0163-769X/09/$20.00/0
Printed in U.S.A.

Endocrine Reviews 30(2):152–177

doi: 10.1210/er.2008-0027

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

Niels Møller and Jens Otto Lunde Jørgensen

Medical Department M, Aarhus University Hospital, and Clinical Institute, Aarhus University, DK-8000 Aarhus, Denmark

In evolutionary terms, GH and intracellular STAT 5 signaling is a very old regulatory system. Whereas insulin dominates periprandially, 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)

First Published Online February 24, 2009

Abbreviations: FFA, Free fatty acid(s); GHD, GH-deficient; GHDA, GHD adults; GHR, GH receptor; GIR, glucose infusion rate; HbA1c, glycosylated hemoglobin; HGP, hepatic glucose production; HSL, hormone-sensitive lipase; IGFBP, IGF binding protein; IRS, insulin receptor substrate; JAK, Janus kinase; LBM, lean body mass; LPL, lipoprotein lipase; OGTT, oral glucose tolerance test; PI 3-kinase, phosphoinositol 3-kinase; PKB, protein kinase B; REE, resting energy expenditure; SOCS, suppressors of cytokine signaling; STAT, signal transducers and activators of transcription; UCP, uncoupling protein.

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

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 β-cell proliferation, insulin 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

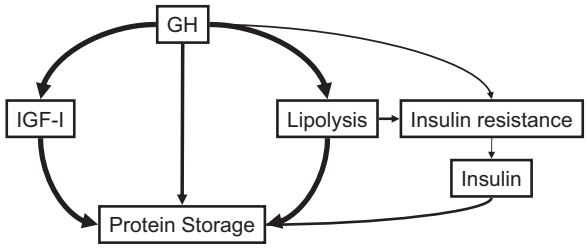


FIG. 1. Schematic presentation of the metabolic actions of GH with emphasis on the direct stimulation of lipolysis and the more indirect preservation of protein. These two actions are the most important, and particularly so under conditions of food deficiency and stress. Protein storage occurs through inhibition of protein breakdown and stimulation of protein synthesis in muscle and other tissues and through inhibition of amino acid degradation/ureagenesis in liver.

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 inflicted 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,

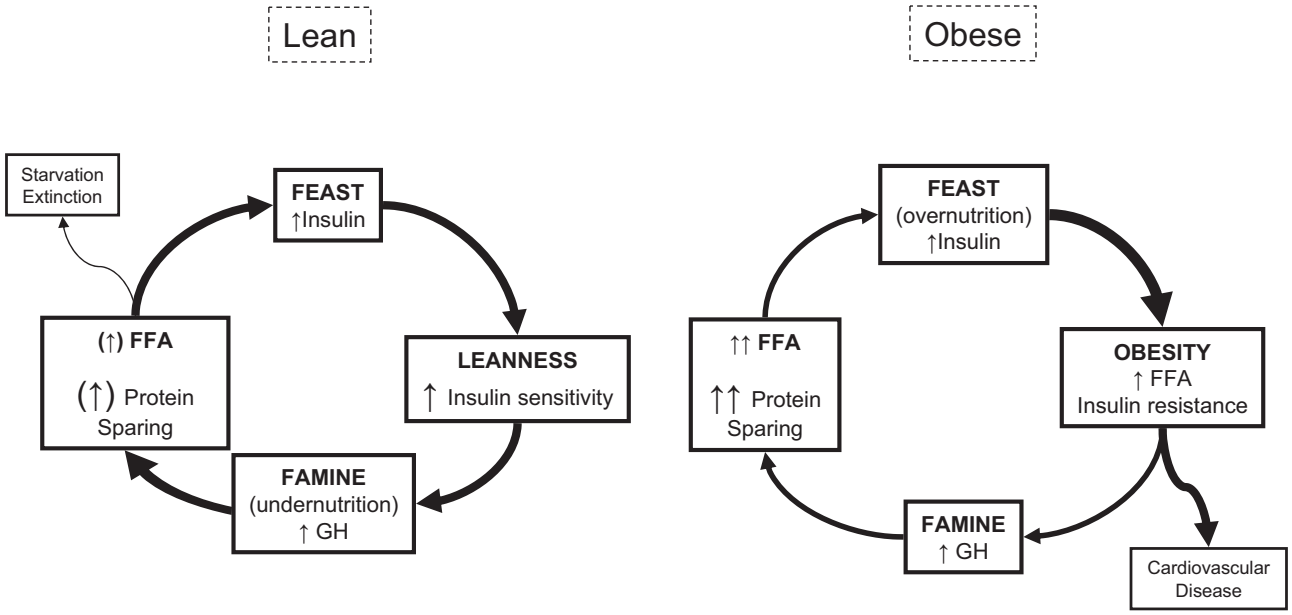


FIG. 2. Schematic integration of the "feast and famine cycle" by Rabinowitz and Zierler, the "thrifty genotype hypothesis" by Neel, and the "glucose-fatty acid cycle" by Randle in the obese and in the lean phenotype. GH is the principal anabolic hormone during food restriction and stress, and insulin is the principal anabolic hormone during food excess. People with the lean phenotype are exposed to and threatened by hunger, and obese people by cardiovascular disease. FFA play a dual role in promoting insulin resistance during feast and preserving protein during famine.

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/IGF-I axis at puberty is causally linked to the concomitant 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 (LBM), 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 sc 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 hyperinsulinemia on whole body and muscle protein metabolism in humans and in a pig model (37, 38).

III. Growth Hormone Signaling in Human Models

GHR 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

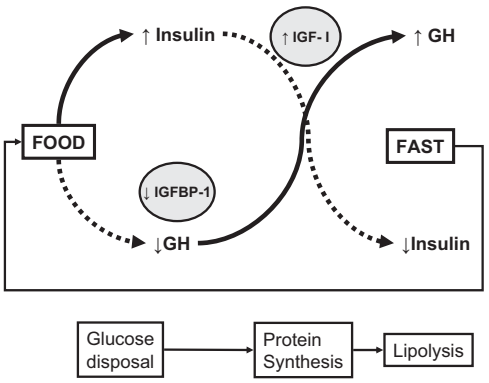


FIG. 3. A modified version of the feast-famine cycle including variations in the secretion and action of insulin and GH and the ensuing changes in IGFBP-1 and IGF-I. In the immediate postprandial period, insulin acts alone to promote storage of glucose. In the remote postabsorptive or fasting state, 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-I 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 phosphotyrosine 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 GHR 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

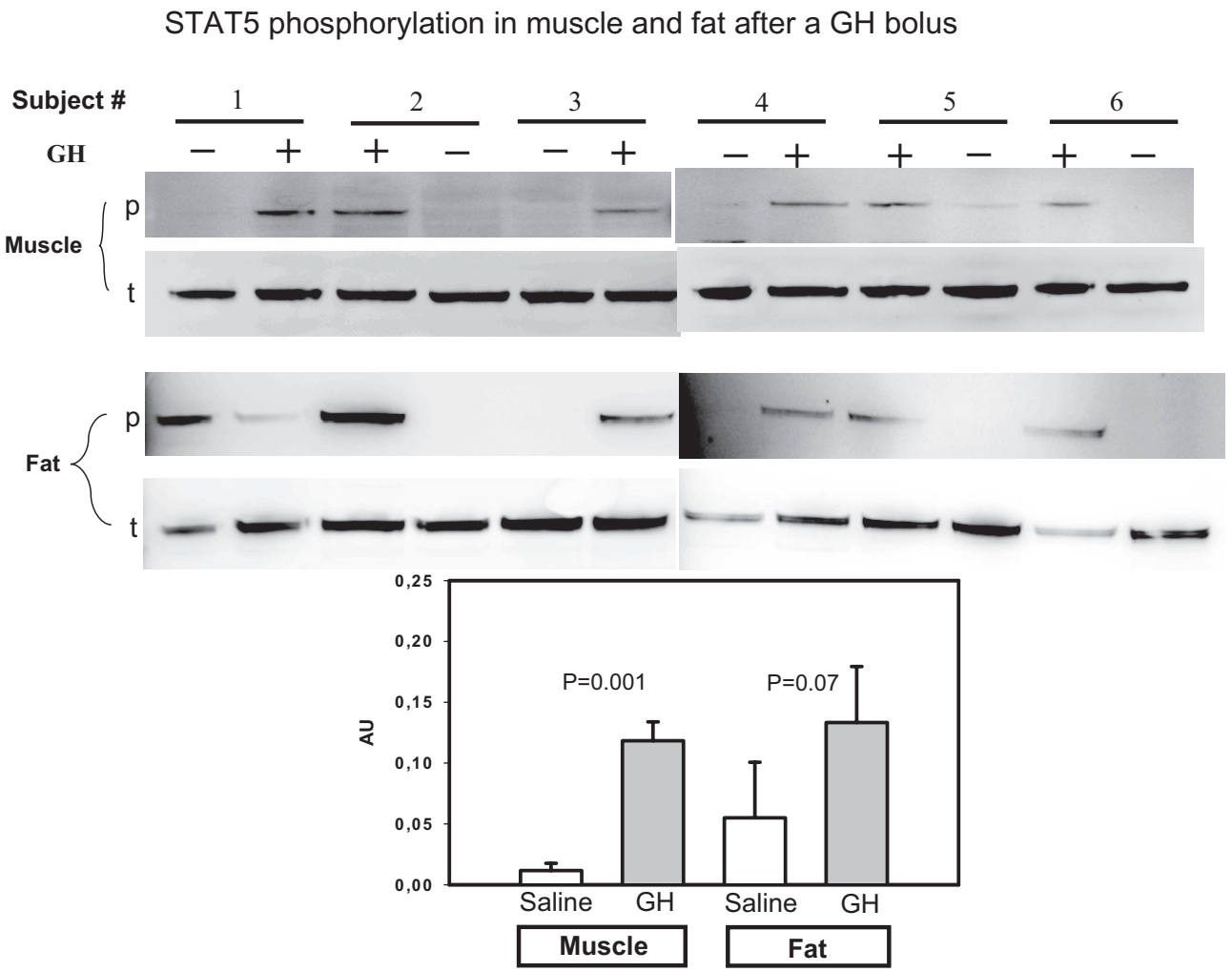


FIG. 4. The effect of an iv GH bolus (+) *vs.*, saline (−) in healthy human subjects on total (t) and tyrosine phosphorylated (p) STAT5 expression assessed by Western blotting in muscle and fat biopsies obtained 30–60 min after exposure. [Adapted from Ref. 46 with permission from The American Physiological Society].

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

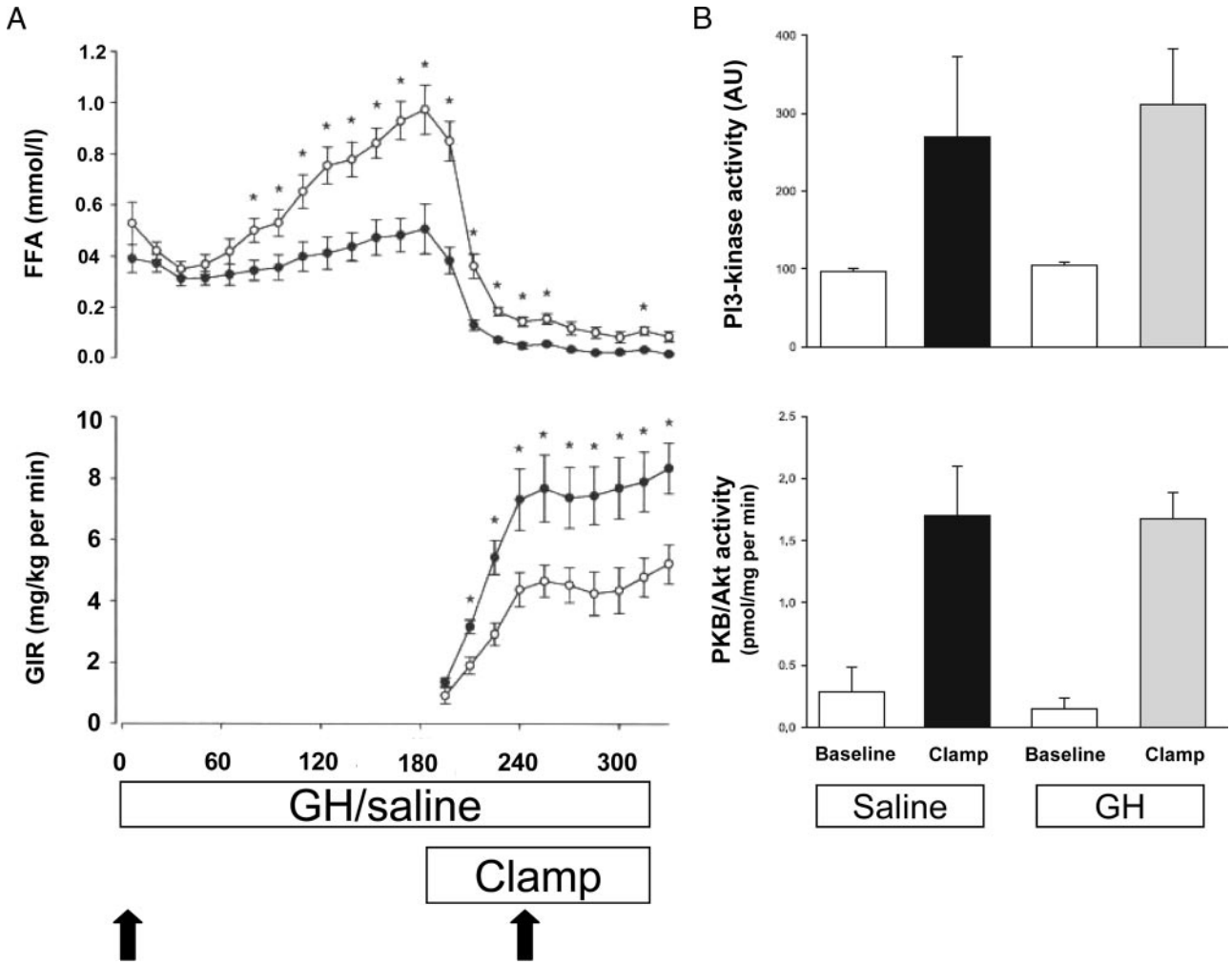


FIG. 5. A, The effects of GH (○) *vs.* saline infusions (●) on circulating FFA levels (*top*) and GIR (*bottom*) during a euglycemic clamp. The *arrows* indicate the time points for muscle biopsies. B, IRS-1-associated PI 3-kinase (*top*) and Akt/PKB activity (*bottom*) in muscle at baseline (*open bars*) 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].

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 cortisone to cortisol 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

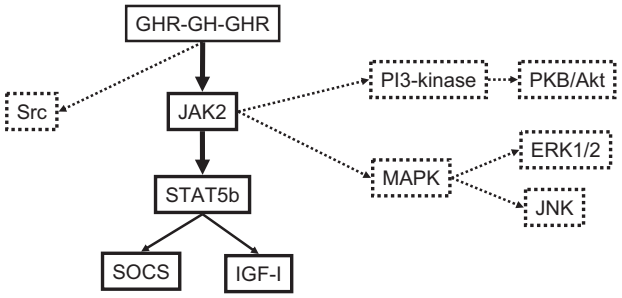


FIG. 6. Schematic and simplified depiction of alleged GH signaling proteins, which so far have been investigated in human muscle and adipose tissue. The *solid lines and boxes* indicate pathways that have been shown to be activated by GH; the *hatched lines and boxes* represent signaling proteins where activation by GH so far has not been documented. Src, Tyrosine kinase src; JNK, Jun N-terminal kinase.

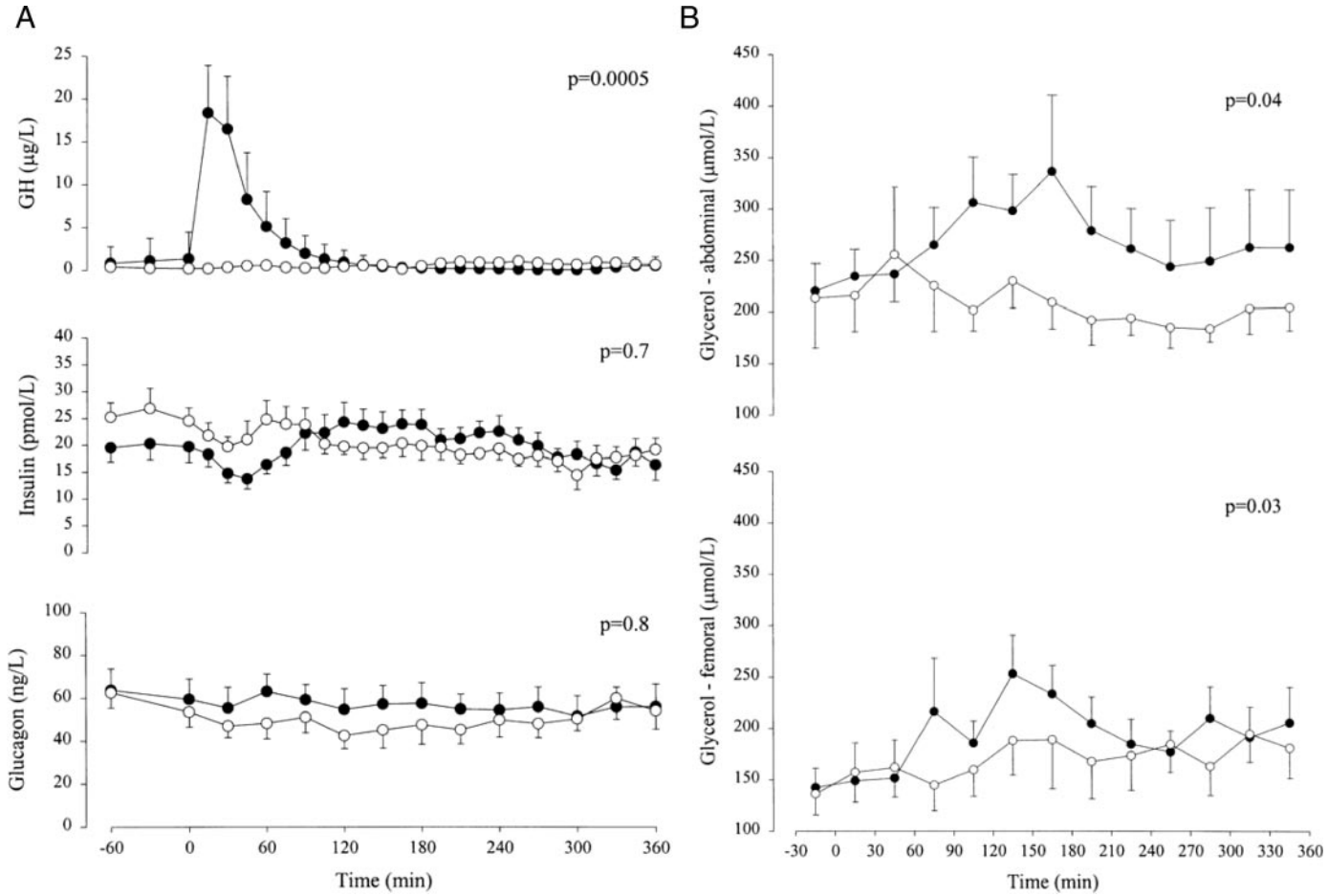


FIG. 7. The effects of a physiological iv GH bolus injection (●) *vs.* saline (○) in healthy subjects after an overnight fast. A, Circulating concentrations of GH (*top*), insulin (*middle*), and glucagon (*bottom*). B, Interstitial levels of glycerol in abdominal (*top*) and femoral (*bottom*) fat assessed by microdialysis. [Adapted from Ref. 56 with permission from The American Physiological Society].

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 im 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.

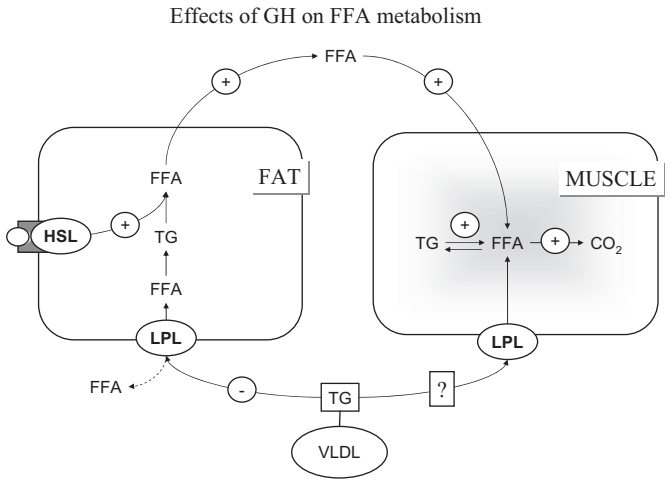


FIG. 8. Schematic and simplified illustration of studied effects of GH on fat metabolism in adipose tissue and skeletal muscle. +, Activation by GH; −, inhibition by GH. It is not yet clear whether GH impacts LPL in muscle. GH seems not to impact the turnover of triglycerides (TG) associated with very low density lipoprotein (VLDL). For additional information, see text.

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). Alternatively, GH may increase gluconeogenesis and glucose cycling in, *e.g.*, splanchnic tissues/liver or kidney. Large doses of GH have been reported to decrease net postabsorptive splanchnic glucose output acutely, compatible with increased glucose uptake (89), and *in vitro* experiments have shown increased gluconeogenesis from either alanine, or more likely, lactate in canine kidney cortex incubated with GH (90). The kidney is an important contributor to endogenous glucose production, which accounts for close to 50% during fasting (91, 92). In further favor of this notion, studies in acromegalic patients have revealed a 50% increase in glucose/glucose-6-phosphate cycling, presumably in liver or kidney (91–93); this increase could explain the major part of the increased glucose turnover recorded in these patients. Besides, Butler *et al.* (94) have reported that overnight exposure to high levels of GH in normal man stimulated gluconeogenesis, as judged by the incorporation of labeled carbon dioxide into glucose, and dogs treated with high GH doses for several days presented more than a doubling of liver glycogen content—from 5 to 11 g/100 g of liver (95). A more recent study of GH treatment in HIV-infected patients showed that gluconeogenesis assessed by mass isotopomer distribution analysis increased, and hepatic *de novo* lipogenesis decreased after months of treatment (96). It is likely that increased FFA levels contribute to this putative stimulation of gluconeogenesis (97). On the whole, there is circumstantial evidence that GH increases gluconeogenesis, probably lactate-dependently, but there is a need of acute studies using, *e.g.*, the doubly labeled water method of Landau and colleagues (98).

3. Protein metabolism. "Since GH causes new protoplasm to be formed, the effect on protein metabolism tends, rightly or not, to be viewed as the prime function of the hormone" (274).

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 artery 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-

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 calorigenic 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 T_4 to T_3 (119, 120), but experimental data indicate that the ensuing approximately 10% increase in T_3 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 [^{13}C]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

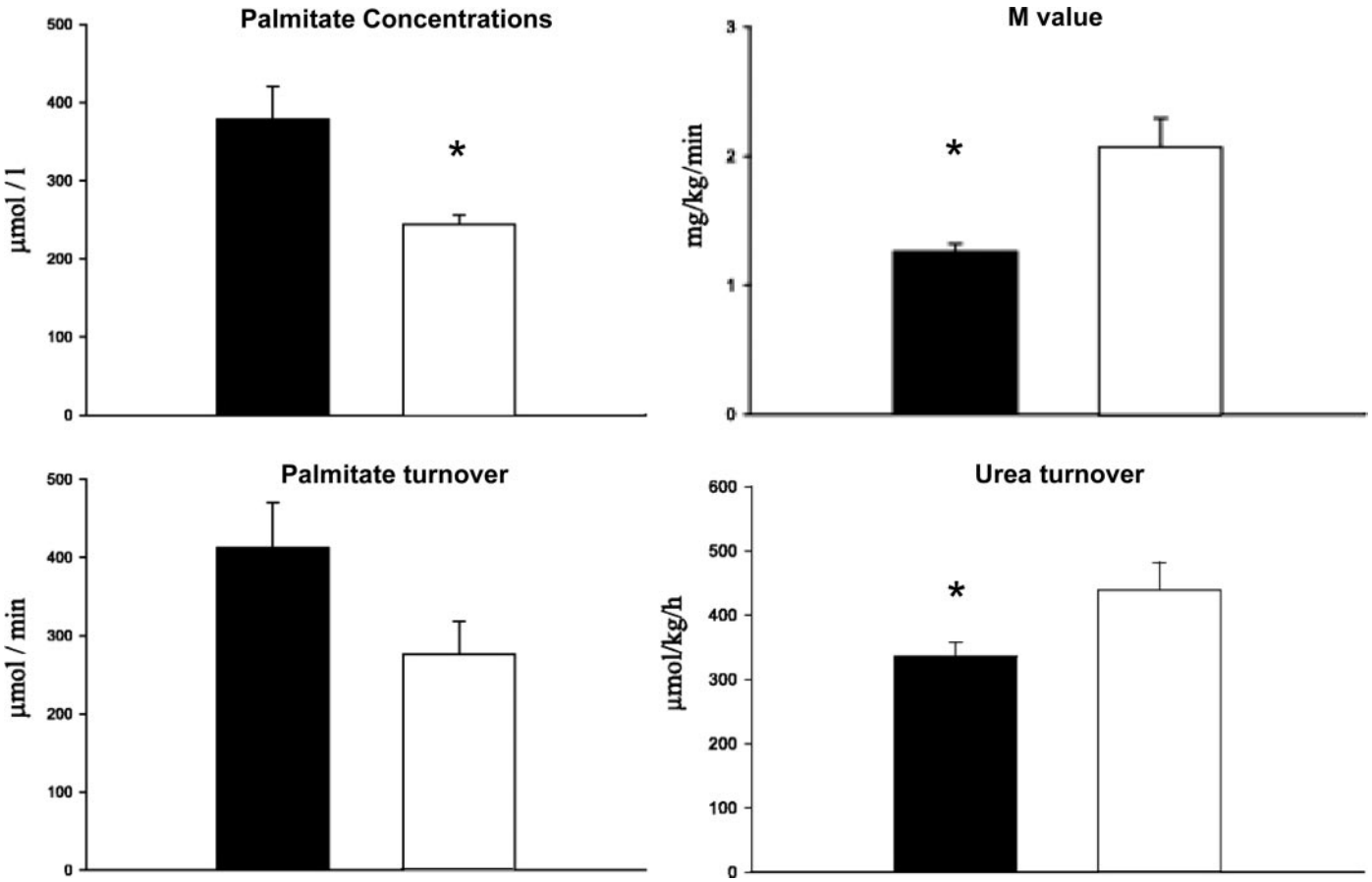


FIG. 9. Effects of continued *vs.* discontinued GH administration during 42.5 h of fasting in GHDA. *Black bars*, With GH; *white bars*, without GH. M-value is the amount of glucose infused during a euglycemic clamp performed during the last 2.5 h of the fast. *, $P < 0.05$. [Adapted from Ref. 136 with permission from The American Physiological Society].

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/hypothalamopituitary 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 periexercise 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 sc 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 increased 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 —rather than an increase— 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 proneness 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 GHDA compared with healthy subjects. Determinants of abnormal/impaired glucose tolerance included old age, female sex, and obesity. Johansson *et al.* (204) observed distinctly impaired insulin sensitivity (>50%) in 15 adult patients by means of the glucose clamp technique also after correction for differences in LBM. In both studies, fasting levels of plasma glucose and insulin were comparable between patients and controls. Similar results have been obtained by Hew *et al.* (205), who also documented decreased insulin-stimulated glycogen synthase activity in skeletal muscle. In the latter study, duration of GH deficiency was the single most important predictor of insulin resistance (200). The mechanisms underlying the impairment of insulin sensitivity in long-standing untreated GHDA are unclear, but one plausible candidate is increased FFA flux from visceral fat because visceral adiposity is a hallmark of adult GH deficiency. In this regard, it is noteworthy that a normal body mass index does not exclude visceral obesity (206). It is also

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). Beshyah *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 a 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—insulin 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-

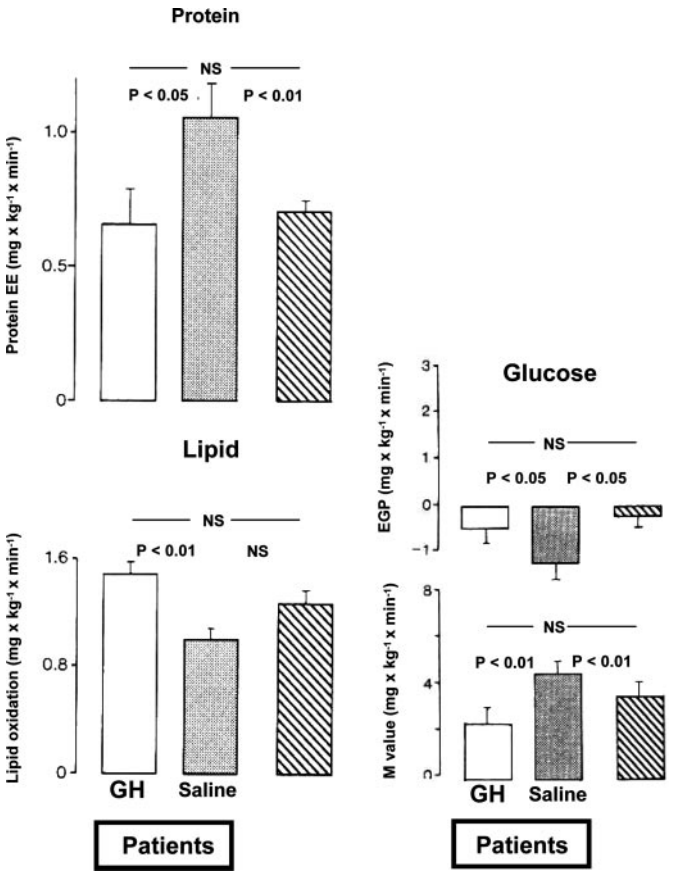


FIG. 10. Effects of continuation *vs.* discontinuation of evening GH replacement in adolescent GHD patients on basal rates of lipid oxidation (*bottom left*), protein oxidation (*top left*), and hepatic and peripheral insulin sensitivity (*right*). Lipid oxidation estimated by indirect calorimetry; protein 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 (≈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 either 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 (≈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

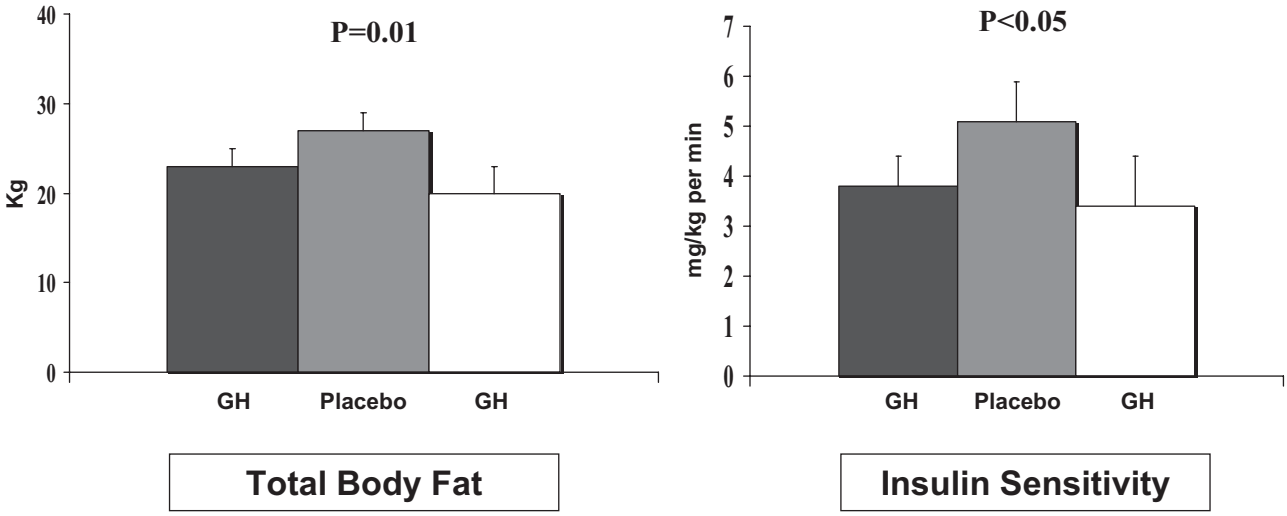
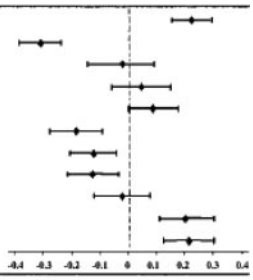


FIG. 11. Effects of discontinuation of GH replacement therapy for 1 yr in GHD patients in the transition phase from childhood to adulthood on total body fat and insulin sensitivity. The patients were studied at baseline on GH therapy (*black bar*), after 1 yr of placebo treatment (*gray bar*), and subsequently 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].

Factors	No. of trials	Treatment		Q test	Weighted mean (SD) change (GH-placebo)	Global effect size (95% CI)
		GH	Placebo			
Lean B mass	19	473	474	ns	2.82 kg (2.68)	
Fat mass	13	352	345	ns	−3.05 kg (3.29)	
BMI	8	134	134	ns	−0.12 kg/m^2 (1.40)	
TG	11	202	203	ns	0.07 mmol/liter (0.36)	
HDL Chol.	13	267	261	ns	0.06 mmol/liter (0.09)	
LDL Chol.	13	255	248	ns	−0.53 mmol/liter (0.29)	
Total Chol.	15	310	306	ns	−0.34 mmol/liter (0.31)	
D.B.P.	10	200	201	ns	−1.80 mm Hg (3.77)	
S.B.P.	9	190	191	ns	2.06 mm Hg (5.34)	
Insulin	11	192	194	ns	8.66 pmol/liter (6.98)	
Glucose	13	254	257	ns	0.22 mmol/liter (0.14)	



Lean B mass, Lean body mass; TG, triglycerides; Chol., cholesterol; D.B.P., diastolic blood pressure; S.B.P., systolic blood pressure; ns, nonsignificant.

FIG. 12. Results of meta-analysis of GH effects on cardiovascular risk factors. [Reproduced from Ref. 226 with permission from The Endocrine Society].

protein anabolic effects recorded after 2 wk were not maintained after 6 months. In two other studies of protein kinetics in the fed state, improved protein balances were observed after 1 and 2 months of GH replacement, respectively (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 reduced 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 sensitivity 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 acipimox 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 improves insulin sensitivity in GH-treated GHDA (232). The explanation why insulin sensitivity and glucose tolerance tend to improve or normalize during more prolonged GH substitution is not proven, but it is probably a combination of a gradual reduction in GH dosage and favorable effects of GH on body composition and physical fitness. The observation, however, that placebo-controlled discontinuation of GH substitution for 1 yr improves insulin sensitivity despite accumulation of fat mass underscores that induction of absolute or relative insulin resistance is an inherent attribute of conventional GH substitution.

Stimulation of lipolysis in concomitance with increased protein synthesis and reduced protein oxidation is also observed when GH is used as replacement therapy. The observation that protein synthesis in the fed state reaches a steady state after prolonged GH replacement is not surprising, but it is noteworthy that the protein-conserving actions seem to prevail in the fed state and become accentuated during fasting where lipid oxidation is concomitantly 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 cycling, was recorded in a study employing infusion of different 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 during 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 nonoxidative 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 glucose were significantly elevated before surgery and became

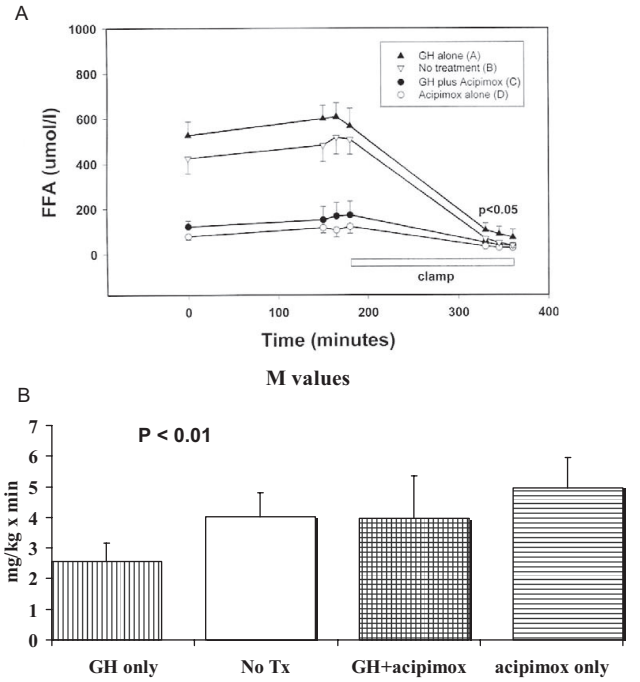


FIG. 13. Effects of pharmacological antilipolysis on serum FFA levels and insulin sensitivity in GHDA. Each patient was studied on four occasions in a randomized design: 1) on regular GH therapy (GH only); 2) no treatment for 2 d; 3) regular GH therapy plus acipimox for 2 d (GH+axipimox); and 4) only acipimox administration for 2 d (acipimox only). Acipimox blocks lipolysis by inhibition of the hormone sensitive lipase. A, Serum FFA levels in the basal state and during a euglycemic clamp on each occasion. B, Insulin sensitivity assessed by the euglycemic clamp. [Adapted from Ref. 76 with permission from The American Diabetes Association].

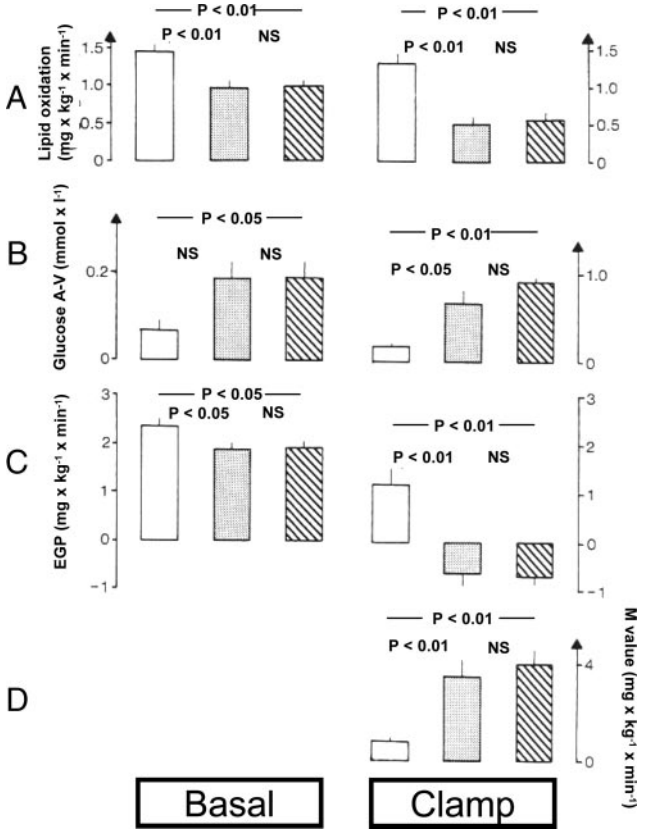


FIG. 14. Substrate metabolism and insulin sensitivity in acromegalic patients before (*white bar*) and after successful adenomectomy (*gray bar*) and compared with a matched group of healthy subjects (*hatched bar*). A, Lipid oxidation assessed by indirect calorimetry. B, Glucose uptake across the forearm. C, Endogenous glucose production. D, Insulin sensitivity as assessed by the M value. Measurements were performed in the basal state (Basal) and during a euglycemic glucose clamp (Clamp). [Adapted from Ref. 166 with permission from The Endocrine Society].

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 = 21) or without (n = 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 limited (249).

Octreotide, a somatostatin analog with a prolonged half-life relative to native somatostatin, was introduced for the treatment of acromegaly more that 20 yr ago. The impact of

somatostatin analogs on glucose metabolism is difficult to predict *à 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 tolerance were performed by Baldelli *et al.* (259) in 24 patients with active acromegaly. The majority of patients had residual disease after surgery, and a baseline assessment was performed after withdrawal of medical treatment for at least 8 wk. The patients were then randomized to one of two depot preparations of somatostatin [octreotide-LAR (20 mg im every 4 wk; n = 10) or slow-release Lanreotide (30 mg im every 2 wk; n = 14)] and restudied after 6 months. The plasma glucose value at 120 min after OGTT increased significantly after somatostatin analog treatment among the patients, who had a normal glucose tolerance at baseline (n = 16). In all patients, basal insulin levels were significantly reduced by the treatment, which also resulted in a delayed and reduced insulin response to the OGTT (259). This was accompanied by a minor but significant increase in HbA1c levels after treatment. By contrast, insulin sensitivity (n = 12) increased significantly and became normalized compared with a reference group of healthy subjects (259). No difference was evident between the effects of the two somatostatin analogs. In a retrospective survey including 110 patients treated with octreotide-LAR for 18–54 months, no "clinically meaningful increase in fasting glucose levels was observed (data not shown)" (260). By contrast, a recent retrospective 6-yr follow-up reported a deterioration in glucose tolerance in patients treated with long-acting somatostatin analogs (n = 36) compared with patients who were successfully treated with surgery alone (n = 33) (261). Fasting plasma glucose levels, HbA1c levels, as well as plasma glucose levels during an OGTT rose during medical treatment irrespective of the effect on GH status. In the surgically "cured" patients, the corresponding glycemic indices were lower and remained stable (261). However, insulin sensitivity, as indirectly estimated from glucose and insulin levels in the basal state and during the OGTT increased in patients who achieved acceptable control of GH status with somatostatin analogs (261).

Pegvisomant is a GH analog that functions as a specific GHR antagonist. It includes a single-amino acid substitution at position 120, which corresponds to binding site 2 for the GHR, and eight amino acid substitutions within binding site 1, in addition to polyethylene glycol moieties that increase the half-life of the molecule (262). It binds to the GHR in competition with native GH and prevents conformational changes of the preformed GHR dimer, which are critical for signal transduction (262). Pegvisomant therapy effectively normalizes IGF-I levels in more than 90% of patients, many of whom 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 RIAs 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 III), 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."

Acknowledgments

Received June 18, 2009. Accepted January 30, 2009.

Address all correspondence and requests for reprints to: Jens Otto Lunde Jørgensen, Medical Department M, Aarhus University Hospital, Aarhus Sygehus, Norrebrogade 44, DK 8000 C, Aarhus, Denmak. E-mail: joj@ki.au.dk

Disclosure Summary: N.M. has nothing to disclose. J.O.L.J. received grants from Ipsen and Pfizer, serves on an advisory council for Norvo Nordisk, and received an honorarium from Novartis.

References

1. **Kawauchi H, Sower SA** 2006 The dawn and evolution of hormones in the adenohypophysis. Gen Comp Endocrinol 148:3–14
2. **Schindler C, Levy DE, Decker T** 2007 JAK-STAT signaling: from interferons to cytokines. J Biol Chem 282:20059–20063
3. **Hernandez-Sanchez C, Mansilla A, de la Rosa EJ, de PF** 2006 Proinsulin in development: new roles for an ancient prohormone. Diabetologia 49:1142–1150
4. **Nielsen JH, Galsgaard ED, Moldrup A, Friedrichsen BN, Billestrup N, Hansen JA, Lee YC, Carlsson C** 2001 Regulation of β-cell mass by hormones and growth factors. Diabetes 50(Suppl 1):S25–S29
5. **Neel JV** 1962 Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet 14:353–362
6. **Randle PJ, Garland PB, Hales CN, Newsholme EA** 1963 The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1:785–789
7. **Rabinowitz D, Zierler KL** 1963 A metabolic regulating device based on the actions of human growth hormone and of insulin, singly and together, on the human forearm. Nature 199:913–915
8. **Davidson MB** 1987 Effect of growth hormone on carbohydrate and lipid metabolism. Endocr Rev 8:115–131
9. **Press M** 1988 Growth hormone and metabolism. Diabetes Metab Rev 4:391–414
10. **Baumann G** 1991 Growth hormone heterogeneity: genes, isohormones, variants, and binding proteins. Endocr Rev 12:424–449
11. **Baumann G** 2002 Growth hormone binding protein. The soluble growth hormone receptor. Minerva Endocrinol 27:265–276
12. **Frystyk J, Andreasen CM, Fisker S** 2008 Determination of free growth hormone. J Clin Endocrinol Metab 93:3008–3014
13. **Hartman ML, Faria AC, Vance ML, Johnson ML, Thorner MO, Veldhuis JD** 1991 Temporal structure of in vivo growth hormone secretory events in humans. Am J Physiol 260:E101–E110
14. **Ho KY, Veldhuis JD, Johnson ML, Furlanetto R, Evans WS, Alberti KG, Thorner MO** 1988 Fasting enhances growth hormone secretion and amplifies the complex rhythms of growth hormone secretion in man. J Clin Invest 81:968–975
15. **Parker DC, Sassin JF, Mace JW, Gotlin RW, Rossman LG** 1969 Human growth hormone release during sleep: electroencephalographic correlation. J Clin Endocrinol Metab 29:871–874
16. **Takahashi Y, Kipnis DM, Daughaday WH** 1968 Growth hormone secretion during sleep. J Clin Invest 47:2079–2090
17. **Roth J, Glick SM, Yalow RS, Berson SA** 1963 Secretion of human growth hormone: physiologic and experimental modification. Metabolism 12:577–579
18. **Hansen AP** 1973 Abnormal serum growth hormone response to exercise in maturity-onset diabetics. Diabetes 22:619–628

19. **Veldhuis JD, Roemmich JN, Richmond EJ, Bowers CY** 2006 Somatotropic and gonadotropic axes linkages in infancy, childhood, and the puberty-adult transition. Endocr Rev 27:101–140
20. **Moran A, Jacobs Jr DR, Steinberger J, Cohen P, Hong CP, Prineas R, Sinaiko AR** 2002 Association between the insulin resistance of puberty and the insulin-like growth factor-I/growth hormone axis. J Clin Endocrinol Metab 87:4817–4820
21. **Corpas E, Harman SM, Blackman MR** 1993 Human growth hormone and human aging. Endocr Rev 14:20–39
22. **Vahl N, Jorgensen JO, Skjaerbaek C, Veldhuis JD, Orskov H, Christiansen JS** 1997 Abdominal adiposity rather than age and sex predicts mass and regularity of GH secretion in healthy adults. Am J Physiol 272:E1108–E1116
23. **Wurzburger MI, Prelevic GM, Sonksen PH, Balint-Peric LA, Wheeler M** 1993 The effect of recombinant human growth hormone on regulation of growth hormone secretion and blood glucose in insulin-dependent diabetes. J Clin Endocrinol Metab 77:267–272
24. **Clemmons DR, Underwood LE** 1991 Nutritional regulation of IGF-I and IGF binding proteins. Annu Rev Nutr 11:393–412
25. **Hartman ML, Clayton PE, Johnson ML, Celniker A, Perlman AJ, Alberti KG, Thorner MO** 1993 A low dose euglycemic infusion of recombinant human insulin-like growth factor I rapidly suppresses fasting-enhanced pulsatile growth hormone secretion in humans. J Clin Invest 91:2453–2462
26. **Cheetham TD, Clayton KL, Taylor AM, Holly J, Matthews DR, Dunger DB** 1994 The effects of recombinant human insulin-like growth factor I on growth hormone secretion in adolescents with insulin dependent diabetes mellitus. Clin Endocrinol (Oxf) 40:515–522
27. **Le Roith D, Bondy C, Yakar S, Liu JL, Butler A** 2001 The somatomedin hypothesis: 2001. Endocr Rev 22:53–74
28. **Houssay BA** 1936 The hypophysis and metabolism. N Engl J Med 214:961–985
29. **Beck JC, McGarry EE, Dyrenfurth I, Venning EH** 1958 The metabolic effects of human and monkey growth hormone in man. Ann Intern Med 49:1090–1105
30. **Ikkos D, Luft R, Gemzell CA** 1958 The effect of human growth hormone in man. Lancet 1:720–721
31. **Raben MS, Hollenberg CH** 1959 Effect of growth hormone on plasma fatty acids. J Clin Invest 38:484–488
32. **Fineberg SE, Merimee TJ** 1974 Acute metabolic effects of human growth hormone. Diabetes 23:499–504
33. **Rabinowitz D, Klassen GA, Zierler KL** 1965 Effect of human growth hormone on muscle and adipose tissue metabolism in the forearm of man. J Clin Invest 44:51–61
34. **Zierler KL, Rabinowitz D** 1963 Roles of insulin and growth hormone, based on studies of forearm metabolism in man. Medicine (Baltimore) 42:385–402
35. **Djurhuus CB, Gravholt CH, Nielsen S, Pedersen SB, Moller N, Schmitz O** 2004 Additive effects of cortisol and growth hormone on regional and systemic lipolysis in humans. Am J Physiol Endocrinol Metab 286:E488–E494
36. **Krag MB, Gormsen LC, Guo Z, Christiansen JS, Jensen MD, Nielsen S, Jorgensen 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
37. **Wilson FA, Orellana RA, Suryawan A, Nguyen HV, Jeyapalan AS, Frank JW, Davis TA** 2008 Stimulation of muscle protein synthesis by somatotropin in pigs is independent of the somatotropin-induced increase in circulating insulin. Am J Physiol Endocrinol Metab 295:E187–E194
38. **Giannoulis MG, Jackson N, Shojaee-Moradie F, Nair KS, Sonksen PH, Martin F, Umpleby AM** 2008 The effects of growth hormone and/or testosterone on whole body protein kinetics and skeletal muscle gene expression in healthy elderly men: a randomized controlled trial. J Clin Endocrinol Metab 93:3066–3074
39. **Lanning NJ, Carter-Su C** 2006 Recent advances in growth hormone signaling. Rev Endocr Metab Disord 7:225–235
40. **O'Sullivan LA, Liongue C, Lewis RS, Stephenson SE, Ward AC** 2007 Cytokine receptor signaling through the Jak-Stat-Socs pathway in disease. Mol Immunol 44:2497–2506
41. **Kelly PA, Djiane J, Postel-Vinay MC, Edery M** 1991 The prolactin/growth hormone receptor family. Endocr Rev 12:235–251
42. **Woelfle J, Chia DJ, Rotwein P** 2003 Mechanisms of growth hormone (GH) action. Identification of conserved Stat5 binding sites that mediate GH-induced insulin-like growth factor-I gene activation. J Biol Chem 278:51261–51266
43. **Wormald S, Hilton DJ** 2004 Inhibitors of cytokine signal transduction. J Biol Chem 279:821–824
44. **Silva CM, Kloth MT, Whatmore AJ, Freeth JS, Anderson N, Laughlin KK, Huynh T, Woodall AJ, Clayton PE** 2002 GH and epidermal growth factor signaling in normal and Laron syndrome fibroblasts. Endocrinology 143:2610–2617
45. **Hwa V, Little B, Adiyaman P, Kofoed EM, Pratt KL, Ocal G, Berberoglu M, Rosenfeld RG** 2005 Severe growth hormone insensitivity resulting from total absence of signal transducer and activator of transcription 5b. J Clin Endocrinol Metab 90:4260–4266
46. **Jorgensen JOL, Jessen N, Pedersen SB, Vestergaard E, Gormsen L, Lund SA, Billestrup N** 2006 Growth hormone 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
47. **Dominici FP, Argentino DP, Munoz MC, Miquet JG, Sotelo AI, Turyn D** 2005 Influence of the crosstalk between growth hormone and insulin signalling on the modulation of insulin sensitivity. Growth Horm IGF Res 15:324–336
48. **Emanuelli B, Peraldi P, Filloux C, Sawka-Verhelle D, Hilton D, Van OE** 2000 SOCS-3 is an insulin-induced negative regulator of insulin signaling. J Biol Chem 275:15985–15991
49. **Ridderstrale M, Degerman E, Tornqvist H** 1995 Growth hormone stimulates the tyrosine phosphorylation of the insulin receptor substrate-1 and its association with phosphatidylinositol 3-kinase in primary adipocytes. J Biol Chem 270:3471–3474
50. **Thirone AC, Carvalho CR, Saad MJ** 1999 Growth hormone stimulates the tyrosine kinase activity of JAK2 and induces tyrosine phosphorylation of insulin receptor substrates and Shc in rat tissues. Endocrinology 140:55–62
51. **del Rincon JP, Iida K, Gaylinn BD, McCurdy CE, Leitner JW, Barbour LA, Kopchick JJ, Friedman JE, Draznin B, Thorner MO** 2007 Growth hormone regulation of p85α expression and phosphoinositide 3-kinase activity in adipose tissue: mechanism for growth hormone-mediated insulin resistance. Diabetes 56:1638–1646
52. **Jessen N, Djurhuus CB, Jorgensen JO, Jensen LS, Moller N, Lund S, Schmitz O** 2005 Evidence against a role for insulin-signaling proteins PI 3-kinase and Akt in insulin resistance in human skeletal muscle induced by short-term GH infusion. Am J Physiol Endocrinol Metab 288:E194–E199
53. **Gormsen LC, Jessen N, Gjedsted J, Gjedde S, Norrelund H, Lund S, Christiansen JS, Nielsen S, Schmitz O, Moller N** 2007 Dose-response effects of free fatty acids on glucose and lipid metabolism during somatostatin blockade of growth hormone and insulin in humans. J Clin Endocrinol Metab 92:1834–1842
54. **Nielsen C, Gormsen LC, Jessen N, Pedersen SB, Moller N, Lund S, Jorgensen JO** 2008 Growth hormone signaling *in vivo* in human muscle and adipose tissue: impact of insulin, substrate background and growth hormone receptor blockade. J Clin Endocrinol Metab 93:2842–2850
55. **Moller N, Jorgensen JO, Schmitz O, Moller 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
56. **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–E854
57. **Moller N, Jorgensen JO, Alberti KG, 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
58. **Moller N, Schmitz O, Porksen N, Moller J, Jorgensen JO** 1992 Dose-response studies on the metabolic effects of a growth hormone pulse in humans. Metabolism 41:172–175
59. **Hansen TK, Gravholt CH, Orskov H, Rasmussen MH, Christiansen JS, Jorgensen JO** 2002 Dose dependency of the pharmacokinetics and acute lipolytic actions of growth hormone. J Clin Endocrinol Metab 87:4691–4698

60. **Cersosimo E, Danou F, Persson M, Miles JM** 1996 Effects of pulsatile delivery of basal growth hormone on lipolysis in humans. Am J Physiol 271:E123–E126
61. **Attallah H, Friedlander AL, Nino-Murcia M, Hoffman AR** 2007 Effects of growth hormone and pioglitazone in viscerally obese adults with impaired glucose tolerance: a factorial clinical trial. PLoS Clin Trials 2:e21
62. **Rosenthal MJ, Woodside WF** 1988 Nocturnal regulation of free fatty acids in healthy young and elderly men. Metabolism 37:645–648
63. **Boyle PJ, Avogaro A, Smith L, Bier DM, Pappu AS, Illingworth DR, Cryer PE** 1992 Role of GH in regulating nocturnal rates of lipolysis and plasma mevalonate levels in normal and diabetic humans. Am J Physiol 263:E168–E172
64. **Kousta E, Chrisoulidou A, Lawrence NJ, Anyaoku V, Al-Shoumer KA, Johnston DG** 2000 The effects of growth hormone replacement therapy on overnight metabolic fuels in hypopituitary patients. Clin Endocrinol (Oxf) 52:17–24
65. **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
66. **Edge JA, Harris DA, Phillips PE, Pal BR, Matthews DR, Dunger DB** 1993 Evidence for a role for insulin and growth hormone in overnight regulation of 3-hydroxybutyrate in normal and diabetic adolescents. Diabetes Care 16:1011–1018
67. **Hagstrom-Toft E, Bolinder J, Ungerstedt U, Arner P** 1997 A circadian rhythm in lipid mobilization which is altered in IDDM. Diabetologia 40:1070–1078
68. **Buijs MM, Burggraaf J, Langendonk JG, Schoemaker RC, Frolich M, Arndt JW, Cohen AF, Romijn JA, Ackermans MT, Sauerwein HP, Meinders AE, Pijl H** 2002 Hyposomatotropism blunts lipolysis in abdominally obese women. J Clin Endocrinol Metab 87:3851–3858
69. **Vahl N, Moller N, Lauritzen T, Christiansen JS, Jorgensen JO** 1997 Metabolic effects and pharmacokinetics of a growth hormone pulse in healthy adults: relation to age, sex, and body composition. J Clin Endocrinol Metab 82:3612–3618
70. **Betley S, Alberti KG, Agius L** 1989 Regulation of fatty acid and carbohydrate metabolism by insulin, growth hormone and triiodothyronine in hepatocyte cultures from normal and hypophysectomized rats. Biochem J 258:547–552
71. **Emmison N, Agius L, Zammit VA** 1991 Regulation of fatty acid metabolism and gluconeogenesis by growth hormone and insulin in sheep hepatocyte cultures. Effects of lactation and pregnancy. Biochem J 274:21–26
72. **Keller U, Schnell H, Girard J, Stauffacher W** 1984 Effect of physiological elevation of plasma growth hormone levels on ketone body kinetics and lipolysis in normal and acutely insulin-deficient man. Diabetologia 26:103–108
73. **Louveau I, Gondret F** 2004 Regulation of development and metabolism of adipose tissue by growth hormone and the insulin-like growth factor system. Domest Anim Endocrinol 27:241–255
74. **Yin D, Clarke SD, Peters JL, Etherton TD** 1998 Somatotropin-dependent decrease in fatty acid synthase mRNA abundance in 3T3–F442A adipocytes is the result of a decrease in both gene transcription and mRNA stability. Biochem J 331:815–820
75. **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 Endocrinol Metab 263:E467–E472
76. **Nielsen S, Moller N, Christiansen JS, Jorgensen JO** 2001 Pharmacological antilipolysis restores insulin sensitivity during growth hormone exposure. Diabetes 50:2301–2308
77. **Norrelund H, Nielsen S, Christiansen JS, Jorgensen JO, Moller N** 2004 Modulation of basal glucose metabolism and insulin sensitivity by growth hormone and free fatty acids during short-term fasting. Eur J Endocrinol 150:779–787
78. **Segerlantz M, Bramnert M, Manhem P, Laurila E, Groop LC** 2001 Inhibition of the rise in FFA by acipimox partially prevents GH-induced insulin resistance in GH-deficient adults. J Clin Endocrinol Metab 86:5813–5818
79. **Piatti PM, Monti LD, Caumo A, Conti M, Magni F, Galli-Kienle M, Fochesato E, Pizzini A, Baldi L, Valsecchi G, Pontiroli AE** 1999 Mediation of the hepatic effects of growth hormone by its lipolytic activity. J Clin Endocrinol Metab 84:1658–1663
80. **Leung KC, Ho KK** 1997 Stimulation of mitochondrial fatty acid oxidation by growth hormone in human fibroblasts. J Clin Endocrinol Metab 82:4208–4213
81. **Richelsen B** 1999 Effect of growth hormone on adipose tissue and skeletal muscle lipoprotein lipase activity in humans. J Endocrinol Invest 22:10–15
82. **Richelsen B, Pedersen SB, Kristensen K, Borglum JD, Norrelund H, Christiansen JS, Jorgensen JO** 2000 Regulation of lipoprotein lipase and hormone-sensitive lipase activity and gene expression in adipose and muscle tissue by growth hormone treatment during weight loss in obese patients. Metabolism 49:906–911
83. **Ottosson M, Vikman-Adolfsson K, Enerback S, Elander A, Bjorntorp P, Eden S** 1995 Growth hormone inhibits lipoprotein lipase activity in human adipose tissue. J Clin Endocrinol Metab 80:936–941
84. **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
85. **Paulsen SK, Pedersen SB, Jorgensen JO, Fisker S, Christiansen JS, Flyvbjerg A, Richelsen B** 2006 Growth hormone (GH) substitution in GH-deficient patients inhibits 11β-hydroxysteroid dehydrogenase type 1 messenger ribonucleic acid expression in adipose tissue. J Clin Endocrinol Metab 91:1093–1098
86. **Dagenais GR, Tancredi RG, Zierler KL** 1976 Free fatty acid oxidation by forearm muscle at rest, and evidence for an intramuscular lipid pool in the human forearm. J Clin Invest 58:421–431
87. **Tancredi RG, Dagenais GR, Zierler KL** 1976 Free fatty acid metabolism in the forearm at rest: muscle uptake and adipose tissue release of free fatty acids. Johns Hopkins Med J 138:167–179
88. **Frayn KN** 1983 Calculation of substrate oxidation rates in vivo from gaseous exchange. J Appl Physiol 55:628–634
89. **Adamson U, Wahren J, Cerasi E** 1977 Influence of growth hormone on splanchnic glucose production in man. Acta Endocrinol (Copenh) 86:803–812
90. **Rogers SA, Miller SB, Hammerman MR** 1990 Growth hormone stimulates IGF I gene expression in isolated rat renal collecting duct. Am J Physiol 259:F474–F479
91. **Moller N, Rizza RA, Ford GC, Nair KS** 2001 Assessment of postabsorptive renal glucose metabolism in humans with multiple glucose tracers. Diabetes 50:747–751
92. **Owen OE, Felig P, Morgan AP, Wahren J, Cahill Jr GF** 1969 Liver and kidney metabolism during prolonged starvation. J Clin Invest 48:574–583
93. **Karlander S, Vranic M, Efendic S** 1986 Increased glucose turnover and glucose cycling in acromegalic patients with normal glucose tolerance. Diabetologia 29:778–783
94. **Butler P, Kryshak E, Rizza R** 1991 Mechanism of growth hormone-induced postprandial carbohydrate intolerance in humans. Am J Physiol 260:E513–E520
95. **Altszuler N, Rathgeb I, Winkler B, De Bodo RC, Steele R** 1968 The effects of growth hormone on carbohydrate and lipid metabolism in the dog. Ann NY Acad Sci 148:441–458
96. **Schwarz JM, Mulligan K, Lee J, Lo JC, Wen M, Noor MA, Grunfeld C, Schambelan M** 2002 Effects of recombinant human growth hormone on hepatic lipid and carbohydrate metabolism in HIV-infected patients with fat accumulation. J Clin Endocrinol Metab 87:942
97. **Staehr P, Hother-Nielsen O, Landau BR, Chandramouli V, Holst JJ, Beck-Nielsen H** 2003 Effects of free fatty acids per se on glucose production, gluconeogenesis, and glycogenolysis. Diabetes 52:260–267
98. **Bock G, Schumann WC, Basu R, Burgess SC, Yan Z, Chandramouli V, Rizza RA, Landau BR** 2008 Evidence that processes other than gluconeogenesis may influence the ratio of deuterium on the fifth and third carbons of glucose: implications for the use of $2H_2O$ to measure gluconeogenesis in humans. Diabetes 57:50–55
99. **Fryburg DA, Louard RJ, Gerow KE, Gelfand RA, Barrett EJ** 1992 Growth hormone stimulates skeletal muscle protein synthesis and

antagonizes insulin's antiproteolytic action in humans. Diabetes 41:424–429
100. **Fryburg DA, Gelfand RA, Barrett EJ** 1991 Growth hormone acutely stimulates forearm muscle protein synthesis in normal humans. Am J Physiol 260:E499–E504
101. **Copeland KC, Nair KS** 1994 Acute growth hormone effects on amino acid and lipid metabolism. J Clin Endocrinol Metab 78: 1040–1047
102. **Nielsen S, Jorgensen JO, Hartmund T, Norrelund H, Nair KS, Christiansen JS, Moller N** 2002 Effects of lowering circulating free fatty acid levels on protein metabolism in adult growth hormone deficient patients. Growth Horm IGF Res 12:425–433
103. **Fryburg DA, Barrett EJ** 1993 Growth hormone acutely stimulates skeletal muscle but not whole-body protein synthesis in humans. Metabolism 42:1223–1227
104. **Horber FF, Haymond MW** 1990 Human growth hormone prevents the protein catabolic side effects of prednisone in humans. J Clin Invest 86:265–272
105. **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
106. **Garibotto G** 1999 Muscle amino acid metabolism and the control of muscle protein turnover in patients with chronic renal failure. Nutrition 15:145–155
107. **Zachwieja JJ, Bier DM, Yarasheski KE** 1994 Growth hormone administration in older adults: effects on albumin synthesis. Am J Physiol 266:E840–E844
108. **Hoffman DM, Pallasser R, Duncan M, Nguyen TV, Ho KK** 1998 How is whole body protein turnover perturbed in growth hormone-deficient adults? J Clin Endocrinol Metab 83:4344–4349
109. **Beshyah SA, Sharp PS, Gelding SV, Halliday D, Johnston DG** 1993 Whole-body leucine turnover in adults on conventional treatment for hypopituitarism. Acta Endocrinol (Copenh) 129:158–164
110. **Welbourne T, Joshi S, McVie R** 1989 Growth hormone effects on hepatic glutamate handling in vivo. Am J Physiol 257:E959–E962
111. **Wolthers T, Grofte T, Jorgensen JO, Moller N, Vahl N, Christiansen JS, Vilstrup H** 1994 Effects of growth hormone (GH) administration on functional hepatic nitrogen clearance: studies in normal subjects and GH-deficient patients. J Clin Endocrinol Metab 78:1220–1224
112. **Wolthers T, Grofte T, Moller N, Vilstrup H, Jorgensen JO** 1996 Effects of long-term growth hormone (GH) and triiodothyronine (T_3) administration on functional hepatic nitrogen clearance in normal man. J Hepatol 24:313–319
113. **Bray GA** 1969 Calorigenic effect of human growth hormone in obesity. J Clin Endocrinol Metab 29:119–122
114. **Wolthers T, Groftne T, Moller N, Christiansen JS, Orskov H, Weeke J, Jorgensen JO** 1996 Calorigenic effects of growth hormone: the role of thyroid hormones. J Clin Endocrinol Metab 81: 1416–1419
115. **Bak JF, Moller 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
116. **Jorgensen JO, Moller J, Alberti KG, Schmitz O, Christiansen JS, Orskov H, Moller N** 1993 Marked effects of sustained low growth hormone (GH) levels on day-to-day fuel metabolism: studies in GH-deficient patients and healthy untreated subjects. J Clin Endocrinol Metab 77:1589–1596
117. **Stenlof K, Johansson JO, Lonn L, Sjostrom L, Bengtsson BA** 1997 Diurnal variations in twenty-four-hour energy expenditure during growth hormone treatment of adults with pituitary deficiency. J Clin Endocrinol Metab 82:1255–1260
118. **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
119. **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
120. **Jorgensen JO, Moller J, Laursen T, Orskov H, Christiansen JS, Weeke J** 1994 Growth hormone administration stimulates energy expenditure and extrathyroidal conversion of thyroxine to triiodothyronine in a dose-dependent manner and suppresses circadian thyrotrophin levels: studies in GH-deficient adults. Clin Endocrinol (Oxf) 41:609–614
121. **Short KR, Moller N, Bigelow ML, Coenen-Schimke J, Nair KS** 2008 Enhancement of muscle mitochondrial function by growth hormone. J Clin Endocrinol Metab 93:597–604
122. **Pedersen SB, Kristensen K, Fisker S, Jorgensen JO, Christiansen JS, Richelsen B** 1999 Regulation of uncoupling protein-2 and -3 by growth hormone in skeletal muscle and adipose tissue in growth hormone-deficient adults. J Clin Endocrinol Metab 84:4073–4078
123. **Thuesen L, Jorgensen JO, Muller 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
124. **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
125. **Jorgensen JO, Pedersen SA, Thuesen L, Jorgensen J, Ingemann-Hansen T, Skakkebaek NE, Christiansen JS** 1989 Beneficial effects of growth hormone treatment in GH-deficient adults. Lancet 1:1221–1225
126. **Cahill Jr GF** 1970 Starvation in man. N Engl J Med 282:668–675
127. **Jensen MD, Haymond MW, Gerich JE, Cryer PE, Miles JM** 1987 Lipolysis during fasting. Decreased suppression by insulin and increased stimulation by epinephrine. J Clin Invest 79:207–213
128. **Owen OE, Reichard Jr GA** 1971 Human forearm metabolism during progressive starvation. J Clin Invest 50:1536–1545
129. **Owen OE, Smalley KJ, D'Alessio DA, Mozzoli MA, Dawson EK** 1998 Protein, fat, and carbohydrate requirements during starvation: anaplerosis and cataplerosis. Am J Clin Nutr 68:12–34
130. **Gjedsted J, Gormsen LC, Nielsen S, Schmitz O, Djurhuus CB, Keiding S, Orskov H, Tonnesen E, Moller N** 2007 Effects of a 3-day fast on regional lipid and glucose metabolism in human skeletal muscle and adipose tissue. Acta Physiol (Oxf) 191:205–216
131. **Henneman PH, Forbes AP, Moldawer M, Dempsey EF, Carroll EL** 1960 Effects of human growth hormone in man. J Clin Invest 39: 1223–1238
132. **Manson JM, Wilmore DW** 1986 Positive nitrogen balance with human growth hormone and hypocaloric intravenous feeding. Surgery 100:188–197
133. **Lundeberg S, Belfrage M, Wernerman J, von der Decken A, Thunell S, Vinnars E** 1991 Growth hormone improves muscle protein metabolism and whole body nitrogen economy in man during a hyponitrogenous diet. Metabolism 40:315–322
134. **Norrelund H, Moller N, Nair KS, Christiansen JS, Jorgensen JO** 2001 Continuation of growth hormone (GH) substitution during fasting in GH-deficient patients decreases urea excretion and conserves protein synthesis. J Clin Endocrinol Metab 86:3120–3129
135. **Norrelund H, Nair KS, Jorgensen JO, Christiansen JS, Moller N** 2001 The protein-retaining effects of growth hormone during fasting involve inhibition of muscle-protein breakdown. Diabetes 50: 96–104
136. **Norrelund H, Djurhuus C, Jorgensen JO, Nielsen S, Nair KS, Schmitz O, Christiansen JS, Moller N** 2003 Effects of GH on urea, glucose and lipid metabolism, and insulin sensitivity during fasting in GH-deficient patients. Am J Physiol Endocrinol Metab 285:E737–E743
137. **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
138. **Felig P, Marliss EB, Cahill Jr GF** 1971 Metabolic response to human growth hormone during prolonged starvation. J Clin Invest 50:411–421
139. **Clemmons DR, Snyder DK, Williams R, Underwood LE** 1987 Growth hormone administration conserves lean body mass during dietary restriction in obese subjects. J Clin Endocrinol Metab 64: 878–883
140. **Snyder DK, Clemmons DR, Underwood LE** 1988 Treatment of

obese, diet-restricted subjects with growth hormone for 11 weeks: effects on anabolism, lipolysis, and body composition. J Clin Endocrinol Metab 67:54–61
141. **Norrelund H, Borglum J, Jorgensen JO, Richelsen B, Moller N, Nair KS, Christiansen JS** 2000 Effects of growth hormone administration on protein dynamics and substrate metabolism during 4 weeks of dietary restriction in obese women. Clin Endocrinol (Oxf) 52:305–312
142. **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
143. **Sakharova AA, Horowitz JF, Surya S, Goldenberg N, Harber MP, Symons K, Barkan A** 2008 Role of growth hormone in regulating lipolysis, proteolysis, and hepatic glucose production during fasting. J Clin Endocrinol Metab 93:2755–2759
144. **Nair KS, Welle SL, Halliday D, Campbell RG** 1988 Effect of β-hydroxybutyrate on whole-body leucine kinetics and fractional mixed skeletal muscle protein synthesis in humans. J Clin Invest 82:198–205
145. **Sherwin RS, Hendler RG, Felig P** 1975 Effect of ketone infusions on amino acid and nitrogen metabolism in man. J Clin Invest 55:1382–1390
146. **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
147. **Gibney J, Healy ML, Sonksen PH** 2007 The growth hormone/insulin-like growth factor-I axis in exercise and sport. Endocr Rev 28:603–624
148. **Liu H, Bravata DM, Olkin I, Friedlander A, Liu V, Roberts B, Bendavid E, Saynina O, Salpeter SR, Garber AM, Hoffman AR** 2008 Systematic review: the effects of growth hormone on athletic performance. Ann Intern Med 148:747–758
149. **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
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. **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
152. **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
153. **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
154. **Lange KH, Isaksson F, Juul A, Rasmussen MH, Bulow J, Kjaer M** 2000 Growth hormone enhances effects of endurance training on oxidative muscle metabolism in elderly women. Am J Physiol Endocrinol Metab 279:E989–E996
155. **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
156. **Healy ML, Gibney J, Pentecost C, Croos P, Russell-Jones DL, Sonksen 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
157. **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
158. **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
159. **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
160. **Van den Berghe G, de Zegher F, Veldhuis JD, Wouters P, Awouters M, Verbruggen W, Schetz M, Verwaest C, Lauwers P, Bouillon R, Bowers CY** 1997 The somatotropic axis in critical illness: effect of continuous growth hormone (GH)-releasing hormone and GH-releasing peptide-2 infusion. J Clin Endocrinol Metab 82:590–599
161. **Vila G, Maier C, Riedl M, Nowotny P, Ludvik B, Luger A, Clodi M** 2007 Bacterial endotoxin induces biphasic changes in plasma ghrelin in healthy humans. J Clin Endocrinol Metab 92:3930–3934
162. **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
163. **Freda PU, Shen W, Heymsfield SB, Reyes-Vidal CM, Geer EB, Bruce JN, Gallagher D** 2008 Lower visceral and subcutaneous but higher intermuscular adipose tissue depots in patients with GH and IGF-I excess due to acromegaly. J Clin Endocrinol Metab 93:2334–2343
164. **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
165. **Hansen TB, Gram J, Bjerre P, Hagen C, Bollerslev J** 1994 Body composition in active acromegaly during treatment with octreotide: a double-blind, placebo-controlled cross-over study. Clin Endocrinol (Oxf) 41:323–329
166. **Moller N, Schmitz O, Joorgensen 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
167. **McNurlan MA, Garlick PJ, Steigbigel RT, DeCristofaro KA, Frost RA, Lang CH, Johnson RW, Santasier AM, Cabahug CJ, Fuhrer J, Gelato MC** 1997 Responsiveness of muscle protein synthesis to growth hormone administration in HIV-infected individuals declines with severity of disease. J Clin Invest 100:2125–2132
168. **Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, Hinds CJ** 1999 Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 341:785–792
169. **Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R** 2001 Intensive insulin therapy in the critically ill patients. N Engl J Med 345:1359–1367
170. **Moller N, Butler PC, Antsiferov MA, Alberti KG** 1989 Effects of growth hormone on insulin sensitivity and forearm metabolism in normal man. Diabetologia 32:105–110
171. **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
172. **Roden M, Price TB, Perseghin G, Petersen KF, Rothman DL, Cline GW, Shulman GI** 1996 Mechanism of free fatty acid-induced insulin resistance in humans. J Clin Invest 97:2859–2865
173. **Itani SI, Ruderman NB, Schmieder F, Boden G** 2002 Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and IκB-α. Diabetes 51:2005–2011
174. **Griffin ME, Marcucci MJ, Cline GW, Bell K, Barucci N, Lee D, Goodyear LJ, Kraegen EW, White MF, Shulman GI** 1999 Free fatty acid-induced insulin resistance is associated with activation of protein kinase C θ and alterations in the insulin signaling cascade. Diabetes 48:1270–1274
175. **Shulman GI** 2004 Unraveling the cellular mechanism of insulin resistance in humans: new insights from magnetic resonance spectroscopy. Physiology 19:183–190
176. **Hansen AP, Johansen K** 1970 Diurnal patterns of blood glucose, serum free fatty acids, insulin, glucagon and growth hormone in normals and juvenile diabetics. Diabetologia 6:27–33

177. **Asplin CM, Faria AC, Carlsen EC, Vaccaro VA, Barr RE, Iranmanesh A, Lee MM, Veldhuis JD, Evans WS** 1989 Alterations in the pulsatile mode of growth hormone release in men and women with insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 69:239–245
178. **Amiel SA, Sherwin RS, Hintz RL, Gertner JM, Press CM, Tamborlane WV** 1984 Effect of diabetes and its control on insulin-like growth factors in the young subject with type I diabetes. Diabetes 33:1175–1179
179. **Boni-Schnetzler M, Schmid C, Meier PJ, Froesch ER** 1991 Insulin regulates insulin-like growth factor I mRNA in rat hepatocytes. Am J Physiol 260:E846–E851
180. **Russell-Jones DL, Rattray M, Wilson VJ, Jones RH, Sonksen PH, Thomas CR** 1992 Intraperitoneal insulin is more potent than subcutaneous insulin at restoring hepatic insulin-like growth factor-I mRNA levels in the diabetic rat: a functional role for the portal vascular link. J Mol Endocrinol 9:257–263
181. **Boyle PJ, Cryer PE** 1991 Growth hormone, cortisol, or both are involved in defense against, but are not critical to recovery from, hypoglycemia. Am J Physiol 260:E395–E402
182. **De Feo P, Perriello G, Torlone E, Ventura MM, Santeusanio F, Brunetti P, Gerich JE, Bolli GB** 1989 Demonstration of a role for growth hormone in glucose counterregulation. Am J Physiol 256: E835–E843
183. **Cryer PE** 2005 Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. Diabetes 54: 3592–3601
184. **Moller N, Schmitz O, Moller J, Butler PC** 1992 Effects of a physiological growth hormone pulse on substrate metabolism in insulin-dependent (type 1) diabetic subjects. J Clin Endocrinol Metab 75:432–436
185. **Christ ER, Simpson HL, Breen L, Sonksen PH, Russell-Jones DL, Kohner EM** 2003 The effect of growth hormone (GH) replacement therapy in adult patients with type 1 diabetes mellitus and GH deficiency. Clin Endocrinol (Oxf) 58:309–315
186. **Press M, Tamborlane WV, Sherwin RS** 1984 Importance of raised growth hormone levels in mediating the metabolic derangements of diabetes. N Engl J Med 310:810–815
187. **Clemmons DR, Moses AC, McKay MJ, Sommer A, Rosen DM, Ruckle J** 2000 The combination of insulin-like growth factor I and insulin-like growth factor-binding protein-3 reduces insulin requirements in insulin-dependent type 1 diabetes: evidence for *in vivo* biological activity. J Clin Endocrinol Metab 85:1518–1524
188. **Bratusch-Marrain PR, Smith D, DeFronzo RA** 1982 The effect of growth hormone on glucose metabolism and insulin secretion in man. J Clin Endocrinol Metab 55:973–982
189. **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
190. **Orskov L, Schmitz O, Jorgensen JO, Arnfred J, Abildgaard N, Christiansen JS, Alberti KG, Orskov H** 1989 Influence of growth hormone on glucose-induced glucose uptake in normal men as assessed by the hyperglycemic clamp technique. J Clin Endocrinol Metab 68:276–282
191. **Fowelin J, Attvall S, von SH, Smith U, Lager I** 1991 Characterization of the insulin-antagonistic effect of growth hormone in man. Diabetologia 34:500–506
192. **Unger RH** 1965 High growth-hormone levels in diabetic ketoacidosis: a possible cause of insulin resistance. JAMA 191:945–947
193. **Schade DS, Eaton RP, Peake GT** 1978 The regulation of plasma ketone body concentration by counter-regulatory hormones in man. II. Effects of growth hormone in diabetic man. Diabetes 27: 916–924
194. **Campbell PJ, Bolli GB, Cryer PE, Gerich JE** 1985 Pathogenesis of the dawn phenomenon in patients with insulin-dependent diabetes mellitus. Accelerated glucose production and impaired glucose utilization due to nocturnal surges in growth hormone secretion. N Engl J Med 312:1473–1479
195. **Perriello G, De Feo P, Torlone E, Fanelli C, Santeusanio F, Brunetti P, Bolli GB** 1990 Nocturnal spikes of growth hormone secretion cause the dawn phenomenon in type 1 (insulin-dependent) diabetes mellitus by decreasing hepatic (and extrahepatic) sensitivity to insulin in the absence of insulin waning. Diabetologia 33:52–59
196. **Blackard WG, Barlascini CO, Clore JN, Nestler JE** 1989 Morning insulin requirements. Critique of dawn and meal phenomena. Diabetes 38:273–277
197. **Nielsen MF, Dinneen S, Basu A, Basu R, Alzaid A, Rizza RR** 1998 Failure of nocturnal changes in growth hormone to alter carbohydrate tolerance the following morning. Diabetologia 41:1064–1072
198. **Van Cauter E, Blackman JD, Roland D, Spire JP, Refetoff S, Polonsky KS** 1991 Modulation of glucose regulation and insulin secretion by circadian rhythmicity and sleep. J Clin Invest 88:934–942
199. **Clore JN, Nestler JE, Blackard WG** 1989 Sleep-associated fall in glucose disposal and hepatic glucose output in normal humans. Putative signaling mechanism linking peripheral and hepatic events. Diabetes 38:285–290
200. **Yuen KC, Frystyk J, White DK, Twickler TB, Koppeschaar HP, Harris PE, Fryklund L, Murgatroyd PR, Dunger DB** 2005 Improvement in insulin sensitivity without concomitant changes in body composition and cardiovascular risk markers following fixed administration of a very low growth hormone (GH) dose in adults with severe GH deficiency. Clin Endocrinol (Oxf) 63:428–436
201. **Hopwood NJ, Forsman PJ, Kenny FM, Drash AL** 1975 Hypoglycemia in hypopituitary children. Am J Dis Child 129:918–926
202. **Bougneres PF, Artavia-Loria E, Ferre P, Chaussain JL, Job JC** 1985 Effects of hypopituitarism and growth hormone replacement therapy on the production and utilization of glucose in childhood. J Clin Endocrinol Metab 61:1152–1157
203. **Beshyah SA, Gelding SV, Andres C, Johnston DG, Gray IP** 1995 β-Cell function in hypopituitary adults before and during growth hormone treatment. Clin Sci (Lond) 89:321–328
204. **Johansson JO, Fowelin J, Landin K, Lager I, Bengtsson BA** 1995 Growth hormone-deficient adults are insulin-resistant. Metabolism 44:1126–1129
205. **Hew FL, Koschmann M, Christopher M, Rantzau C, Vaag A, Ward G, Beck-Nielsen H, Alford F** 1996 Insulin resistance in growth hormone-deficient adults: defects in glucose utilization and glycogen synthase activity. J Clin Endocrinol Metab 81:555–564
206. **Vahl N, Jorgensen JO, Jurik AG, Christiansen JS** 1996 Abdominal adiposity and physical fitness are major determinants of the age associated decline in stimulated GH secretion in healthy adults. J Clin Endocrinol Metab 81:2209–2215
207. **Fowelin J, Attvall S, Lager I, Bengtsson BA** 1993 Effects of treatment with recombinant human growth hormone on insulin sensitivity and glucose metabolism in adults with growth hormone deficiency. Metabolism 42:1443–1447
208. **O'Neal DN, Kalfas A, Dunning PL, Christopher MJ, Sawyer SD, Ward GM, Alford FP** 1994 The effect of 3 months of recombinant human growth hormone (GH) therapy on insulin and glucose-mediated glucose disposal and insulin secretion in GH-deficient adults: a minimal model analysis. J Clin Endocrinol Metab 79:975–983
209. **Rosenfalck AM, Fisker S, Hilsted J, Dinesen B, Volund A, Jorgensen JO, Christiansen JS, Madsbad S** 1999 The effect of the deterioration of insulin sensitivity on β-cell function in growth-hormone-deficient adults following 4-month growth hormone replacement therapy. Growth Horm IGF Res 9:96–105
210. **Beshyah SA, Henderson A, Niththyananthan R, Skinner E, Anyaoku V, Richmond W, Sharp P, Johnston DG** 1995 The effects of short and long-term growth hormone replacement therapy in hypopituitary adults on lipid metabolism and carbohydrate tolerance. J Clin Endocrinol Metab 80:356–363
211. **Hwu CM, Kwok CF, Lai TY, Shih KC, Lee TS, Hsiao LC, Lee SH, Fang VS, Ho LT** 1997 Growth hormone (GH) replacement reduces total body fat and normalizes insulin sensitivity in GH-deficient adults: a report of one-year clinical experience. J Clin Endocrinol Metab 82:3285–3292
212. **Weaver JU, Monson JP, Noonan K, John WG, Edwards A, Evans KA, Cunningham J** 1995 The effect of low dose recombinant human growth hormone replacement on regional fat distribution, insulin sensitivity, and cardiovascular risk factors in hypopituitary adults. J Clin Endocrinol Metab 80:153–159
213. **Bulow B, Erfurth EM** 1999 A low individualized GH dose in young

patients with childhood onset GH deficiency normalized serum IGF-I without significant deterioration in glucose tolerance. Clin Endocrinol (Oxf) 50:45–55
214. **Christopher M, Hew FL, Oakley M, Rantzau C, Alford F** 1998 Defects of insulin action and skeletal muscle glucose metabolism in growth hormone-deficient adults persist after 24 months of recombinant human growth hormone therapy. J Clin Endocrinol Metab 83:1668–1681
215. **Rosenfalck AM, Maghsoudi S, Fisker S, Jorgensen JO, Christiansen JS, Hilsted J, Volund AA, Madsbad S** 2000 The effect of 30 months of low-dose replacement therapy with recombinant human growth hormone (rhGH) on insulin and C-peptide kinetics, insulin secretion, insulin sensitivity, glucose effectiveness, and body composition in GH-deficient adults. J Clin Endocrinol Metab 85:4173–4181
216. **al Shoumer KA, Gray R, Anyaoku V, Hughes C, Beshyah S, Richmond W, Johnston DG** 1998 Effects of four years' treatment with biosynthetic human growth hormone (GH) on glucose homeostasis, insulin secretion and lipid metabolism in GH-deficient adults. Clin Endocrinol (Oxf) 48:795–802
217. **Jorgensen JO, Vahl N, Nyholm B, Juul A, Muller J, Moller N, Schmitz O, Skakkebaek NE, Christiansen J** 1996 Substrate metabolism and insulin sensitivity following long-term growth hormone (GH) replacement therapy in GH-deficient adults. Endocrinol Metab 3:281–286
218. **Svensson J, Fowelin J, Landin K, Bengtsson BA, Johansson JO** 2002 Effects of seven years of GH-replacement therapy on insulin sensitivity in GH-deficient adults. J Clin Endocrinol Metab 87: 2121–2127
219. **Gibney J, Wallace JD, Spinks T, Schnorr L, Ranicar A, Cuneo RC, Lockhart S, Burnand KG, Salomon F, Sonksen PH, Russell-Jones D** 1999 The effects of 10 years of recombinant human growth hormone (GH) in adult GH-deficient patients. J Clin Endocrinol Metab 84:2596–2602
220. **Blank D, Riedl M, Reitner A, Schnack C, Schernthaner G, Clodi M, Frisch H, Luger A** 2000 Growth hormone replacement therapy is not associated with retinal changes. J Clin Endocrinol Metab 85:634–636
221. **Oomen PH, Beentjes JA, Bosma E, Smit AJ, Reitsma WD, Dullaart RP** 2002 Reduced capillary permeability and capillary density in the skin of GH-deficient adults: improvement after 12 months GH replacement. Clin Endocrinol (Oxf) 56:519–524
222. **Johannsson G, Albertsson-Wikland K, Bengtsson BA** 1999 Discontinuation of growth hormone (GH) treatment: metabolic effects in GH-deficient and GH-sufficient adolescent patients compared with control subjects. Swedish Study Group for Growth Hormone Treatment in Children. J Clin Endocrinol Metab 84:4516–4524
223. **Norrelund H, Vahl N, Juul A, Moller N, Alberti KG, Skakkebaek NE, Christiansen JS, Jorgensen JO** 2000 Continuation of growth hormone (GH) therapy in GH-deficient patients during transition from childhood to adulthood: impact on insulin sensitivity and substrate metabolism. J Clin Endocrinol Metab 85:1912–1917
224. **Carroll PV, Drake WM, Maher KT, Metcalfe K, Shaw NJ, Dunger DB, Cheetham TD, Camacho-Hubner C, Savage MO, Monson JP** 2004 Comparison of continuation or cessation of growth hormone (GH) therapy on body composition and metabolic status in adolescents with severe GH deficiency at completion of linear growth. J Clin Endocrinol Metab 89:3890–3895
225. **Jorgensen JO, 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 normalization of body composition. Clin Endocrinol (Oxf) 45:681–688
226. **Maison P, Griffin S, Nicoue-Beglah M, Haddad N, Balkau B, Chanson P** 2004 Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a metaanalysis of blinded, randomized, placebo-controlled trials. J Clin Endocrinol Metab 89:2192–2199
227. **Lucidi P, Lauteri M, Laureti S, Celleno R, Santoni S, Volpi E, Angeletti G, Santeusanio F, De Feo P** 1998 A dose-response study of growth hormone (GH) replacement on whole body protein and lipid kinetics in GH-deficient adults. J Clin Endocrinol Metab 83: 353–357
228. **Russell-Jones DL, Weissberger AJ, Bowes SB, Kelly JM, Thomason M, Umpleby AM, Jones RH, Sonksen PH** 1993 The effects of growth hormone on protein metabolism in adult growth hormone deficient patients. Clin Endocrinol (Oxf) 38:427–431
229. **Shi J, Sekhar RV, Balasubramanyam A, Ellis K, Reeds PJ, Jahoor F, Sharma MD** 2003 Short- and long-term effects of growth hormone (GH) replacement on protein metabolism in GH-deficient adults. J Clin Endocrinol Metab 88:5827–5833
230. **Binnerts A, Swart GR, Wilson JH, Hoogerbrugge N, Pols HA, Birkenhager JC, Lamberts SW** 1992 The effect of growth hormone administration in growth hormone deficient adults on bone, protein, carbohydrate and lipid homeostasis, as well as on body composition. Clin Endocrinol (Oxf) 37:79–87
231. **Russell-Jones DL, Bowes SB, Rees SE, Jackson NC, Weissberger AJ, Hovorka R, Sonksen PH, Umpleby AM** 1998 Effect of growth hormone treatment on postprandial protein metabolism in growth hormone-deficient adults. Am J Physiol 274:E1050–E1056
232. **Krag MB, Nielsen S, Guo Z, Pedersen SB, Schmitz O, Christiansen JS, Jorgensen JO** 2008 Peroxisome proliferator-activated receptor γ agonism modifies the effects of growth hormone on lipolysis and insulin sensitivity. Clin Endocrinol (Oxf) 69:452–461
233. **Nabarro JD** 1987 Acromegaly. Clin Endocrinol (Oxf) 26:481–512
234. **Sonksen 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
235. **Puder JJ, Nilavar S, Post KD, Freda PU** 2005 Relationship between disease-related morbidity and biochemical markers of activity in patients with acromegaly. J Clin Endocrinol Metab 90:1972–1978
236. **Dekkers OM, Biermasz NR, Pereira AM, Romijn JA, Vandenbroucke JP** 2008 Mortality in acromegaly: a metaanalysis. J Clin Endocrinol Metab 93:61–67
237. **Hansen I, Tsalikian E, Beaufrere B, Gerich J, Haymond M, Rizza R** 1986 Insulin resistance in acromegaly: defects in both hepatic and extrahepatic insulin action. Am J Physiol Endocrinol Metab 250: E269–E273
238. **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
239. **Roelfsema F, Frolich M** 1985 Glucose tolerance and plasma immunoreactive insulin levels in acromegalics before and after selective transsphenoidal surgery. Clin Endocrinol (Oxf) 22:531–537
240. **Kasayama S, Otsuki M, Takagi M, Saito H, Sumitani S, Kouhara H, Koga M, Saitoh Y, Ohnishi T, Arita N** 2000 Impaired β-cell function in the presence of reduced insulin sensitivity determines glucose tolerance status in acromegalic patients. Clin Endocrinol (Oxf) 52:549–555
241. **Serri O, Beauregard C, Hardy J** 2004 Long-term biochemical status and disease-related morbidity in 53 postoperative patients with acromegaly. J Clin Endocrinol Metab 89:658–661
242. **Melmed S, Ho K, Klibanski A, Reichlin S, Thorner M** 1995 Clinical review 75: recent advances in pathogenesis, diagnosis, and management of acromegaly. J Clin Endocrinol Metab 80:3395–3402
243. **Melmed S, Casanueva F, Cavagnini F, Chanson P, Frohman LA, Gaillard R, Ghigo E, Ho K, Jaquet P, Kleinberg D, Lamberts S, Laws E, Lombardi G, Sheppard MC, Thorner M, Vance ML, Wass JAH, Giustina A** 2005 Consensus statement: medical management of acromegaly. Eur J Endocrinol 153:737–740
244. 2004 Biochemical assessment and long-term monitoring in patients with acromegaly. Statement from a Joint Consensus Conference of The Growth Hormone Research Society and The Pituitary Society. J Clin Endocrinol Metab 89:3099–3102
245. **Melmed S, Casanueva FF, Cavagnini F, Chanson P, Frohman L, Grossman A, Ho K, Kleinberg D, Lamberts S, Laws E, Lombardi G, Vance ML, Werder KV, Wass J, Giustina A** 2002 Guidelines for acromegaly management. J Clin Endocrinol Metab 87:4054–4058
246. **Trainer PJ** 2002 Acromegaly—consensus, what consensus? J Clin Endocrinol Metab 87:3534–3536
247. **Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, von Werder K, Melmed S** 2000 Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 85:526–529

248. **Abs R, Verhelst J, Maiter D, Van Acker K, Nobels F, Coolens JL, Mahler C, Beckers A** 1998 Cabergoline in the treatment of acromegaly: a study in 64 patients. J Clin Endocrinol Metab 83:374–378
249. **Colao A, Ferone D, Marzullo P, Di Sarno A, Cerbone G, Sarnacchiaro F, Cirillo S, Merola B, Lombardi G** 1997 Effect of different dopaminergic agents in the treatment of acromegaly. J Clin Endocrinol Metab 82:518–523
250. **Alberti KG, Christensen NJ, Christensen SE, Hansen AP, Iversen J, Lundbaek K, Seyer-Hansen K, Orskov H** 1973 Inhibition of insulin secretion by somatostatin. Lancet 2:1299–1301
251. **Davies RR, Miller M, Turner SJ, Goodship TH, Cook DB, Watson M, McGill A, Orskov H, Alberti KG, Johnston DG** 1986 Effects of somatostatin analogue SMS 201–995 in normal man. Clin Endocrinol (Oxf) 24:665–674
252. **Krejs GJ, Browne R, Raskin P** 1980 Effect of intravenous somatostatin on jejunal absorption of glucose, amino acids, water, and electrolytes. Gastroenterology 78:26–31
253. **Moller N, Petrany G, Cassidy D, Sheldon WL, Johnston DG, Laker MF** 1988 Effects of the somatostatin analogue SMS 201–995 (sandostatin) on mouth-to-caecum transit time and absorption of fat and carbohydrates in normal man. Clin Sci (Lond) 75:345–350
254. **Ipp E, Sinai Y, Bar-Oz B, Nesher R, Cerasi E** 1987 Somatostatin impairs clearance of exogenous insulin in humans. Diabetes 36: 673–677
255. **Moller N, Bagger JP, Schmitz O, Jorgensen JO, Ovesen P, Moller J, Alberti KG, Orskov H** 1995 Somatostatin enhances insulin-stimulated glucose uptake in the perfused human forearm. J Clin Endocrinol Metab 80:1789–1793
256. **Ho KK, Jenkins AB, Furler SM, Borkman M, Chisholm DJ** 1992 Impact of octreotide, a long-acting somatostatin analogue, on glucose tolerance and insulin sensitivity in acromegaly. Clin Endocrinol (Oxf) 36:271–279
257. **Koop BL, Harris AG, Ezzat S** 1994 Effect of octreotide on glucose tolerance in acromegaly. Eur J Endocrinol 130:581–586
258. **Sheppard MC** 2003 Primary medical therapy for acromegaly. Clin Endocrinol (Oxf) 58:387–399
259. **Baldelli R, Battista C, Leonetti F, Ghiggi MR, Ribaudo MC, Paoloni A, D'Amico E, Ferretti E, Baratta R, Liuzzi A, Trischitta V, Tamburrano G** 2003 Glucose homeostasis in acromegaly: effects of long-acting somatostatin analogues treatment. Clin Endocrinol (Oxf) 59:492–499
260. **Cozzi R, Attanasio R, Montini M, Pagani G, Lasio G, Lodrini S, Barausse M, Albizzi M, Dallabonzana D, Pedroncelli AM** 2003 Four-year treatment with octreotide-long-acting repeatable in 110 acromegalic patients: predictive value of short-term results? J Clin Endocrinol Metab 88:3090–3098
261. **Ronchi CL, Varca V, Beck-Peccoz P, Orsi E, Donadio F, Baccarelli A, Giavoli C, Ferrante E, Lania A, Spada A, Arosio M** 2006 Comparison between six-year therapy with long-acting somatostatin analogs and successful surgery in acromegaly: effects on cardiovascular risk factors. J Clin Endocrinol Metab 91:121–128
262. **Kopchick JJ, Parkinson C, Stevens EC, Trainer PJ** 2002 Growth hormone receptor antagonists: discovery, development, and use in patients with acromegaly. Endocr Rev 23:623–646
263. **Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, Dimaraki EV, Stewart PM, Friend KE, Vance ML, Besser GM, Scarlett JA, Thorner MO, Parkinson C, Klibanski A, Powell JS, Barkan AL, Sheppard MC, Malsonado M, Rose DR, Clemmons DR, Johannsson G, Bengtsson BA, Stavrou S, Kleinberg DL, Cook DM, Phillips LS, Bidlingmaier M, Strasburger CJ, Hackett S, Zib K, Bennett WF, Davis RJ** 2000 Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med 342:1171–1177
264. **van der Lely AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L, Klibanski A, Herman-Bonert V, Melmed S, Vance ML, Freda PU, Stewart PM, Friend KE, Clemmons DR, Johannsson G, Stavrou S, Cook DM, Phillips LS, Strasburger CJ, Hackett S, Zib KA, Davis RJ, Scarlett JA, Thorner MO** 2001 Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet 358:1754–1759
265. **Barkan AL, Burman P, Clemmons DR, Drake WM, Gagel RF, Harris PE, Trainer PJ, van der Lely AJ, Vance ML** 2005 Glucose homeostasis and safety in patients with acromegaly converted from long-acting octreotide to pegvisomant. J Clin Endocrinol Metab 90:5684–5691
266. **Rose DR, Clemmons DR** 2002 Growth hormone receptor antagonist improves insulin resistance in acromegaly. Growth Horm IGF Res 12:418–424
267. **Jorgensen JOL, Feldt-Rasmussen U, Frystyk J, Chen JW, Kristensen LO, Hagen C, Orskov H** 2005 Cotreatment of acromegaly with a somatostatin analog and a growth hormone receptor antagonist. J Clin Endocrinol Metab 90:5627–5631
268. **Drake WM, Rowles SV, Roberts ME, Fode FK, Besser GM, Monson JP, Trainer PJ** 2003 Insulin sensitivity and glucose tolerance improve in patients with acromegaly converted from depot octreotide to pegvisomant. Eur J Endocrinol 149:521–527
269. **Lindberg-Larsen R, Moller N, Schmitz O, Nielsen S, Andersen M, Orskov H, Jorgensen JOL** 2007 The impact of pegvisomant treatment on substrate metabolism and insulin sensitivity in patients with acromegaly. J Clin Endocrinol Metab 92:1724–1728
270. **De Marinis L, Bianchi A, Fusco A, Cimino V, Mormando M, Tilaro L, Mazziotti G, Pontecorvi A, Giustina A** 2007 Long-term effects of the combination of pegvisomant with somatostatin analogs (SSA) on glucose homeostasis in non-diabetic patients with active acromegaly partially resistant to SSA. Pituitary 10:227–232
271. **O'Connell T, Clemmons DR** 2002 IGF-I/IGF-binding protein-3 combination improves insulin resistance by GH-dependent and independent mechanisms. J Clin Endocrinol Metab 87:4356–4360
272. **O'Sullivan AJ, Kelly JJ, Hoffman DM, Freund J, Ho KK** 1994 Body composition and energy expenditure in acromegaly. J Clin Endocrinol Metab 78:381–386
273. **Ikkos D, Luft R, Sjogren B** 1954 Body water and sodium in patients with acromegaly. J Clin Invest 33:989–994
274. **Raben MS** 1962 Growth hormone. 1. Physiologic aspects. N Engl J Med 266:31–35
275. **Raben MS** 1962 Growth hormone. 2. Clinical use of human growth hormone. N Engl J Med 266:82–86
276. **Liu H, Bravata DM, Olkin I, Nayak S, Roberts B, Garber AM, Hoffman AR** 2007 Systematic review: the safety and efficacy of growth hormone in the healthy elderly. Ann Intern Med 146:104–115
277. **Mekala KC, Tritos NA** 2009 Effects of recombinant human growth hormone therapy in obesity in adults: a metaanalysis. J Clin Endocrinol Metab 94:130–137
278. **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
279. **Nass R, Pezzoli SS, Oliveri MC, Patrie JT, Harrell Jr FE, Clasey JL, Heymsfield SB, Bach MA, Vance ML, Thorner MO** 2008 Effects of an oral ghrelin mimetic on body composition and clinical outcomes in healthy older adults: a randomized trial. Ann Intern Med 149:601–611
280. **Smith RG** 2005 Development of growth hormone secretagogues. Endocr Rev 26:346–360

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