critical as regards the effects of GH on linear growth in childhood. There is also evidence that GH may activate the MAPK pathway in human fibroblasts in vitro. The signaling mechanisms subserving the insulin antagonistic effects of GH in humans, however, remain to be unveiled. The available data in humans have failed to demonstrate significant effects of GH on either basal or insulin-stimulated PI 3-kinase activity (Fig. 6).

The human in vivo studies were performed in healthy subjects with single biopsies obtained 30–60 min (46) and 240 min (52) after the start of acute GH exposure. It remains to be investigated whether sampling at different time points in relation to acute GH exposure or biopsies obtained in states of chronic excess or deficiency of GH may reveal additional effects on the same signaling pathways.

IV. Metabolic Effects of GH in Normal Subjects

A. The basal postabsorptive state

In the basal state, i.e., after an overnight fast, the dominant effect of GH is stimulation of lipolysis and lipid oxidation. As previously mentioned, GH secretion in this state occurs in small discrete bursts, whereas many clinical studies have employed prolonged exposure to higher levels of GH.

1. Lipid metabolism. “The rise in fatty acids is perhaps the most sensitive response to GH of any yet described” (274).

The most striking effect of a single exogenous GH pulse is a marked increase in circulating levels of FFA and ketone bodies (55), reflecting stimulation of lipolysis and ketogenesis (Fig. 7). Baseline FFA values usually more than double with peak values of approximately 1 mmol/liter recorded after 2–3 h. The increase in FFA levels is also robust and lasts for 1–8 h (35, 36, 56). Pulsatile as well as continuous administration of 70–500 μg of GH, i.e., from the low to the very high physiological range) to healthy postabsorptive subjects induces a clear dose-dependent
elevation of circulating FFA and glycerol levels and increased lipid oxidation rates, assessed by indirect calorimetry (36, 57–59). In addition, palmitate tracer dilution has shown a similar increase in palmitate flux after pulsatile GH exposure (35, 60), indicative of increased FFA turnover.

As regards the source of FFA, microdialysis studies have shown that a GH pulse increases glycerol concentrations—indicative of in situ lipolysis—in both femoral and abdominal adipose tissue, indicating that both regions contribute (56, 59) (Fig. 7). It is not known whether visceral adipose tissue participates, but the finding that long-term GH treatment decreases visceral fat volume supports this (61). It has been observed that interstitial muscle glycerol concentrations increase after a GH bolus (35), but this could also reflect spillover from the circulating glycerol pool. The finding of increased intramyocellular triglyceride content after GH exposure (36) argues against mobilization of FFA stored in muscle as the primary event. The secretory pattern of GH plays an important role in the diurnal supply of fuel substrates. An investigation of young healthy subjects reported that the nocturnal GH peaks preceded the early morning rise of FFA by 2 h (62), a time lag very close to the one found after GH bolus administration, thus providing evidence that GH regulates the circadian oscillations in the release and oxidation of lipids and other fuel substrates. The idea is corroborated by studies showing that lack of nocturnal GH release compromises the physiological overnight surge of lipid fuels (62–65) and studies implying a correlation between nocturnal GH and ketone body concentrations in terms of time and magnitude (65, 66). Finally, it has been reported that nocturnal surges of both GH and FFA are increased, and that circulating levels of FFA and GH correlate in patients with type 1 diabetes (67). There is evidence that the lipolytic response to GH may be blunted in females, older subjects, and abdominally obese subjects (64, 68, 69), whereas Hansen et al. (59) failed to demonstrate any impact of either age or body composition.

It remains unresolved whether GH directly impacts hepatic ketogenesis. Some studies suggest so (70–72), but increased hepatic precursor supply of FFA is probably more important. The potential role of GH in the regulation of lipogenesis and adipose tissue growth and differentiation in
humans is also controversial, and it appears that major species-specific differences exist (73). Porcine studies suggest that GH may inhibit lipogenesis and fatty acid synthase (74), thus contributing to loss of fat mass. It is uncertain whether GH affects lipid deposition in muscle and liver, but one study in healthy subjects has recorded increased intramyocellular lipid disposition after 8-d GH treatment (36). There is no evidence that GH acutely affects triglyceride synthesis rates (36). The lipolytic effects are at least partly mediated via the hormone-sensitive lipase (HSL) (75), and in accordance with this administration of acipimox, a nicotinic derivative that blocks the actions of HSL has been shown to suppress the lipolytic effects of GH in humans (76–79). In addition, in vitro data suggest that GH directly stimulates FFA oxidation in human fibroblasts (80), and several studies also demonstrate that GH suppresses the lipoprotein lipase (LPL) activity in human adipose tissue (81–83) (Fig. 8). Finally, there is in vitro and in vivo evidence to suggest that GH, probably via IGF-I, inhibits the conversion of cortisol to cortisone in human adipose tissue from the abdomen by inhibiting the expression and activity of 11β-hydroxysteroid dehydrogenase 1 (84, 85). Several animal and human studies have shown that reduced 11β-hydroxysteroid dehydrogenase 1 expression and activity, and thus low cortisol levels, protect

![Diagram](https://academic.oup.com/edrv/article-abstract/30/2/152/2355062)

**Fig. 5.** A, The effects of GH (○) vs. saline infusions (●) on circulating FFA levels (top) and GIR (bottom) during a euglycemic clamp. The arrows indicate the time points for muscle biopsies. B, IRS-1-associated PI 3-kinase (top) and Akt/PKB activity (bottom) in muscle at baseline (open bars) and under insulin stimulation during GH (gray bars) and saline infusions (black bars). Values are means ± se. IRS-1-associated PI 3-kinase activity is expressed in arbitrary units (AU), and Akt/PKB activity is expressed as picomoles incorporated ATP mg protein⁻¹ min⁻¹. [Adapted from Ref. 52 with permission from The American Physiological Society].

![Diagram](https://academic.oup.com/edrv/article-abstract/30/2/152/2355062)

**Fig. 6.** Schematic and simplified depiction of alleged GH signaling proteins, which so far have been investigated in human muscle and adipose tissue. The solid lines and boxes indicate pathways that have been shown to be activated by GH; the hatched lines and boxes represent signaling proteins where activation by GH so far has not been documented. Src, Tyrosine kinase src; JNK, Jun N-terminal kinase.
against central obesity via mechanisms that may involve reduced LPL activity, reduced differentiation of preadipocytes to mature adipocytes, and induction of a more favorable profile of inflammatory adipokines. To what degree this intriguing effect of IGF-I contributes to the lipolytic and insulin-antagonistic effects of GH remains, however, uncertain.

Thus, the primary effect of GH in the basal state is to promote lipid mobilization and oxidation. As pointed out by Rabinowitz and Zierler (7) these actions may be viewed as a means of switching substrate metabolism from glucose and protein utilization to lipid oxidation.

2. Glucose metabolism. “In human studies, anabolic amounts of human GH have been found to cause no increase in blood sugar in normal subjects but may decrease the sensitivity to injected insulin” (274).

When a physiological dose of GH (100 μg/h) is infused to healthy postabsorptive subjects for 4 h, an abrupt early 40% decrease in glucose uptake of the forearm muscles is recorded, together with a more delayed 50% decrease in glucose oxidation and a proportionate increase in nonoxidative glucose utilization, whereas total glucose turnover remain unaltered (57). Similar observations have emerged from studies using discrete GH pulses, i.e., acute inhibition of muscle glucose uptake and subsequent stimulation of lipid oxidation and suppression of glucose oxidation (35, 55, 56, 58). These data are in line with the original studies that reported a rapid and robust greater than 50% decrease in forearm glucose uptake after local GH exposure (33, 34).

The rapid initial decrease in muscle glucose uptake may either be a direct effect of GH or secondary to local augmentation of lipid utilization (86). In this context, it is noteworthy that lipids in the basal state constitute the major fuel substrate for muscle (87), and that basal muscle uptake of glucose accounts for only 15–20% of total glucose turnover (57). Rabinowitz et al. (33) noted an acute decrease in the respiratory exchange ratio across the GH-perfused forearm, indicating increased lipid oxidation, which could directly inhibit glucose utilization. It is also noteworthy that GH signaling in muscle and fat tissues is detectable 30 min after a GH pulse (46).

Acknowledging that GH decreases glucose oxidation and muscle glucose uptake in the presence of unchanged endogenous glucose production and plasma glucose concentrations implies that GH must promote nonoxidative glucose utilization in some nonmuscle compartment of the body.
Neither the tissues nor the biochemical “destinations” for this surplus glucose flux are known. Stimulated lipogenesis in adipose tissue or liver is an unlikely candidate because there is no evidence of any such effects and because ongoing lipogenesis would increase the respiratory exchange ratio, whereas the opposite is recorded after GH exposure (88).

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For additional information, see text.

Data on the acute effects of GH on protein metabolism in the basal state are not very consistent. Fryburg et al. (99, 100) perfused GH locally in the brachial arterial of the forearm and demonstrated an increase in muscle protein synthesis, without effects on muscle protein breakdown, when comparing 3-h values to 6-h values during 6 h of GH perfusion. In a placebo-controlled study, Copeland and Nair (101) reported an acute 20% decrease in whole body leucine oxidation and a borderline increase in nonoxidative leucine disposal (protein synthesis), a reduced leg leucine balance together with relatively lower muscle protein breakdown rates for phenylalanine (P = 0.05) and leucine (P = 0.09). Another study did not detect any effects of acute GH withdrawal on whole body or forearm muscle phenylalanine kinetics in GH-deficient (GHD) adults (GHDA) (102), whereas Fryburg and Barrett (103) reported decreased whole body leucine oxidation, unaltered whole body leucine proteolysis and protein synthesis, and increased muscle protein synthesis after acute GH exposure in healthy humans. In general, circulating amino acid concentrations do not consistently change after acute GH administration.

As regards more prolonged effects, a study assessing the impact of GH on protein metabolism postabsorptively has shown that high doses of GH (0.1 mg/kg·d) for 7 d increases both leucine protein synthesis and leucine oxidation at the whole body level (104). These observations were confirmed by Yarasheski et al. (105), who failed to detect any effect on fractional muscle protein synthesis after 14 wk of GH treatment. In addition, it has been reported that 6 wk of high-dose GH treatment to malnourished hemodialysis patients stimulated muscle protein synthesis without any effects on muscle protein degradation (106). Some studies have, however, not been able to find any effects of prolonged GH exposure on whole body protein turnover or albumin synthesis (103, 107). A study of protein turnover in GHDA has demonstrated reduced rates of protein synthesis and breakdown and subsequent normal net protein loss compared with normal controls (108), in line with earlier observations of the effect of chronic GH deficiency on protein metabolism (109). It should be noted that most studies assessing the protein metabolic effects of prolonged GH exposure have used relatively high GH doses and invariably have affected insulin, IGF-I, and FFA levels, which together with changes in body composition have independent effects on substrate metabolism, discussed below.

In addition, experiments in hypophysectomized rats show that GH acts on the liver to decrease urea synthesis and, in parallel, increase glutamine release, thereby diminishing hepatorenal clearance of the circulating nitrogen pool (110). In the postabsorptive state, Wolthers et al. (111, 112) recorded unchanged rates of urea synthesis during short-term GH exposure and a decrease with more prolonged administration in an experimental model that provided constant blood levels of and hepatic exposure to circulating amino acids. This suggests that the anabolic effect of GH on whole body protein metabolism in normal subjects involves both periph-

![Fig. 8. Schematic and simplified illustration of studied effects of GH on fat metabolism in adipose tissue and skeletal muscle. +, Activation by GH; −, inhibition by GH. It is not yet clear whether GH impacts LPL in muscle. GH seems not to impact the turnover of triglycerides (TG) associated with very low density lipoprotein (VLDL). For additional information, see text.](image-url)
eral protein synthesis and degradation as well as a specific reduction of hepatic urea nitrogen synthesis.

On the whole, the acute effects of GH on protein metabolism in the basal state are not straightforward and perhaps of minor biological significance, and studies of the effects of GH on protein metabolism in stress states (e.g., exercise and fasting) and pathological states (acromegaly and GH deficiency) are probably more relevant and rewarding. The majority of studies suggest modest anabolic actions that may include increased protein synthesis and decreased breakdown at the whole body level and in muscle together with decreased amino acid degradation/oxidation and decreased hepatic urea formation. With more prolonged GH exposure and ensuing elevated levels of insulin, IGF-I, and FFA and increased LBM, the protein anabolic effects become more consistent.

4. Energy expenditure. Several lines of evidence suggest that high GH levels stimulate resting energy expenditure (REE) independent of changes in LBM (113, 114). An increase in REE has been observed 5 h after GH infusion (compared with saline) in normal subjects during a concomitant euglycemic clamp (115). Comparable rapid-onset caloricergic effects of GH have been recorded in GHD patients (116, 117). The underlying mechanisms are not fully clarified, but it is noteworthy that IGF-I administration does not to the same extent increase REE (118), which could relate to its suppressive effect on insulin secretion.

GH stimulates the peripheral conversion of T₄ to T₃ (119, 120), but experimental data indicate that the ensuing approximately 10% increase in T₃ levels is insufficient to account for the GH-induced 10–20% increase in REE (114). A primary stimulatory effect of GH infusion on key mitochondrial enzymes involved in biological oxidation was recently recorded in muscle biopsies from healthy subjects, although that particular study did not observe an increase in REE (121). An increase in the expression of mRNA for uncoupling protein (UCP) 3 in skeletal muscle, and fat has been reported after 4-month GH substitution in hypopituitary patients (122); the UCPs, which are assumed to be under sympathoadrenal control, act by uncoupling oxidative phosphorylation resulting in heat production without ATP generation. But it remains to be verified whether GH also influences the activity of UCPs. GH increases resting cardiac output (123) and blood flow in several organs, including skeletal muscle and kidneys (124, 125), all of which are likely to elevate REE.

B. Fasting, exercise, and stress

As outlined above GH secretion is amplified during fasting, exercise, and stress, and these catabolic conditions may be regarded as the natural domains for GH, in which the body benefits from the impact of GH on substrate metabolism. These conditions are all characterized by progressive fuel depletion, because of either reduced supply or increased demand.

1. Fasting. “However, one of the most salient characteristics of pituitary insufficiency is the tendency to hypoglycemia during fasting, which becomes manifest after a few hours” [Bernardo A. Houssay, 1936 (28)].

Classic observations by Cahill (126) have suggested that a normally proportioned 70-kg man stores 300–400 g glycogen (1500 cal), 6–7 kg mobilizable muscle protein (25,000 cal), and 10–15 kg triacylglycerol in adipose tissue (125,000 cal). With sustained fasting, the degree of glucose oxidation becomes rate limiting for protein degradation because amino acids are major substrates for gluconeogenesis. Therefore, maintenance of metabolic homeostasis becomes increasingly dependent on mobilization and utilization of FFA and ketone bodies (92, 127–129), and GH plays a central role in this process.

During fasting, GH is the only anabolic hormone to increase, whereas insulin and IGF-I levels decrease, and levels of catabolic hormones such as glucagons, epinephrine, and cortisol increase (130). Many studies using high-dose GH administration have shown that GH reduces serum urea concentrations and urea excretion (29, 30, 131), including conditions of dietary restriction (132) or a hyponitrogenous diet (133). The magnitude of this response is quite remarkable, and more recent studies aiming at physiologically appropriate GH levels during short-term fasting have reported 50% increases in urea-nitrogen excretion in normal subjects during GH suppression with somatostatin and in GHD subjects off GH therapy (134, 135) together with a 30–35% increase in [¹³C]urea production rate (136) (Fig. 9). Muscle protein breakdown increased by 25% among participants fasted without GH, and forearm phenylalanine release increased by 40%. The increase in whole-body protein loss secondary to GH deprivation was accounted for by a net reduction in protein synthesis. Furthermore, a significant decrease in branched-chain amino acid levels, consistent with decreased proteolysis, was seen during fasting with GH substitution (134, 136).

Studies in obese subjects have generated similar results. Obesity is associated with suppressed levels of circulating GH compared with normal-weight subjects (137). In the treatment of obesity with caloric restriction, protein loss presents a major therapeutic obstacle, and the concurrence of increased lipolysis and protein conservation observed during GH administration could make adjunct GH therapy a rational approach. The metabolic response to GH during prolonged fasting in obese subjects was first studied more than 30 yr ago by Felig et al. (138), who showed that high doses of GH induced a significant reduction in urinary urea excretion. It has also been shown that GH treatment in combination with a hypocaloric diet in 20 obese subjects resulted in a significantly more positive nitrogen balance, although the effect faded after 4–5 wk of GH treatment (139, 140). Finally, it has been reported that GH administration preserves LBM and protein stores and leads to a relative decrease of phenylalanine-to-tyrosine degradation in obese women during well-defined hypocaloric regimens for 4 wk (141).

Another central feature of GH during fasting is stimulation of lipolysis, although this effect may be partially masked by insulin. When insulin release is controlled with somatostatin, exogenous GH increases FFA levels during fasting (135), and palmitate concentrations and fluxes increase by approximately 50% (136). More importantly, when lipolysis is blocked with acipimox during fasting, urinary urea excretion
and muscle protein breakdown increase by approximately 50%, and the ability of GH to decrease urea formation and muscle protein breakdown is abrogated (142). These defects are to a large degree restored when intralipid is infused to raise FFA levels. As would be predicted, GH-induced lipolysis during fasting also leads to insulin resistance (77). On the other hand, Sakharova et al. (143) have shown recently that partial suppression of GH secretion with a GHRH receptor antagonist significantly reduces lipolysis but leaves glucose and protein metabolism unaffected during fasting.

In conclusion, fasting unmasks the marked ability of GH to preserve protein. When GH is lacking, protein loss and urea production rates increase by 50%. This is to a large extent due to a similar increase in muscle protein breakdown and appears to depend on the protein sparing effects of FFA and other lipid fuels. The concept of a central role of lipolysis and lipid intermediates is supported by a number of classic studies reporting protein conserving actions of FFA and ketone bodies (144–146).

2. Exercise. The role of GH and IGF-I in exercise and sport has been extensively reviewed recently (147, 148), and this review will not cover the potential effects of GH to improve athletic performance. Interestingly, it appears that exercise-induced GH release may depend upon increases in hypothalamic temperature (149, 150), and vice versa, that intact GH secretion/hypothalamicpituitary function seems to be a prerequisite for appropriate thermoregulation during exercise (151).

Only a few studies have addressed the acute physiological role of GH during exercise. When the normal physiological GH surge is mimicked in GHD subjects during 45 min at moderate intensity exercise, FFA fluxes during and after exercise increase, whereas glucose and amino acid metabolism are unaltered (152). There is also a significant correlation between the peak GH response to exercise and subsequent indices of lipolysis (153). Notably, recent studies in human subjects have recorded increased mitochondrial oxidative capacity and expression of mRNAs that encode mitochondrial proteins after GH exposure alone and in combination with exercise (121, 154).

The possible metabolic significance of repeated or prolonged GH bursts during repetitive exercise or during more prolonged and exhaustive exercise is largely unknown. Administration of very high doses of GH for 4 wk to trained athletes reduced leucine oxidation and increased leucine protein synthesis and FFA levels and lipolysis in the basal state and in the perieexercise period (155, 156). Other studies have shown that GH treatment increases lipolysis and FFA availability before and during exercise, but not necessarily FFA oxidation during exercise (157, 158). Studies in GHD subjects...
have also shown that withdrawal of GH for 3 months reduces glycerol and FFA (palmitate) release and utilization during exercise (159).

Thus, the major metabolic effect of GH during moderate exercise appears to be stimulation of lipolysis, whereas protein and glucose metabolism remain unaffected. When GH is administered in high doses for a long time, lipolysis prevails and protein oxidation decreases. Again, this is partially confounded by high levels of insulin, FFA, and IGF-I and changes in body composition and there is a need for studies addressing the more direct effects of GH during more prolonged exhaustive and/or repetitive exercise of high calorie-consuming caliber, in particular as regards protein metabolism.

3. Stress and critical illness. In the acute phase of severe critical illness, GH secretion is amplified, whereas protracted (less severe) critical illness suppresses GH release (160, 161). Knowledge about the role of GH under these different circumstances is very limited. A number of protocols have assessed the effects of adjuvant GH therapy during a variety of acute and chronic disease states, and in general these studies show that GH induces an acromegaly-like state characterized by 1) increased lipolysis and elevated FFA levels; 2) insulin resistance with elevated endogenous glucose production and decreased peripheral (muscle) glucose uptake; 3) protein preservation due to decreased oxidation; 4) elevated levels of IGF-I and insulin; and 5) increased LBM and decreased fat mass (162–166). When GH is administered to patients with HIV, an increase in muscle protein synthesis is observed, whereas muscle protein synthesis is decreased in patients with HIV-associated wasting, and this condition is an FDA-approved indication for GH treatment (167). It is of particular interest that GH reduces visceral and subcutaneous fat mass, whereas intermuscular fat deposition increases (163), although the mechanisms remain elusive.

When assessing all the studies using GH therapy in catabolic illness, it should be noted that the metabolic outcome depends heavily on the timing between GH administration and the subsequent metabolic investigations. When GH levels are high, the acute metabolic effects of GH will prevail, followed by waning of these direct GH effects and increasing effects of high IGF-I levels and decreased LBM.

Insulin resistance, lipotoxicity, and glucose toxicity raise particular concerns as regards both acute mortality and long-term cardiovascular disease. In the late 1990s, a large multicenter study including more than 500 patients in the acute phase of severe critical illness reported that high-dose GH treatment doubled mortality from 20 to 40% (168). The detrimental outcome was associated with significant elevations in blood glucose levels despite more than a doubling of insulin administration in the GH-treated group. Whether the dramatic increase in mortality related to insulin resistance and metabolic disarray, as suggested by the subsequent studies by van den Berghe et al. (169), showing beneficial effects of targeted insulin therapy, or perhaps also involved potential proinflammatory effects of GH remains uncertain.

As indicated above, in this section, there is a lack of controlled studies addressing the putative effects of “physiological” GH exposure during the chronic phase of critical illness. A large number of small and often uncontrolled studies have confirmed the ability of GH to conserve protein and LBM during catabolic illness. A large multicenter trial with GH treatment in adult patients with chronic renal insufficiency, with reduced mortality as a primary end point, is currently in progress. The fatal outcome of GH administration in patients with severe and acute critical illness emphasizes that any future studies with GH in catabolic patients must be very carefully targeted and rigorously monitored.

V. Insulin Sensitivity and Diabetes

“It is tempting to seek a unified explanation in which the hyperglycemia as well as ketosis is related to the increased mobilization and use of fat that occurs with GH” (274).

Acute and chronic GH exposure induces insulin resistance in terms of increased endogenous glucose production and decreased peripheral glucose disposal in muscle (166, 170). These effects appear to be largely secondary to stimulation of lipolysis and subsequent glucose-fatty acid substrate competition (76, 79, 171). The existence of the glucose-fatty acid cycle was proposed in 1963 by Randle et al. (6), who suggested that increased FFA oxidation inhibits insulin-stimulated glucose uptake in muscle because of intracellular accumulation of citrate and glucose-6-phosphate. This substrate competition hypothesis was later expanded by Shulman and colleagues (172), who showed a decrease in intracellular glucose and glucose-6-phosphate after FFA exposure and suggested that accumulation of lipid metabolites (e.g., fatty acyl CoA and diacylglycerol) initiates a cascade, which inhibits PI 3-kinase activity and translocation of the GLUT-4 glucose transporter to the cell surface (173-175). Not all studies have supported this concept, and there is no evidence in humans that the insulin antagonistic actions of GH involve inhibition of the PI 3-kinase pathway (52). Furthermore, it is also likely that GH possesses FFA-independent actions to induce insulin sensitivity because acute GH exposure generates insulin resistance before elevations of FFA in the circulation (170).

Patients with type 1 diabetes exhibit elevated and fluctuating GH levels, in particular when poorly controlled (176); it has been estimated that poorly controlled patients [glycosylated hemoglobin (HbA1c) >12%] are characterized by 2- to 3-fold elevated GH levels with a secretory pattern similar to fasting in normal subjects (177). At the same time, serum IGF-I levels are reduced in poorly controlled patients (178), which may be caused by a combination of a negative nitrogen balance and low portal insulin levels (179, 180). It is, in turn, likely that the low IGF-I levels cause or contribute to the increased GH secretion via classic feedback mechanisms.

Hypoglycemia remains an inevitable counterpart to treatment of diabetes, and intact GH secretion is important in combating hypoglycemia (181, 182). This is particularly so in patients with autonomic failure and inadequate glucagon and epinephrine responses to hypoglycemia (183). In patients with appropriately controlled diabetes, GH may be considered as a physiological modulator of metabolic homeostasis (184). These findings, which are very similar to observations in normal man, suggest that in well-insulinized...
diabetic subjects, modest amounts of GH may serve as a beneficial metabolic regulator working to preserve carbohydrate and protein at the cost of lipid consumption. In further support of this, low-dose GH replacement therapy for 6 months in hypopituitary patients with type 1 diabetes decreases asymptomatic hypoglycemic attacks in the presence of increased (normalized) insulin dosage requirements and unaltered glycemic control (185).

It is, however, equally well documented that GH hypersecretion worsens metabolic control in type 1 diabetes (186). In these experiments, it was clearly shown that administration of hourly 100-μg GH pulses after a latency of several hours induced dramatic 100% increases in circulating glucose values, together with marked increments in circulating lipid fuels.

Lowering of GH levels, in turn, by means of infusion of IGF-I in combination with IGFBP-3 for 2 wk in patients with type 1 diabetes in average control (mean HbA1c, 8.6%) has been shown to reduce blood glucose levels as well as insulin requirements without causing hypoglycemia (187). Whether circulating free IGF-I levels in the physiological range also improves insulin action or sensitivity via GH-independent mechanisms remains uncertain.

The effects of GH on insulin sensitivity in healthy subjects have been assessed in some detail. Reports from the early 1980s repeatedly demonstrated that continuous infusion of 1.5-mg GH impaired both hepatic and peripheral insulin sensitivity of normal man after 12 h (188, 189). A subsequent study using smaller doses of GH and insulin showed that: 1) GH impairs hepatic and peripheral insulin sensitivity after approximately 2 h; 2) the impairment of peripheral insulin sensitivity largely resides in muscle; and 3) GH has the potency to offset the antilipolytic properties of light hyperinsulinemia (170). There is also evidence to suggest that GH diminishes both insulin- and glucose-dependent glucose disposal (190). Fowelin et al. (191) in a thorough design observed precipitation of insulin resistance after 2 h of GH exposure, maximal effect on glucose metabolism after 5–6 h, and waning of this effect after 6–7 h in a dose-dependent manner after semipulsatile exposure to GH doses between 0.2 and 0.5 mg in healthy subjects. It has been reported that GH exposure blunts the activity of glycogen synthase in striated muscle (115).

In the course of diabetic ketoacidosis, circulating GH concentrations are inappropriately elevated (192), which worsens the pronounced insulin resistance of this state and may aggravate the life-threatening ketosis (193). Nocturnal surges of GH have been implicated in the pathogenesis of the so-called “dawn phenomenon,” i.e., an increase in the insulin requirements in the early morning hours (194, 195), although the concept has been challenged (196). This challenge has received support from a study failing to detect any effect of nocturnal GH surges on morning insulin sensitivity (197). Conversely, Van Cauter et al. (198) have reported that sleep-induced increments in glucose concentrations correlated strongly with the magnitude of GH secretion, in particular when normal nocturnal sleep and circadian rhythmicity were preserved. If indeed involved, GH therefore seems to act as a permissive factor rather than a prime generator of the dawn phenomenon; as pointed out by Clore, Blackard, and co-workers (196, 199), it is credible that increased early morning insulin requirements may predominantly be explained by transient sleep-correlated decrements in glucose appearance and disposal, as well as diminished insulin demands, and a subsequent normalization of these parameters at arousal waning of insulin action from precedent meals may also be involved.

Adding to the lack of clarity in the field, it has been reported that administration of very low GH doses may actually improve insulin sensitivity in GHD subjects (200). This could relate to the fact that when low doses of GH are administered long before metabolic assessment, the direct insulin antagonistic actions of GH have waned and the insulin agonistic effects of IGF-I and increased LBM prevail.

On the whole, it is beyond doubt that GH may contribute significantly to the overall insulin resistance in type 1 diabetes and also acts as an initiator of the vicious circles leading to acute metabolic derangement. It is also likely that GH plays a permissive role in the pathogenesis of the dawn phenomenon. As in other stress states, GH plays a beneficial role in the protection against hypoglycemia.

VI. GH-Deficient Patients

A. Untreated GH deficiency

Fasting hypoglycemia is a frequent occurrence in GH-naive children with isolated GH deficiency (201). The propensity to hypoglycemia is related to young age (<4 yr) and a lean body composition. Moreover, GHD children with symptomatic hypoglycemia exhibit lower elevations in both glucose and insulin during exposure to oral glucose and iv arginine, respectively. Finally, GHD children are hyperresponsive to insulin, including a delayed recovery from hypoglycemia in response to iv insulin. Based on assessment of glucose turnover rates, fasting hypoglycemia in GHD children is attributable to decreased hepatic glucose production (HGP) rather than an increase in peripheral glucose uptake (202). It was therefore somewhat unexpected when Beshyah et al. (203) observed an increased prevalence of abnormal/impaired glucose tolerance despite compensatory hyperinsulinemia among GHD children with normal or increased LBM. This could relate to the fact that when low doses of GH actually improve insulin sensitivity in GHD subjects (200). This could relate to the fact that when low doses of GH are administered long before metabolic assessment, the direct insulin antagonistic actions of GH have waned and the insulin agonistic effects of IGF-I and increased LBM prevail.

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On the whole, it is beyond doubt that GH may contribute significantly to the overall insulin resistance in type 1 diabetes and also acts as an initiator of the vicious circles leading to acute metabolic derangement. It is also likely that GH plays a permissive role in the pathogenesis of the dawn phenomenon. As in other stress states, GH plays a beneficial role in the protection against hypoglycemia.
likely that additional pituitary deficits and/or lifestyle factors (e.g., a more sedentary lifestyle) contribute to insulin resistance in these patients.

B. Effects of GH replacement

In a study of adolescent GHD patients on GH replacement therapy, the impact of replacing one daily (evening) injection with a 10-h iv infusion of either saline or GH in a low dose (35 μg/h), starting the evening before the study, was investigated (116). Continued GH infusion was associated with reduced basal rates of glucose oxidation and reciprocal changes in lipid oxidation. Insulin sensitivity was increased relative to control subjects during saline infusion and became reduced during GH infusion to a level comparable to the control group (Fig. 10). Fowelin et al. (207) studied insulin sensitivity and glucose metabolism in GHDA in a double-blind, placebo-controlled crossover trial including assessments at baseline and after 6 and 26 wk of GH treatment, respectively. Fasting plasma levels of glucose and insulin increased after 6 wk of GH but returned toward baseline values after 26 wk. A significant 35% decrease in the glucose infusion rate (GIR) during the clamp was recorded after 6-wk GH treatment. After 26 wk, GIR was decreased with 25%, a difference no longer significantly different. In an open design, O’Neal et al. (208) studied 10 patients with adult-onset disease after 1 wk and 3 months of GH replacement (~1.2 mg/d), respectively. Based on frequent sampling of arterialized blood for 180 min after an iv glucose load, several indices of insulin kinetics and sensitivity were calculated. Fasting plasma levels of glucose increased after 1 wk but normalized after 3 months. This was associated with sustained elevations in fasting insulin levels and unaltered HbA1c levels. In addition, insulin sensitivity decreased significantly in concomitance with a reciprocal rise in FFA levels after 1 wk of GH. By 3 months, most parameters had returned to pretreatment levels, apart from modest hyperinsulinemia. Of note, the patients at baseline were insulin resistant compared with a healthy, normal-weight reference group (208). In a placebo-controlled study using a similar GH dose in adult-onset GHDA, 4-month GH treatment was associated with sustained insulin resistance calculated from an iv glucose tolerance test (209). Moreover, the so-called disposition index, which is the product of the first phase insulin response and insulin sensitivity, was reduced after GH treatment, indicating that the insulin response was not sufficiently increased to compensate for the reduction in insulin sensitivity (209). This contrasts with O’Neal et al. (208), who recorded an unchanged disposition index after 3 months of GH. A number of studies have assessed insulin sensitivity or glucose tolerance before and after 6 months of GH replacement in a parallel, placebo-controlled design followed by an open phase of additional GH treatment for up to 12 months (210–212). An increase in fasting insulin levels was recorded after 6 months in two studies (210, 212), which in one case was associated with a small increase in fasting plasma glucose levels (212). Beşyah et al. (210) documented elevated glucose and insulin levels during an oral glucose tolerance test (OGTT) when comparing baseline data with those after 6 months of GH, whereas Weaver et al. (212) used homeostatic model assessment and an iv glucose infusion to demonstrate impaired insulin sensitivity and an increase in first phase insulin secretion. Hwu et al. (211), who used a so-called modified insulin suppression test to assess insulin sensitivity, observed that GHD patients exhibited insulin resistance at baseline compared with a healthy reference group, whereas fasting plasma glucose levels remained stable (211). During prolonged open GH treatment, the impairment of insulin sensitivity and glucose tolerance prevailed (210, 212), with the exception of the study by Hwu et al. (211) in which insulin sensitivity improved and became normalized. In an open design including 10 young patients with childhood-onset GHD, 9-month GH replacement in a final daily dose of approximately 0.5 mg, glucose homeostasis assessed by fasting glucose and insulin levels, an OGTT, and an iv glucose tolerance test remained unchanged and apparently within the range of normality (213). Christopher et al. (214) reported sustained peripheral—but not hepatic—inulin resistance in 11 patients treated with GH (~0.7 mg/d) for 24 months in an open design. Based on measurements of total glucose levels and glucose 6-phosphate content in muscle biopsies, the au-

Fig. 10. Effects of continuation vs. discontinuation of evening GH replacement in adolescent GHD patients on basal rates of lipid oxidation (bottom left), protein oxidation (top left), and hepatic and peripheral insulin sensitivity (right). Lipid oxidation estimated by indirect calorimetry; protein oxidation estimated from urinary urea excretion; insulin sensitivity estimated by a euglycemic clamp in combination with a glucose tracer infusion. A group of healthy, age- and sex-matched subjects were studied once without treatment. EE, Energy expenditure; EGP, endogenous glucose production. [Adapted from Ref. 116 with permission from The Endocrine Society].
thors hypothesized that a prime defect in glucose disposal at the level of glucose phosphorylation exists in GHD patients both before and after GH therapy (214). Impairment of glucose tolerance and moderate insulin resistance in combination with increased secretion and clearance of insulin were also recorded after 30 months of GH substitution ($\approx 0.5$ mg/d) in an open trial (215). Of note, the insulin disposition index was not reduced after GH treatment for 30 months, which contrasts with the short-term study from the same group (209).

Data from two observational studies lasting 4 and 5 yr reported normalization of glucose tolerance (216) and insulin sensitivity (217), respectively. Euglycemic glucose clamps in combination with glucose tracer infusions were performed in 11 GHDA at baseline and subsequently after 6 months and 1, 2, and 7 yr of GH replacement (218). The daily GH dose was gradually lowered from approximately 1 mg to approximately 0.6 mg during the study period. Fasting blood glucose levels were transiently increased during the first year of treatment, whereas fasting (morning) levels of insulin and FFA remained completely stable (218). Basal hepatic glucose output remained increased after GH replacement, whereas insulin sensitivity (assessed by a glucose clamp) decreased significantly during the first year with a nadir at 6 months. After 7 yr, insulin sensitivity was comparable to baseline levels (218). Compared with healthy individuals, insulin sensitivity was lower in the patients both at baseline and at the end of the study period, with a trend ($P = 0.06$) toward a relative improvement in insulin sensitivity after 7 yr (218). A subsequent, quasi-controlled study of 10 yr GH replacement in adult-onset patients did not detect changes in fasting levels of glucose, insulin, or C-peptide (219). There is no evidence to suggest that GH replacement therapy is associated with increased urinary albumin excretion or retinal changes (220, 221).

The impact of discontinuing GH replacement after completion of longitudinal growth on body composition and glucose homeostasis has been addressed in a number of trials (222–224). Johannsson et al. (222) followed 40 adolescent patients for 2 yr after discontinuation of GH replacement, compared with 16 closely matched healthy controls. Based on renewed testing, the patients were classified as either severely GHD ($n = 21$) or GH sufficient ($n = 19$). Fasting blood glucose levels were in the normal range and did not change in either group during the 2 yr, whereas the levels of HbA1c and fasting insulin decreased slightly, but significantly, in both patient groups (222). Norrelund et al. (223) evaluated insulin sensitivity (euglycemic glucose clamp) and substrate metabolism in 18 adolescent patients with reconfirmed GH deficiency in a placebo-controlled, parallel study. The patients were randomized to either continued GH replacement or placebo for 12 months, followed by 12 months of open-labeled GH therapy in both groups. In the group that continued GH therapy, no significant changes were recorded in insulin sensitivity. By contrast, placebo treatment was accompanied by increased insulin sensitivity despite a concomitant increase in fat mass (Fig. 11). After resumption of GH treatment in that group, fat mass decreased together with insulin sensitivity (223). In an open design, Carroll et al. (224) followed 24 adolescents with reconfirmed GH deficiency for 12 months, during which 12 patients remained on GH and 12 patients ceased GH replacement. Cessation of GH resulted in increased insulin sensitivity, but no significant change was seen during 12 months of GH continuation (224).

The ability of GH replacement to increase LBM is well documented (225, 226), whereas relatively few studies have investigated the underlying changes in protein metabolism. The rates of whole body proteolysis, oxidation, and synthesis by means of leucine kinetics have been assessed after 1, 2, 8, and 26 wk of low-dose GH replacement ($\approx 0.25–0.45$ mg/d) in adult patients (227–229). In all studies, the turnover rates of leucine remained unchanged, whereas protein synthesis increased at the expense of oxidation. Shi et al. (229) also included measurements in the fed state during which the

![Fig. 11. Effects of discontinuation of GH replacement therapy for 1 yr in GHD patients in the transition phase from childhood to adulthood on total body fat and insulin sensitivity. The patients were studied at baseline on GH therapy (black bar), after 1 yr of placebo treatment (gray bar), and subsequently after 1 yr of resumed GH replacement (white bar). Total body fat was measured by dual-energy x-ray absorptiometry, and insulin sensitivity was measured by a euglycemic clamp. (Adapted from Ref. 223 with permission from The Endocrine Society).](https://academic.oup.com/edrv/article-abstract/30/2/152/2355062)
protein anabolic effects recorded after 2 wk were not main-
tained after 6 months. In two other studies of protein ki-
netics in the fed state, improved protein balances were
observed after 1 and 2 months of GH replacement, re-
spectively (230, 231). In support of the significance of
substrate availability for the protein-conserving effects of
GH replacement, Norrelund et al. (134, 136) observed that
continued GH replacement during 40 h of fasting was
associated with increased protein synthesis (134) and re-
duced protein loss (136) in concomitance with increased
lipid oxidation.

C. Conclusion

Hallmarks of adult-onset GH deficiency include visceral
obesity, reduced LBM, and impaired physical fitness, which
may result from a combination of prolonged GH deficiency,
**i.e.**, lack of the lipolytic and protein anabolic effects, and the
underlying disease and its treatment, all of which translates
into a state resembling the metabolic syndrome.

Impairment of glucose tolerance as well as insulin sensi-
tivity after GH substitution is almost unanimously reported
(Fig. 12), and these effects seem to correlate positively with
GH dosage and inversely with duration of therapy, although
the individual impact of the two factors is difficult to isolate
because the dosage in most studies is reduced with time.
Experimental studies suggest that FFA play a causal role in
the development of insulin resistance associated with GH
substitution by demonstrating that coadministration of acipi-
mox is able to restore insulin sensitivity (Fig. 13) (76). More
recently, it has also been recorded that administration of a
peroxisome-proliferator-activated receptor **γ** agonist im-
proves insulin sensitivity in GH-treated GHDA (232). The
explanation why insulin sensitivity and glucose tolerance
**tend to improve or normalize during prolonged GH substi-
tution is not proven, but it is noteworthy that the protein-conserving
actions seem to prevail in the fed state and become ac-
centuated during fasting where lipid oxidation is concom-
antly stimulated.

VII. Acromegaly before and after Treatment

Hyperinsulinemia, impaired glucose tolerance, and overt
diabetes mellitus are common features of active acromegaly
(233, 234), and it is likely, albeit not formally demonstrated,
that these abnormalities contribute to the observed increase
in cardiovascular morbidity and mortality (235, 236). This
section will deal mainly with studies focusing on glucose
tolerance and insulin sensitivity in acromegaly before and
after surgery and medical treatment.

Elevated basal HGP, together with hepatic and peripheral
resistance to insulin stimulation and increased glucose cy-
cling, was recorded in a study employing infusion of differ-
ent glucose tracers in the basal state and during an OGTT
(93). Hansen et al. (237) established insulin dose-response
curves for stimulation of glucose uptake and suppression of
HGP by means of glucose tracer infusion in combination
with euglycemic glucose clamps with graded infusion rates
of insulin. Basal hyperinsulinemia but normal glucose levels
were recorded in the patients (**n** = 5) compared with control
subjects (**n** = 6) together with elevated HGP. The GIRs dur-
ing the clamps were significantly lower in the patients at any
insulin infusion rate, which was accompanied by elevated
HGP at the two lower insulin infusion rates (237). Insulin
resistance in skeletal muscle in terms of reduced nonoxida-
tive glucose disposal has also been documented with the
forearm technique in combination with indirect calorimetry
(238). Moller et al. (166) studied substrate metabolism and
insulin sensitivity in newly diagnosed acromegalic patients
before and several months after successful transsphenoidal
surgery. In the basal state, plasma levels of insulin and glu-
cose were significantly elevated before surgery and became

![FIG. 12. Results of meta-analysis of GH effects on cardiovascular risk factors. [Reproduced from Ref. 226 with permission from The Endocrine Society.](https://academic.oup.com/edrv/article-abstract/30/2/152/2355062)
normalized afterward. This was associated with reduced forearm uptake of glucose and increased hepatic glucose output. The GIR during a subsequent clamp was abnormally low in active acromegaly and became normalized with surgery (Fig. 14). Comparative results were reported in a study involving 23 patients who underwent an OGTT before and after transsphenoidal (239). Kasayama et al. (240) evaluated glucose tolerance and insulin sensitivity (homeostatic model assessment) in 24 acromegalic patients before and after surgery compared with healthy control subjects. Insulin sensitivity was decreased preoperatively and became normalized in the patients, who were considered cured by surgery (46%) (240). A relationship between biochemical markers of disease activity and glucose homeostasis after surgery is also evident from other studies (235, 241). Serri et al. (241) subdivided 53 of such patients. The criterion for “remission” was a normal IGF-I level for age, which was obtained in 34 patients. A significantly higher prevalence of abnormal glucose tolerance was observed in patients with “active” disease (57.9 vs. 20.6%). A normal postoperative serum IGF-I value, rather than GH status, was more predictive of insulin sensitivity in another study involving 66 patients (235). Insulin sensitivity among the 41 patients with normal postoperative IGF-I levels with (n/11005 21) or without (n/11005 20) normal nadir GH levels (cutoff, 0.14 μg/liter) did not differ from healthy control subjects and was significantly higher compared with patients with active disease (n = 25).

A discussion of treatment algorithms and biochemical definitions of disease activity for acromegaly has been the subject for several consensus statements and is not within the scope of this review (235, 242–247). It is reasonable to state that transsphenoidal surgery is the first choice of treatment, but this procedure is not always feasible, and it offers acceptable disease control in no more than 60% of cases. The use of radiation therapy varies between centers and countries, and data on its impact on glucose metabolism are lacking. Medical therapy is frequently used in patients with persistent disease after surgery and less frequently as primary treatment.

Dopamine agonists such as bromocriptine and cabergoline have been used in the management of acromegaly for many years. Cabergoline appears to be superior to bromocriptine (248), but disease control is rarely obtained, and data on the impact of dopamine agonists on glucose homeostasis are lacking. Medical therapy is frequently used in patients with persistent disease after surgery and less frequently as primary treatment.

Octreotide, a somatostatin analog with a prolonged half-life relative to native somatostatin, was introduced for the treatment of acromegaly more than 20 yr ago. The impact of
somatostatin analogs on glucose metabolism is difficult to predict a priori due to their suppressive effects on the secretion of insulin (250) and glucagon (251). Moreover, somatostatin delays gastrointestinal glucose absorption (252, 253), reduces the clearance of insulin (254), and may also improve insulin-stimulated muscle glucose uptake via direct effects (255). The initial formulation of octreotide was administered as sc injections thrice daily, which in most patients resulted in wide circadian fluctuations in serum GH levels with nadir values obtained 2–3 h after each injection, followed by a rebound increase after 4–6 h. Ho et al. (256) investigated the impact of this treatment schedule on glucose tolerance and insulin sensitivity in seven patients who were studied before and after 7–14 months of octreotide with a final dose of 500 µg three times a day, but with octreotide administration being omitted on the days of investigations. Glucose tolerance did not change significantly although insulin levels tended to be lower after treatment. During a glucose clamp, octreotide treatment was associated with an increase in GIR, which however remained lower compared with healthy subjects (256); glucose tracer data indicated that octreotide predominantly acted to suppress HGP during the clamp (256). Koop et al. (257) measured glucose tolerance in 90 patients on thrice daily octreotide from 10 different centers in a design where the morning octreotide dose apparently was maintained. Bidirectional changes in glucose tolerance between patients were observed, but on average a moderate impairment occurred in conjunction with a reduction in insulin secretion (257).

Depot preparations of somatostatin analogs, which are administered every 2–4 wk and provide sustained and stable reductions in circadian GH levels, have been available for more than 10 yr and are now preferred by most clinicians (258). Based on routine assessments, this treatment is traditionally not considered to be associated with major deterioration in glucose homeostasis (258). Measurements of insulin sensitivity by a euglycemic glucose clamp and glucose oxidation during a hyperinsulinemic clamp in untreated acromegaly (259) increased in patients who were partially resistant to somatostatin analogs (263), and this is associated with a reduction in fasting plasma glucose concentrations (264) and HbA1c levels (265, 266).

The beneficial effects of pegvisomant on glucose metabolism seem to involve improvement of glucose tolerance (267) as well as insulin sensitivity (268, 269). There are also data to indicate that glucose tolerance improves in patients partially resistant to somatostatin analogs if that treatment is combined with pegvisomant (267, 270). In an interesting pilot study, O’Connell and Clemmons (271) added the administration of IGF-I plus IGFBP-3 to ongoing pegvisomant treatment in five patients with acromegaly, which resulted in a further improvement of insulin sensitivity. This finding suggests direct insulin-sensitizing effects of IGF-I at least in this experimental setting.

Patients with active acromegaly are characterized by increased levels of FFA and other lipid intermediates together with markedly increased lipid oxidation rates (166). This occurs despite compensatory hyperinsulinemia (166) and substantial changes of body composition, including a decreased fat mass (163), an increased LBM (272), and increased total and extracellular body water (273). Data on protein metabolism in acromegaly are sparse. It has recently been reported that acromegalic patients have a high turnover state with increased leucine rate of appearance (protein breakdown) and a high nonoxidative leucine disposal (protein synthesis) (164). Another study comparing acromegalic patients with surgically cured patients and healthy controls reported normal basal leucine kinetics, but decreased leucine oxidation during a hyperinsulinemic clamp in untreated acromegaly (162). Again, one has to consider the changes in body composition when interpreting these data.

A. Conclusion

Active acromegaly is associated with glucose intolerance despite compensatory hyperinsulinemia, and hepatic as well
as peripheral insulin resistance, and it is likely that these aberrations contribute to the excess mortality. These abnormalities are reversible after successful surgery, which is achieved in approximately 60% of cases. Medical treatment with slow-release formulations of somatostatin analogs is preferred when surgery fails and in some cases also as primary treatment. The net effect on glucose metabolism seems to be a moderate impairment of glucose tolerance, which is not fully compensated by the improvement of insulin sensitivity. Whether this bears any clinical significance remains uncertain. Pegvisomant, which is a GH antagonist, has proven very effective for the treatment of acromegaly because it normalizes IGF-I levels and induces symptom relief in up to 90%. Moreover, pegvisomant treatment seems to improve glucose tolerance as well as insulin sensitivity in most patients.

VIII. Summary and Conclusions

“The growth of tissues in elderly acromegalic patients indicates the continued responsiveness to GH long after full height has been reached.”

The quotation above is one of several statements by Raben in a seminal review of GH published more than 45 yr ago (274, 275). The same paper included considerations about potential indications for GH in addition to “pituitary dwarfism,” e.g., other conditions of short stature in children, GH deficiency in adults, and catabolic states.

Shortly thereafter, the revolutionary development of RIA disclosed the secretory pattern of multiple hormones including GH and insulin. Zierler and Rabinowitz (34) combined this information with metabolic data and proposed the hypothesis of “a metabolic regulating device based on the actions of human GH and of insulin, singly and together, on the human forearm.” According to this, substrate metabolism cycles between feast and famine in three phases. In the immediate postprandial period (phase I), insulin acts alone to promote storage of glucose and fat. In the remote postabsorptive period (phase II), GH acts alone to mobilize FFA. In the intermediate period (phase II), insulin and GH act in synergy, possibly to stimulate protein synthesis. It is tempting to add that untoward effects are to be expected when this pattern is perturbed. Notwithstanding its simplicity, we believe that this model has stood the test of time.

The prolific era of molecular biology led to the identification and cloning of GH and its receptor and, not least, GH signaling. The receptor belongs to the cytokine family, which implies that many of the signaling pathways of GH are shared by, e.g., several IL, erythropoietin, leptin, and prolactin. Most of the data stem from studies in transfected cell lines and rodent models, but it is also established that the JAK/STAT pathway is critical for promoting the effects of GH on longitudinal growth in children. Major areas for the future would be a closer understanding of how specificity is conveyed at the level of cytokine receptor signaling, including the mechanisms whereby GH promotes its impact on substrate metabolism. It has recently been documented that exposure to endogenous as well as exogenous GH rapidly translates into GH signaling events in muscle and fat in human subjects. Moreover, with this model it has so far not been possible to replicate data obtained in rodents which indicate that GH causes insulin resistance in muscle by interference with insulin signaling, in particular IRS-1-associated PI 3-kinase activity. Whether this discrepancy is based on methodological issues or species-specific differences remains to be investigated, but the human model seems to provide a viable tool for translational research in GH signaling. This could have important implications for understanding not only GH physiology and pathophysiology, but also prevalent clinical conditions associated with insulin resistance.

The manufacture of biosynthetic human GH has been another important breakthrough within the last 20 yr. The abundant supply of the authentic hormone prompted a very large number of therapeutic and experimental trials, in particular in adult hypopituitary patients with GH deficiency. As a result of this, replacement therapy with GH in these patients has been a licensed indication for more than 10 yr, although the penetration of the treatment differs considerably between countries. At any rate, the studies in GHDA have provided substantial data regarding the metabolic effects of GH in adulthood. Long-standing GHDA is associated with insulin resistance, which probably is related to increased abdominal adiposity, reduced LBM, and impaired aerobic exercise capacity. Replacement therapy, in turn, normalizes body composition and improves physical function. Despite these effects, GH may further impair insulin sensitivity. This is not surprising when considering that daily sc administration of GH is unable to mimic the endogenous pattern resulting from pituitary GH release, which allows insulin to act independently due to postprandial suppression of GH. With more prolonged GH therapy, the favorable effects on body composition may offset the direct insulin antagonistic effects, in particular if attention is paid to avoid overdosing. Insulin resistance as a side effect to GH administration is no less surprising than the risk of hypoglycemia with insulin therapy.

Studies of a more experimental nature with GH in GHDA have also provided new insight into the mechanisms underlying the metabolic effects such as the close link between the lipolytic effects and the resistance to insulin-induced glucose disposal in muscle, and the important protein-conserving effect of GH during fasting. Moreover, studies in GHDA have generated novel data on the impact of GH on features such as cardiac function, bone metabolism, lipoprotein metabolism, thyroid hormones, and regional glucocorticoid interconversion, most of which has been beyond the scope of this review.

Due to its anabolic and lipolytic properties, GH has also been administered in different catabolic states such as the frail elderly with sarcopenia and obese patients undergoing caloric restriction. At the present stage, it is important to emphasize that metaanalyses of published data do not justify GH as either an antiaging treatment (276) or as adjunct treatment in obesity (277). Whether GH in lower doses and/or in combination with other protein anabolic substances such as androgens (278) could have a role in chronic catabolic conditions is an open question which needs more placebo-controlled trials to be answered. So-called rejuvenation of GH secretion in the elderly by means of GH secretagogues has
also been evaluated, including a recent long-term trial (279, 280), and it does again remain a possibility that some in this age group could benefit from more sophisticated anabolic regimens, e.g., with low-dose GH usage.

GH treatment in HIV-associated wasting has been shown in several randomized controlled trials to increase LBM and body weight and to improve physical endurance and quality of life, and GH is a Food and Drug Administration-approved indication for this condition. It remains to be further investigated whether GH treatment also may cause a sustainable beneficial effect on HIV-associated lipodystrophy. Elevation of blood glucose levels is a frequent side effect of GH also in these patients. The fatal outcome of trials involving patients with acute critical illness as well as the serious complications of acromegaly underscore more than anything that GH treatment outside of the approved indications should not be based on wishful thinking, but rather be confined to appropriately controlled and rigorously monitored trials. Having said this, a worthy subject for future research would be to dissect whether the detrimental effects of GH in acute critical illness are due to metabolic aberrations or hitherto unrecognized proinflammatory actions.

Medical treatment of acromegaly is another area that has undergone major improvements and also provided further insight into the metabolic effects of GH. Treatment with slow-release formulations of somatostatin analogs is well established and provides symptom relief, disease control, and tumor shrinkage in a large proportion of patients. It does, however, also cause a mild impairment of glucose tolerance, in many cases owing to the fact that its suppressive effect on insulin secretion is not always fully balanced by the concomitant improvement of insulin sensitivity. The GHR antagonist, pegvisomant, seems to provide a more complete suppression GH bioactivity, which also includes reversal of glucose intolerance and insulin resistance. Indeed, this compound may even induce functional GH deficiency in patients with acromegaly. Data generated so far suggest that cotreatment with somatostatin analogs and pegvisomant may offer a favorable combination of tumor control and peripheral blockade. Moreover, pegvisomant is an interesting experimental tool for studying the metabolic actions of GH in other conditions.

Future vistas of research related to the metabolic effects of GH are multiple, and not all of them have been addressed in this review. The discovery of ghrelin as an endogenous ligand for the so-called GH secretagogue receptor is one example. This gut-derived peptide is not only a potent stimulator of GH release when administered exogenously, but it also possesses independent effects on substrate metabolism and appetite regulation, which are just beginning to be unveiled. Moreover, it remains to be assessed to what degree endogenous gut-derived ghrelin drives GH secretion. Another white spot on the map is the role of GH as a fat-burning cytokine in the regulation of adipokines and myokines, which may have implications for the understanding of fundamental conditions such as obesity, cardiovascular disease, and aging processes. A third example could be to dissect the contribution of circulating and local IGF-I to the metabolic actions of GH, which may be achieved by continued work with genetically manipulated mice models in combination with renewed research with IGF-I administration—in combination with IGFBPs and/or GH—in human subjects.

Exciting progress within the research of the regulation and function of the GH-IGF-I axis during life span continues to be made, and surprises are hopefully ahead. But data so far confirm the statement by Bernardo A. Houssay in 1936 (28), that “growth, endocrine regulation (including the reproductive functions), and metabolic regulation form the functional trinity of the anterior pituitary gland.”

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