Fuel Metabolism in Growth Hormone–Deficient Adults

Jens Otto Lunde Jørgensen, Niels Møller, Troels Wolthers, Jens Møller, Thorbjørn Grøfte, Nina Vahl, Sanne Fisker, Hans Ørskov, and Jens Sandahl Christiansen

Apart from being a stimulator of longitudinal growth, growth hormone (GH) regulates fuel metabolism in children and adults. A halfmark is mobilization of lipids, which involves an inhibition of lipoprotein lipase activity in adipose tissue and activation of the hormone sensitive lipase. Suppression of basal glucose oxidation and resistance to insulin are other important effects. This may cause concern during GH substitution in GH-deficient adults, some of whom may present with insulin resistance due to concomitant abdominal obesity. However, there are data to suggest that the GH-induced reduction in fat mass and increase in lean body mass may offset the insulin antagonistic actions of the hormone. The nitrogen-retaining effects of GH seem to involve a direct stimulation of protein synthesis in addition to secondary effects such as generation of insulin-like growth factor-I (IGF-I), hyperinsulinemia, and promotion of lipolysis. Thus, during periods of substrate affluence, GH acts in concert with insulin and IGF-I to promote protein anabolism. Postabsorptively, GH is primarily lipolytic and thereby indirectly protein-sparing. This effect becomes further accentuated with more prolonged fasting. In that sense, GH is unique by its preservation of protein during both feast and famine. These fuel metabolic effects add merit to the principle of GH substitution in hypopituitary adults.

THE ABILITY OF growth hormone (GH) to stimulate linear growth and promote retention of nitrogen in hypopituitary children is thoroughly documented.[1-3] That GH administration regulates fuel metabolism is equally well documented but perhaps less appreciated.[4-6] Early animal studies demonstrated that hypophysectomy induced insulin sensitivity, which could be reversed by administering anterior pituitary extracts.[7] Subsequent purification of human pituitary GH prompted a series of studies showing that GH promotes lipolysis at the expense of glucose and protein oxidation and may induce insulin resistance.[6] Most of these studies were conducted in healthy adults using supraphysiological GH dosages. Still, studies using small, physiological amounts of GH do indeed indicate a distinct role for GH in the partitioning of substrate metabolism.[8] It could be inferred from these data that hyposomatropenemia in adults would induce abnormalities in fuel metabolism. However, studies with GH administration in GH-deficient (GHD) patients have mainly focused on height gain in GHD children. Following the availability of biosynthetic GH, a large number of studies from many different groups have uniformly shown that GH deficiency in adults is associated with distinct abnormalities, many of which normalize following GH substitution.[9] Most studies have focused on body composition, physical fitness, lipoprotein metabolism, and cardiovascular function. The subservient changes in fuel metabolism have received relatively little attention. The aim of this article is to review and appraise current data on this important issue.

LIPID METABOLISM

A prompt and significant GH-induced increase in circulating levels of free fatty acids (FFA) in hypopituitary adults was initially reported in 1959[10] and subsequently confirmed.[11] Since this lipolytic effect was abolished with subsequent intake of breakfast and glucose, it was speculated that the physiological metabolic role of GH is to promote postabsorptive lipid oxidation and hence spare protein.[10] The classic studies by Rabinowitz et al[12] demonstrated an acute and direct stimulatory effect of GH on forearm muscle uptake and oxidation of FFA in healthy adults. It was a recognized concern already in that period that the studies used pituitary preparations of uncertain purity and in very high doses. However, the lipolytic actions of GH have been documented with biosynthetic preparations,[13,14] and pulsatile intravenous administration of small biosynthetic GH doses (140 μg) in healthy postabsorptive adults induces a marked increase in circulating FFA.[8] Thus, the lipolytic effect is intrinsic to the GH molecule and operates during physiological conditions.

Varying fasting levels of lipid intermediates in untreated GHD adults have been reported, which could reflect different study conditions, different levels of activity of other counterregulatory hormones, and perhaps more importantly, differences in body composition. As a rule, GHD children are only moderately obese, whereas long-standing GH deficiency in adults may be associated with morbid obesity. Regardless of this, GH administration in GH deficiency unequivocally promotes a dose-dependent increase in both the circulating levels and oxidation of lipid intermediates.[14,15] Furthermore, adolescent patients deprived of GH therapy exhibit a blunting of the normal nocturnal surge in levels of lipid intermediates, which become normalized following evening GH administration (Fig 1).[16] In the same study, deprivation of GH therapy induced a nocturnal increase in levels of gluconeogenic substrate precursors (Fig 1), implying that nocturnal fuel metabolism in that situation was directed toward oxidation of protein-derived carbon fragments rather than lipid. Twenty-four-hour discontinuation of GH therapy in GHD adults has been shown to reduce lipid oxidation to subnormal levels, which could be reverted by GH, altogether supporting a physiological role for GH in day-to-day fuel metabolism.[17]

The cellular and molecular mechanisms subserving the

From the Department of Internal Medicine (Endocrinology and Diabetes), Aarhus University Hospital, and the Institute of Experimental Clinical Research, Aarhus University, Aarhus, Denmark.

Address reprint requests to Jens Otto Lunde Jørgensen, MD, Medical Department M, Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark.

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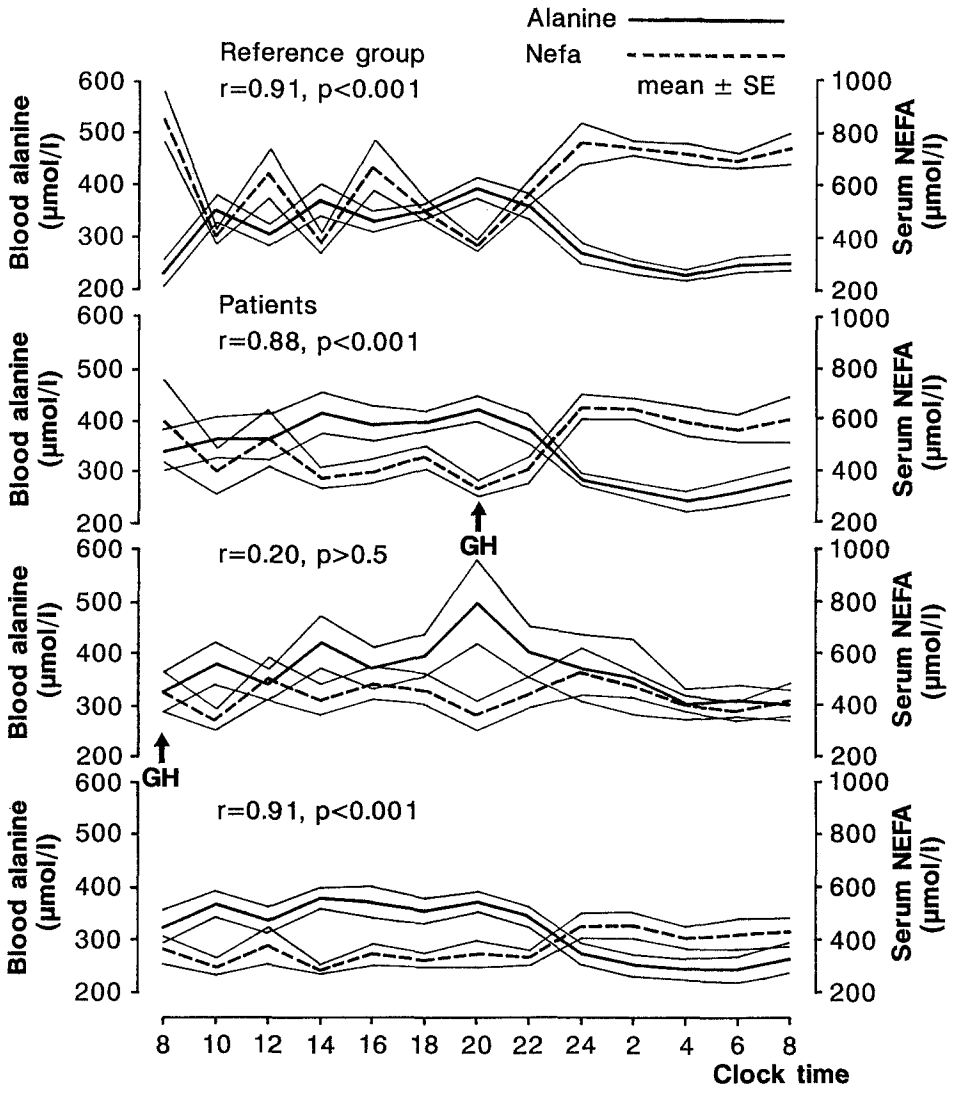

Fig 1. Mean ± SE 24-hour profiles of circulating alanine and nonesterified FFA (NEFA) in 8 GHD patients after evening GH administration (B), morning GH administration (C), and no GH administration (D). (A) Age- and sex-matched control group of untreated children. (Data from Jørgensen et al.[16])

lipolytic effects of GH are poorly characterized. Human adipocytes contain GH receptors, and GH has been shown to directly stimulate in vitro lipolysis in some but definitely not all studies. This is presumed to involve a stimulation of hormone-sensitive lipase activity. It should be emphasized that available in vitro data are conflicting, which partly reflects differences in methodology, duration of GH exposure, and substrate background before biopsy. Fat biopsies from seven GHD children before and after 3 months' GH therapy showed a significant reduction in basal lipogenesis along with a reduction in abdominal but not gluteal lipid content per cell.[18] In the same study, the actions of insulin and catecholamines on lipogenesis/lipolysis were similar before and after GH, but the GH-induced change (reduction) in fat content of abdominal cells correlated positively with the change (decrease) in insulin-mediated antilipolysis. Lipoprotein lipase activity, which promotes tissue uptake and assimilation of triglycerides from the circulation and is stimulated by insulin, was unaffected in the study reported by Rosenbaum et al,[18] whereas a GH-induced decrease in lipoprotein lipase activity has recently been demonstrated in obese women.[19] One study in GHD adults evaluated in vitro lipolysis (ie, glycerol release) in abdominal fat biopsies before and after 6 months' GH therapy in a parallel design,[20] and reported unaltered basal but enhanced β-adrenergic lipolysis. This is discordant with the data in children,[18] which epitomize that although the lipolytic actions of GH are readily detectable with estimates such as FFA measurements in the circulation, rates of whole-body lipid oxidation, and measures of body composition, there still remain uncertainties about the underlying mechanisms.

GLUCOSE METABOLISM

A consistent symptom of GH deficiency in children is fasting hypoglycemia[21,22] despite low to normal insulin levels. There are relatively few detailed studies on glucose metabolism in GH deficiency. Bourgneres et al[23] studied postabsorptive glucose turnover by means of isotope-dilution techniques in five GHD children before and after 2 to 6 weeks of GH therapy. Before GH therapy, plasma glucose concentrations decreased gradually, which could be

ascribed to decreased glucose production. GH therapy normalized plasma glucose levels and increased both endogenous glucose production and disposal. It was speculated that the patients not treated with GH were depleted of hepatic glycogen stores. A more detailed study involved young GHD adults on regular daily GH therapy who were studied twice after an overnight fast, before which the last GH injection was replaced with an intravenous infusion of either placebo or GH, respectively.[17] The study design involved glucose turnover, sequential euglycemic and hypoglycemic glucose clamps, estimation of forearm substrate balances, and indirect calorimetry. Basal levels of plasma glucose were similar in the two situations, as was the rate of total glucose turnover. By contrast, glucose oxidation became significantly reduced during GH infusion. Insulin sensitivity became significantly reduced during GH infusion, in terms of a decreased forearm glucose uptake, a blunted suppression of endogenous (hepatic) glucose production, and a reduced glucose infusion rate (M value) during the euglycemic glucose clamp (Fig 2). The GH-induced impairment of glucose sensitivity is a feature that can be reproduced following GH exposure in normal subjects and in active acromegaly.[6] It is traditionally speculated to be secondary to the increased lipid availability and subsequent substrate competition (Randle cycle), but the underlying cellular and molecular events remain to be unveiled. These effects are compatible with the evidence of insulin hypersensitivity in untreated GHD children and adolescents. By contrast, suggestions of mild insulin resistance have been reported in some elderly GHD adults, which presumably is a consequence of the associated increased fat mass and decreased lean body mass (LBM). Consequently, it has been a concern whether GH substitution would further impair insulin sensitivity in obese GHD adults. Increased basal glucose and insulin levels and reduced insulin-stimulated glucose disposal have been reported following 6 weeks' GH therapy in a group of moderately obese GHD adults.[24] However, following continuation of GH therapy for 6 months, both basal and insulin-stimulated glucose metabolism no longer differed from pretreatment levels.[24] A control group of healthy untreated subjects were not available in that study, but the data may imply that the direct insulin-antagonistic actions of GH may be offset in the long run by the concomitant increment in LBM and reduction in fat content. In this regard, it also merits attention that clinical glucose intolerance is not seen in GHD adults on long-term GH substitution.[25]

As mentioned earlier, fasting hypoglycemia is a feature of GH deficiency in childhood, which suggests a physiological role for GH in the prevention of hypoglycemia. During a hypoglycemic glucose clamp (plasma glucose levels, ~3 mmol/L) in GHD young adults, discontinuation of GH therapy was associated with hypersensitivity to insulin in terms of an increased M value (glucose infusion rate), increased forearm glucose uptake, and suppressed uptake of FFA.[17] These findings are in accordance with a report of reduced lipolysis following insulin-induced hypoglycemia in panhypopituitary adults deprived of GH and cortisol.[26]

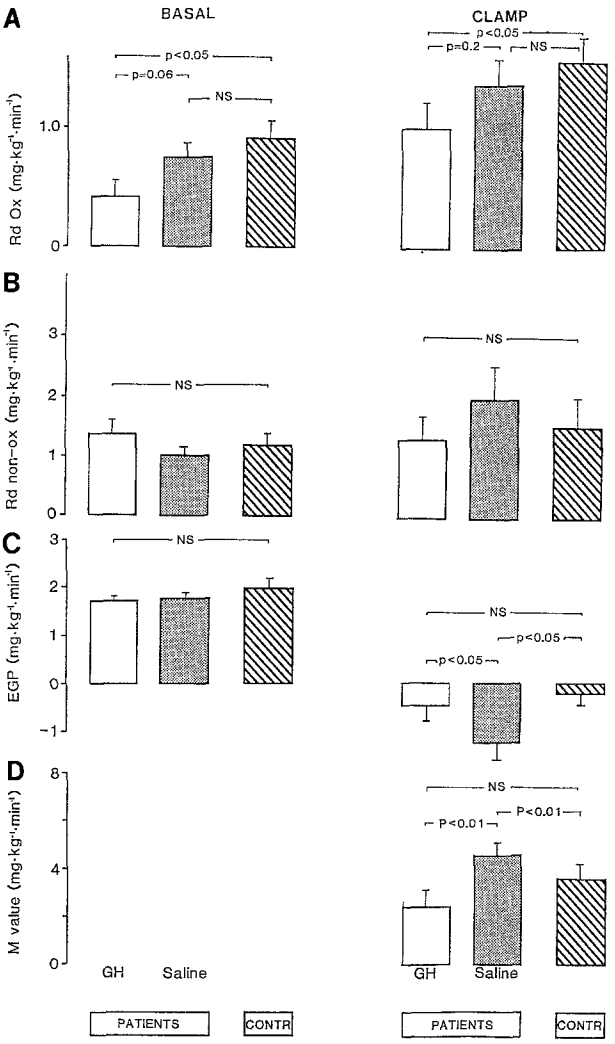

Fig 2. (A) Oxidative (Rd Ox) and (B) nonoxidative (Rd non-ox) glucose turnover and (C) endogenous glucose production (EGP) in the basal state and during a euglycemic glucose clamp in six GHD patients. (D) M value (glucose infusion rate) during the clamp. All patients were on regular daily GH therapy, which was discontinued on the evening before each study and replaced with saline infusion or low-dose GH infusion. For comparison, a control group of healthy, untreated subjects (CONTR) were included. (Reprinted with permission.[17])

Neither of these studies mimic the conditions of short-term fasting, but they do add support to an important role for GH in the regulation of fuel metabolism in postabsorptive and fasting conditions. The ability to mobilize lipids during such conditions is pivotal for an individual, considering that a normal adult has only 1,500 kcal of accessible glycogen as opposed to 125,000 kcal of mobilizable fat.[6]

PROTEIN METABOLISM

It is well known that GH promotes protein anabolism. Retention of nitrogen during metabolic-balance studies is perhaps the most reproducible feature of GH administration. The associated changes in LBM in acromegaly and in GH deficiency before and after therapy are also obvious. Still, the direct effects of GH on protein metabolism are not

fully characterized. In this regard, it is important to note that systemic GH exposure is associated with increments in insulin and insulin-like growth factor-I (IGF-I), both of which are protein-anabolic. It is generally considered that insulin and IGF-I primarily act to inhibit proteolysis, whereas GH per se stimulates protein synthesis and inhibits protein oxidation.[27-30] Furthermore, enhanced lipolysis is known to promote nitrogen retention, but the degree to which this affects protein metabolism during GH exposure has not been assessed.

Protein metabolism in terms of whole-body isotopic leucine turnover in GHD adults has been studied by two groups. Two months of GH therapy resulted in increased rates of total leucine turnover and a reduction in leucine oxidation, indicating a stimulation of protein synthesis.[31] In a subsequent study, 16 untreated GHD adults were compared with a control group of 20 subjects matched for age and sex. Total leucine turnover and leucine oxidation were significantly reduced in the patients even after correction for LBM.[32] Six patients were restudied after 6 months' GH therapy, and in four subjects an increase in protein synthesis was recorded, which failed to reach statistical significance. Notably, both treatment studies were accompanied by significant increments in IGF-I and insulin. Thus, both studies indicate that GH therapy in GHD adults stimulates protein synthesis, similar to that observed in GH-treated healthy adults.

Since ureagenesis is the final metabolic pathway of α-amino nitrogen that is not used for protein synthesis, it is not unexpected that urea excretion is reduced following GH exposure. This is generally considered merely to reflect a decreased supply of amino acids for hepatic urea synthesis. However, it has been shown that several additional factors may regulate ureagenesis. Numerous studies in humans have demonstrated a linear correlation between the rate of urea synthesis and amino acid levels during infusion of amino acids. The slope is termed the functional hepatic nitrogen clearance (FHNC) and thus provides an experimental substrate-independent measure of hepatic urea synthesis. With this method, discontinuation of GH for 2 days in GHD adults had no impact on FHNC.[33] Likewise, short-term GH administration in normal adults was not associated with changes in FHNC. Still, neither of these studies rules out a long-term effect of GH on FHNC.

CONCLUSION

GH replacement therapy in adults has distinct metabolic effects. The long-term effects are characterized by a normalization of body composition in terms of increased LBM and decreased fat mass. The short-term metabolic effects subserving these body compositional changes are composite, but a hallmark is stimulation of lipolysis. The sites of action at the molecular level are still not precisely located, but may involve both an inhibition of lipoprotein lipase activity in adipose tissue and a stimulation of hormone-sensitive lipase. Suppression of basal glucose oxidation and resistance to the actions of insulin are other important effects, which may cause concern from a clinical point of view. On the other hand, non-obese, untreated GH deficiency is associated with insulin hypersensitivity, which makes patients susceptible to postprandial or fasting hypoglycemia. A particular problem pertains to obese GH deficiency, in which institution of GH therapy may induce transient glucose intolerance. The data so far seem to suggest that such effects are offset by the long-term beneficial effects on body composition, but these patients should merit special attention and the substitution dose should be carefully tailored. Finally, GH therapy promotes nitrogen retention, which seems to be corroborated by a stimulation of protein synthesis. It is likely that the protein-anabolic effects are mediated through several factors, including direct GH effects, IGF-I generation, hyperinsulinemia, and enhanced lipolysis. Put together, the simplistic model for the combined metabolic actions of GH may still be used: During periods of substrate affluence, GH acts in synergy with insulin and IGF-I to promote protein anabolism. Postabsorptively, GH acts directly to mobilize lipids and inhibit oxidative glucose utilization, which is indirectly protein-sparing. By perpetuation of this cycle, GH increases LBM and decreases body fat. During prolonged fasting, insulin and IGF-I levels are low, features that stimulate GH secretion and direct fuel metabolism toward lipid consumption, which again protects against excessive protein breakdown. In this regard, GH is unique by preserving LBM during both feast and famine. Although famine is a rare occurrence in affluent societies, it seems that the fuel-metabolic actions of GH add merit to the concept of substituting GHD adults with GH.

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