Two Weeks of Daily Injections and Continuous Infusion of Recombinant Human Growth Hormone (GH) in GH-Deficient Adults. II. Effects on Serum Lipoproteins and Lipoprotein and Hepatic Lipase Activity

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Recombinant human growth hormone (GH) administered as daily subcutaneous (SC) injections has been shown to affect serum lipoproteins in GH-deficient subjects. However, the effects of continuous infusion of GH on serum lipoproteins have not been investigated in GH-deficient adults. The aim of the present study was to compare effects of daily injections and continuous infusion of GH on lipoprotein metabolism. Recombinant human GH (0.25 U/kg/wk) was administered to nine GH-deficient adult men during a period of 14 days in two different ways, ie, as a daily SC injection at 8:00 PM and as a continuous SC infusion, with 1 month of washout between the treatments. Blood samples and tests were performed in the morning after an overnight fast before the start of GH treatment (day 0) and on day 2 and day 14 of treatment. Abdominal SC adipose tissue lipoprotein lipase (LPL), postheparin plasma LPL, and hepatic lipase (HL) activity were measured 120 minutes after the intake of 100 g glucose. Adipose tissue LPL activity decreased and postheparin plasma HL activity increased after 14 days of GH treatment irrespective of the mode of GH administration, whereas GH treatment had no effect on postheparin plasma LPL activity. Serum triglyceride and very-low-density lipoprotein (VLDL) triglyceride concentrations increased during GH treatment. However, VLDL triglyceride concentrations increased to a greater degree during treatment with daily GH injections than during continuous infusion of GH. Serum apolipoprotein (apo) B and low-density lipoprotein (LDL) cholesterol concentrations decreased during treatment with daily GH injections, but were not significantly affected by continuous GH infusion. Thus, apo B and LDL cholesterol concentrations were lower after daily GH injections versus continuous GH infusion. Serum lipoprotein(a) [Lp(a)] and apo E concentrations increased during both modes of GH treatment. However, continuous infusion of GH resulted in a more marked increase in Lp(a) and apo E concentrations than daily GH injections. Minor effects were observed on serum apo A-I concentrations, but high-density lipoprotein (HDL) cholesterol concentrations were not affected. In conclusion, GH treatment of GH-deficient men influenced adipose tissue LPL and postheparin plasma HL activity, as well as serum lipoprotein concentrations. Moreover, continuous GH infusion and daily GH injections differed with respect to the magnitude of effects on several lipoprotein fractions including VLDL triglycerides, LDL cholesterol, apo B, apo E, and Lp(a) concentrations.

GROWTH HORMONE (GH) is episodically secreted in all animals studied so far. In the rat, there is a clear sexual dimorphism with respect to the secretory pattern of GH.[1] This sex difference for GH secretion has been shown to regulate sex differences in serum lipoprotein levels[2-4] and hepatic secretion of lipoproteins[5] in the rat. In man, the secretory pattern of GH does not differ between men and women to the same extent as in the rat. However, women have a higher mean 24-hour integrated GH secretion and higher mean baseline GH levels than men.[6,7] An increase in basal GH levels has also been observed during pregnancy,[8] in fasting,[9] and in poorly controlled diabetes mellitus,[10] and may therefore also involve metabolic adjustments in these conditions. Apart from the effects on growth, the physiological importance of different administration regimens of GH in adults has so far only been investigated in short-term studies lasting 1 to 2 days.[11-13]

GH has been shown to have effects on serum lipoprotein levels in both experimental animals[2-4,14] and man.[15-21] In the rat, GH has been shown to affect hepatic lipoprotein secretion,[5,22,23] low-density lipoprotein (LDL) receptor expression,[24] and lipoprotein lipase (LPL)[25,26] and hepatic lipase (HL) activity.[26,27] In GH-treated GH-deficient children, postheparin plasma LPL and HL activity have been found to be lower than in untreated GH-deficient children.[28] Moreover, postheparin plasma LPL activity has been found to be lower in patients with acromegaly.[29] It was recently observed that subcutaneous (SC) adipose tissue LPL activity decreased following GH treatment of obese women.[30] Before the present study was undertaken, we observed no effect of GH treatment on adipose tissue or postheparin plasma LPL activity measured after an overnight fast in obese middle-aged men.[19] However, it could be that GH primarily affects postprandial adipose tissue LPL activity. Since the postprandial increase in adipose tissue LPL activity has been shown to be more pronounced after a glucose meal versus a fat meal,[31,32] adipose tissue and postheparin plasma LPL activity were determined following a glucose meal in the present study.

The present investigation was performed to evaluate the importance of different regimens of GH on serum lipoproteins, since the question of whether one mode of GH administration or another has different effects on lipoprotein metabolism in man is unanswered. A continuous SC infusion of GH was compared with daily SC injections for effects on LPL and HL activity and serum lipoprotein levels in GH-deficient men.

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SUBJECTS AND METHODS

Subjects

Nine men aged 41 to 63 years who had previously been investigated as inpatients at the Endocrine Unit because of pituitary disorders were asked to participate in the study. After insulin (0.1 U/kg)-induced hypoglycemia with blood glucose less than 2.2 mmol/L, all the men had serum GH concentrations less than 5 mU/L (Table 1). Two subjects had isolated GH deficiency, and seven had multiple pituitary deficiencies that had been present for at least 1 year before the study (Table 1). The patients were on stable replacement therapy with glucocorticoids (cortisone acetate 25 mg/d) and L-thyroxine (0.10 to 0.15 mg/d). Administration of intramuscular injections of testosterone enanthate was changed 1 month before the study from 250 mg/mo to 125 mg every second week to avoid major changes in serum testosterone concentration during the study period.[33]

Subjects were given recombinant human ([GHrhGH] Genotropin; Pharmacia Kabi, Stockholm, Sweden) 0.25 U/kg/wk for 14 days in two different ways, with a 1-month washout period between the two treatment regimens. During the first treatment period, rhGH was administered as a daily SC injection at 8:00 PM (KabiPen 16; Pharmacia). During the second treatment period, rhGH was given in the same dose but as a continuous SC infusion using a MiniMed 404-SP infusion pump (MiniMed Technologies, Sylmar, CA) and a Cliniset Micro Infusion Set (Pharma-Plast, Lynge, Denmark). The needle was inserted 0.1 m from the umbilicus.

Body weight was measured to the nearest 0.1 kg and height to the nearest 0.01 m. Blood samples were taken in the morning (7:30 to 9:00 AM) after an overnight fast at day 0, day 2, and day 14.

An oral glucose tolerance test (OGTT) was performed on day 0 and day 14 starting at 8:00 to 9:00 AM. Immediately after the OGTT (120 minutes after intake of 100 g glucose), a SC abdominal adipose tissue biopsy was obtained by needle aspiration for determination of total LPL activity, triglyceride content, and fat cell size. Needle aspiration was performed 0.1 m from the umbilicus on the opposite side of the infusion needle. Immediately after needle aspiration, heparin (50 U/kg) was given intravenously. Venous blood samples were collected after 15 minutes in Vacutainer tubes containing EDTA (Terumo, Leuven, Belgium) for measurements of postheparin plasma LPL and HL activity. Biopsies for LPL activity analysis (duplicate samples on each occasion) were frozen in liquid nitrogen. Both the fat biopsies and the postheparin plasma were stored at −80°C until assay.

Written informed consent was obtained from the subjects. The study was approved by the local Ethics Committee at Göteborg University and by the Swedish Medical Products Agency (Uppsala, Sweden).

Assays

Serum cholesterol and triglyceride concentrations were determined using fully enzymatic methods (Boehringer, Mannheim, Germany) using a Cobas Fara autoanalyzer (Hoffman LaRoche, Basel, Switzerland). Within-assay coefficients of variation for cholesterol and triglyceride determinations were 0.9% and 1.1%, respectively. Apolipoprotein (apo) A-I and apo B concentrations were determined using immunoturbidometric assays (UniKit Roche; Hoffman LaRoche).[17] Apo E concentrations were determined using an electroimmunoassay.[34] Within-assay coefficients of variation for apo A-I, apo B, and apo E assays were 2.3%, 1.9%, and 4.8%, respectively. Lipoprotein(a) [Lp(a)] concentrations were determined using a radioimmunoassay (Pharmacia).[17,35] This Lp(a) assay was standardized against an electroimmunoassay.[35] The within-assay coefficient of variation for the Lp(a) assay was 4.4%. To exclude the possibility that free apo(a) level was being measured, Lp(a) level was also measured with an enzyme-linked immunosorbent assay (ELISA) that has a first antibody against apo(a) and a second antibody against apo B (Apo-Tek Lp(a), Organon Teknika; Biotechnology Research Institute, Rockville, MD). Radioimmunoassay and ELISA methods produced similar results ($r = .77$, $P < .01$, data not shown), indicating that the increase in Lp(a) was not due to an increase in free apo(a) or other related proteins such as plasminogen. Plasminogen level was also measured and was found not to be influenced by GH treatment (data not shown). High-density lipoprotein (HDL) cholesterol, HDL apo E, and HDL apo A-I were determined after precipitation of apo B–containing lipoproteins with $MgCl_2$ and heparin.[36] Very–low-density lipoprotein (VLDL) cholesterol and triglyceride concentrations were determined in the fraction with a density of less than 1.006 g/L obtained by ultracentrifugation. LDL cholesterol concentrations were calculated from total serum cholesterol, HDL cholesterol, and VLDL cholesterol concentrations. Reference values for serum cholesterol, HDL cholesterol, and serum triglyceride concentrations were obtained from the Göteborg sample of the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study.[37]

Total LPL activity in adipose tissue was determined after homogenization of the tissue in a detergent-containing buffer as described previously.[38,39] Samples of the homogenates (5 μL) were incubated in triplicate in a total volume of 200 μL at 25°C for 2 hours. The procedure developed by Spooner et al[40] was used to

Table 1. Individual Data on the GH-Deficient Men

Patient No.	BMI (kg/m²)	Age (yr)	Diagnosis	Duration of GH Deficiency (yr)	Serum IGF-I (μg/L)†	Maximum Serum GH Response After ITT (mU/L)	Hormonal Therapy
1	30.8	47	Chromophobic A	9	114	4.2	LT_4
2	29.6	43	Idiopathic*	3	122	0.3	LT_4, ADH
3	26.1	45	Chromophobic A	5	68	0	LT_4, cortisone, testosterone
4	26.3	47	Chromophobic A	11	96	0.4	LT_4, cortisone, testosterone
5	26.0	41	Chromophobic A	2	122	1.9	—
6	23.8	63	Chromophobic A	10	58	0	LT_4, testosterone
7	28.8	49	Chromophobic A	4	138	0.9	LT_4, testosterone
8	32.6	41	Prolactinoma	2	193	2.5	Testosterone
9	25.6	49	Chromophobic A	2	181	3.1	—

Abbreviations: A, adenoma; ITT, insulin tolerance test (0.1 U insulin/kg body weight); T_4, thyroxine; ADH, antidiuretic hormone; BMI, body mass index.

*Enlarged and thick fibrous dura mater.

†Serum IGF-I concentration before the start of the study.

extract fatty acids for counting. Bovine skim milk was used as a standard to correct for interassay variation. The amount of triglycerides in the tissue was measured after extraction[41] and weighed after evaporation of solvents. Activity was expressed in milliunits (1 mU = 1 nmol free fatty acids released/min) per gram of triglyceride. The within-assay coefficient of variation was 5.4% (36 triplicates).

Assays for postheparin plasma LPL and HL activity were as described previously,[39,42] using total assay volumes of 200 μL and plasma volumes of 15 and 10 μL for the LPL and HL assay, respectively. Assays for both LPL and HL were performed at 25°C for 20 minutes, and all samples were analyzed in triplicate. Fatty acids were extracted according to the method reported by Spooner et al.[40] For assay of LPL, the substrate was prepared by sonication of [^{3}H]-triolein into Intralipid (Kabi Pharmacia). Plasma samples were preincubated for 2 hours on ice with 0.5 vol of a solution containing goat antibodies against human HL. For assay of HL, a gum-arabic–stabilized [^{3}H]-triolein emulsion was used. Two postheparin plasma samples obtained from two healthy normolipidemic men (25 and 55 years of age), as well as bovine skim milk, were used as standards for lipase assays. Postheparin plasma standards were prepared in the same way as the other samples, placed in aliquots into small tubes, and stored at −80°C. Postheparin LPL and HL activity was expressed as milliunits per milliliter plasma. Control experiments showed that all lipase assays were linear with the amount of sample and time over the range used. Fat cell size was determined using a microscopic method.[43]

Statistics

All values are the mean ± SEM. A one-way ANOVA with the complete-block design followed by Student-Neuman-Keuls multiple-range test was used to test the effects of GH treatment. Values were transformed to logarithms when appropriate. P less than .05 was considered significant.

RESULTS

Serum Lipoproteins

One patient (no. 8) had a serum cholesterol concentration above the 90th percentile of the control population in relation to age.[37] Another patient (no. 1) had a serum triglyceride concentration above the 90th percentile of the control population. HDL cholesterol concentrations were less than the 10th percentile of the control population in relation to age in four patients (no. 1, 3, 4, and 7).

Total serum cholesterol concentrations decreased after 14 days of treatment with one daily injection of GH, but did not change significantly after continuous infusion of GH. Total serum cholesterol concentration was lower after 14 days of daily GH injections versus continuous GH infusion (Table 2). HDL cholesterol concentration did not change significantly during the various treatment periods (Table 2). LDL cholesterol concentration decreased after 14 days of daily GH injections (17% ± 3%), but was not significantly affected by continuous GH infusion (8% ± 4%). Thus, LDL cholesterol decreased to a greater degree during treatment with daily GH injections (Table 2). Serum triglyceride and VLDL triglyceride concentrations increased during daily injections and continuous infusion of GH. However, after 14 days of treatment, the increase in VLDL triglyceride concentration was more pronounced after daily injections (91% ± 22%) than after continuous infusion (57% ± 12%; Table 2).

Serum Lp(a) concentrations increased more after 14 days of continuous infusion of GH (83% ± 17%) than after daily injections (48% ± 15%). Similarly, serum apo E concentrations increased more after 14 days of continuous infusion of GH (41% ± 9%) than after daily injections (19% ± 4%; Fig 1A and C). However, no differences were observed between the two modes of administration for Lp(a) and apo E concentrations following 2 days of treatment. Apo E concentrations were also determined in the HDL fraction obtained by precipitating apo B–containing lipoproteins. GH treatment had no effect on HDL apo E levels (data not shown), thereby indicating that GH treatment affected apo E in other lipoprotein fractions. Serum apo B concentrations decreased after 14 days of daily GH injections, but did not change significantly during continuous infusion of GH. Thus, apo B concentration was lower after 14 days of daily GH injections than after continuous GH infusion (Fig 1B). Continuous infusion of GH resulted in a small decrease in serum apo A-I concentrations (8% ± 2%; Fig 1D). Serum apo A-I concentration did not change significantly during daily GH injections (4% ± 2%), but decreased between 2 and 14 days of treatment (P < .05).

Table 2. Effects of One Daily Injection (PEN) and Continuous Infusion (PUMP) of GH on Serum Lipoprotein Concentrations in GH-Deficient Adult Men

	PEN			PUMP		
Lipoprotein	Day 0	Day 2	Day 14	Day 0	Day 2	Day 14
Cholesterol (mmol/L)						
Total	6.50 ± 0.23	6.66 ± 0.31	5.86 ± 0.33†	6.52 ± 0.29	6.46 ± 0.33	6.24 ± 0.24‡
HDL	1.14 ± 0.13	1.19 ± 0.09	1.02 ± 0.09	1.22 ± 0.11	1.09 ± 0.10	1.16 ± 0.11
LDL	4.70 ± 0.27	4.64 ± 0.32	3.94 ± 0.33†	4.73 ± 0.29	4.51 ± 0.30	4.40 ± 0.26§
VLDL	0.66 ± 0.12	0.83 ± 0.12	0.90 ± 0.19	0.57 ± 0.07	0.86 ± 0.13*	0.80 ± 0.13*
Triglycerides (mmol/L)						
Total	1.81 ± 0.24	2.19 ± 0.21	2.63 ± 0.35†	1.69 ± 0.17	2.18 ± 0.26*	2.26 ± 0.25*
VLDL	1.09 ± 0.22	1.41 ± 0.20	1.87 ± 0.33†	0.98 ± 0.15	1.40 ± 0.22*	1.51 ± 0.25*‡

NOTE. Values are the mean ± SEM of 9 observations.

*P < .05 v day 0 corresponding treatment (PEN or PUMP).

†P < .01 v day 0 corresponding treatment (PEN or PUMP).

‡P < .05 v corresponding day during daily GH injections (PEN).

§P < .01 v corresponding day during daily GH injections (PEN).

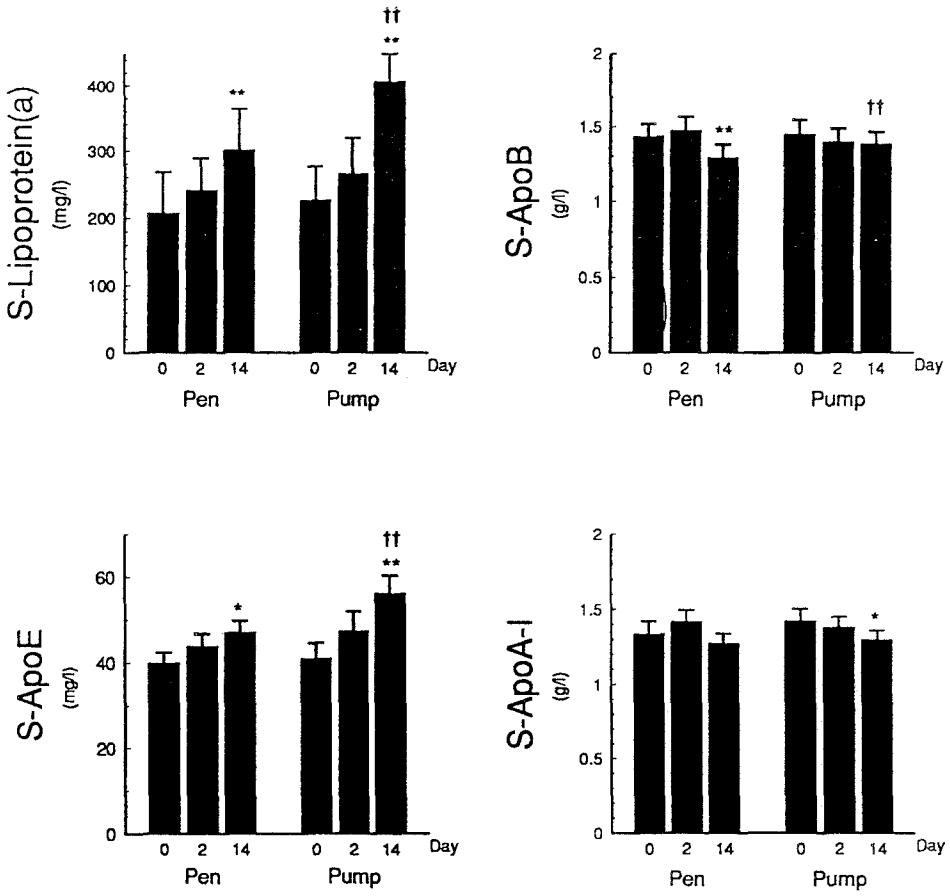

Fig 1. Effects of one daily injection at 8:00 PM (PEN) and continuous infusion (PUMP) of GH on serum concentrations of Lp(a), apo B, apo E, and apo A-I after an overnight fast. Values are the mean ± SEM of 9 observations. *$P < .05$ *v* day 0 corresponding treatment (PEN or PUMP); **$P < .01$ *v* day 0 corresponding treatment (PEN or PUMP); ††$P < .05$ *v* corresponding day during daily GH injections (PEN).

LPL and HL

Postheparin plasma LPL and HL activity, as well as adipose tissue LPL activity, were determined 2 hours after subjects had received 100 g glucose. GH treatment had no effect on postheparin plasma LPL activity (Fig 2A), but HL activity was enhanced (Fig 2B) independently of the mode of GH administration. Adipose tissue LPL activity was reduced by approximately one third after 14 days of GH treatment, independently of the mode of GH administration (Fig 3). GH treatment had no effect on fat cell size (data not shown).

DISCUSSION

The present study confirms previous observations in GH-deficient adults that daily or less frequent injections of GH result in decreased serum concentrations of cholesterol, LDL cholesterol, and apo B and increased serum concentrations of Lp(a).[16-18,20] These observations are extended in this study, which reveals an effect of GH on serum apo E concentrations, as well as inhibition of postprandial adipose tissue LPL activity and stimulation of postprandial HL activity. Moreover, continuous infusion of GH resulted in higher LDL cholesterol, apo B, and Lp(a) concentrations, but also in higher apo E concentrations and lower VLDL triglyceride concentrations, than when GH was administered in the form of daily SC injections.

In this study, one patient was hypercholesterolemic and another was hypertriglyceridemic. Thus, two of nine patients (22%) were hyperlipidemic at onset of the study. This frequency of hyperlipidemia is similar to[21] or less than[20] that previously reported in GH-deficient children. In GH-deficient adults, serum cholesterol concentrations have

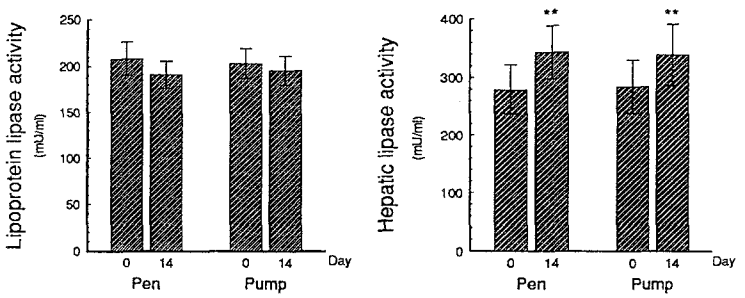

Fig 2. Effects of one daily injection at 8:00 PM (PEN) and continuous infusion (PUMP) of GH on postheparin plasma LPL activity and postheparin plasma HL activity 120 minutes after intake of 100 g glucose. Values are the mean ± SEM of 9 observations. **$P < .01$ *v* day 0 corresponding treatment (PEN or PUMP).

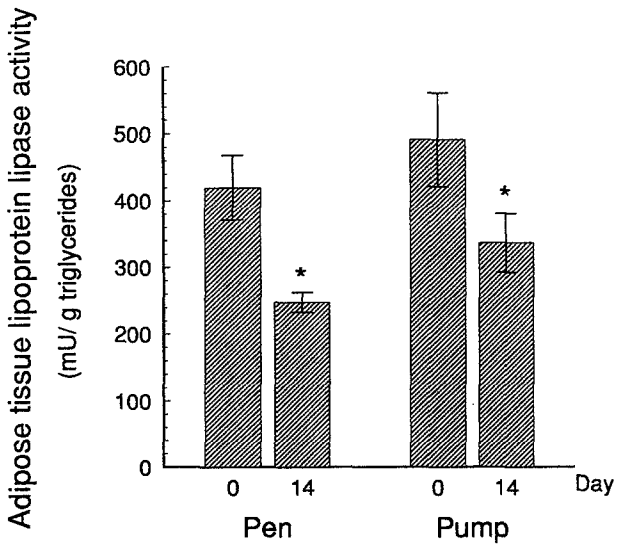

Fig 3. Effects of one daily injection at 8:00 PM (PEN) and continuous infusion (PUMP) of GH on adipose tissue LPL activity. Samples were obtained by needle aspiration from the SC abdominal region 120 minutes after intake of 100 g glucose. Values are the mean ± SEM of 9 observations. *P < .05 v day 0 corresponding treatment (PEN or PUMP).

been reported to be either similar to[44] or higher than[45,46] in a control population. Serum triglyceride concentrations have also been reported to be either higher[44,45] or similar[46] among GH-deficient adults compared with a control population. Moreover, four of nine patients (44%) had low HDL cholesterol concentrations, which is a prevalence in agreement with some previous reports[44,45] but in contrast to others.[21,46] Thus, the number of patients with hyperlipidemia and low HDL cholesterol concentrations was not unexpected, in view of the few patients and the divergent reports on the prevalence of these abnormalities in GH-deficient patients.

In this study, all patients received treatment involving daily injections during the first treatment period and a continuous infusion during the second period. Since there was 1 month of washout between treatment periods and no carryover effects were noted, ie, no difference between baseline values, it is concluded that the first treatment period did not influence the effects of the second regimen. Furthermore, urinary excretion of GH was similar during the different modes of GH administration, indicating that similar amounts of GH reached the circulation.[33] It has been reported that hypothyroidism occurs in children during GH therapy and that thyroxine therapy in these children could correct hypercholesterolemia.[47] However, in the present study, no biochemical[33] or clinical signs of hypothyroidism occurred. In contrast, increased triiodothyronine concentrations occurred.[33] An increased effect of thyroid hormones on lipoprotein metabolism during GH therapy therefore could not be excluded.

We found that 2 weeks of GH treatment suppressed postprandial adipose tissue LPL activity. In a previous study, no effects from 2 weeks of GH treatment were observed on postheparin plasma LPL or adipose tissue LPL activity in obese men after an overnight fast.[19] In contrast, suppressed adipose tissue LPL activity in the fasting state has been observed after 5 weeks of GH treatment in obese women.[30] Thus, GH treatment may result in decreased adipose tissue LPL activity, regardless of whether measurements are preceded by fasting or a glucose load. However, the dose of GH differed in these studies and therefore might partly explain the different results. It might also be that the effect of GH may occur after a shorter period of treatment in complete GH deficiency.

Since postheparin plasma LPL activity was not affected by GH, although there was a decrease in adipose tissue LPL activity, it is likely that LPL activity increased in other tissues. LPL activity in adipose and muscle tissues is quantitatively most important.[48] Since LPL activity in muscle has been shown to be reduced postprandially,[48,49] it is suggested that this reduction is less pronounced during GH treatment of GH-deficient adults. A mechanism of action of this type for GH would favor the postprandial flow of substrate to skeletal muscle tissue. The well-known effects of GH treatment on body composition, ie, a decrease in adipose tissue mass and an increase in muscle mass, are in accordance with this suggestion.[50]

In the present study, an increase in HL activity was observed. In contrast, no effect of GH treatment on postheparin plasma HL activity was observed in obese men,[19] and lower HL activity has been observed during GH treatment of GH-deficient children.[28] Moreover, low HL activity has been observed in acromegaly.[29] The reasons for the discrepant results are unclear, but they may depend on the intake of glucose before the measurement of HL activity. A positive correlation between changes in fasting glucose levels[33] and changes in HL activity was observed (injections, $r = .60$, $P = .09$; infusion, $r = .80$, $P = .01$), indicating that HL activity is influenced by glucose homeostasis. Moreover, after GH treatment, blood glucose levels were enhanced during OGTT,[33] which preceded measurement of HL activity. Acute hyperinsulinemia has been shown to suppress HL activity independently of the degree of insulin sensitivity.[51] Taken together, these results suggest that increased blood glucose concentrations may increase HL activity and possibly mediate the effects of GH on HL activity in this experimental set-up. Androgens are known to markedly enhance HL activity.[52] Since GH treatment had no effect on serum testosterone or sex hormone–binding globulin concentrations,[33] it is unlikely that testosterone plays a mediatory role in the effects of GH on HL activity (or any other androgen-dependent parameter studied).

In contrast to a previous long-term study[17] but in line with other studies,[19,21,45] we were not able to detect any effect of GH treatment on HDL cholesterol. On the contrary, HDL cholesterol and apo A-I concentrations tended to decrease during GH therapy, which is in agreement with previous observations in children.[20,28] We therefore conclude that long-term treatment of GH-deficient adults is needed to reveal a positive effect of GH treatment on HDL cholesterol.

The increase in total serum and VLDL triglyceride concentrations after GH treatment could be due to an enhanced hepatic VLDL secretion or a decrease in the degradation of serum VLDL through suppressed LPL activity. However, postheparin plasma LPL activity was not affected, indicating that the increase in serum VLDL concentrations was due to enhanced hepatic VLDL secretion, which is also in agreement with increased serum apo E concentrations after both modes of GH treatment (see below). In fact, an increase in hepatic VLDL secretion has been demonstrated in perfused livers from GH-treated hypophysectomized rats.[22] Moreover, free fatty acids have been shown to stimulate hepatic VLDL secretion.[53] One possible mechanism for the more pronounced increase in VLDL concentrations after daily injections of GH might therefore be the more marked increase in free fatty acids when GH was administered in the form of daily injections versus continuous infusion.[33]

Continuous infusion of GH was shown to result in higher apo E concentrations than those produced by daily injections. In line with these results, serum apo E concentrations have been shown to be affected by the mode of GH administration in the rat.[2-4] In contrast to observations in the rat, HDL apo E concentrations were not influenced, suggesting that the main increase in serum apo E concentration occurred in apo B–containing lipoproteins. Since studies in the rat have demonstrated that continuous infusion of GH results in increased hepatic secretion of apo E[5] and since the liver is the major source of apo E in man,[54] it is suggested that continuous infusion of GH may also result in a more marked increase in hepatic secretion of apo E in man. A higher apo E content of VLDL may result in an increased turnover of these lipoproteins, which may explain the lower VLDL triglyceride concentration after continuous GH infusion.

It has previously been demonstrated that GH plays a role in the regulation of serum Lp(a) levels.[17,19] Our results extend previous findings by showing a more marked increase in Lp(a) concentrations when GH was given as a continuous infusion. Correlations were observed between changes in insulin-like growth factor-I (IGF-I) levels, which increased to a greater degree following continuous infusion of GH,[33] and changes in Lp(a) levels (injections, $r = .73, P = .0001$; infusion, $r = .54$, $P = .02$), thereby suggesting that IGF-I plays a role in the regulation of serum Lp(a). This observation is in line with a previously observed correlation between Lp(a) and IGF-I levels in nondiabetic male patients with documented cardiovascular disease before 50 years of age.[55] Estrogen treatment of elderly men suffering from prostatic carcinoma was followed by a decrease in Lp(a).[56] Since estrogens have been shown to elevate basal GH concentrations,[57] it is unlikely that estrogens play a mediatory role for the secretory pattern of GH in the regulation of Lp(a). However, estrogen treatment has been shown to suppress serum IGF-I levels,[58] thereby indicating a mediatory role for IGF-I in the regulation of Lp(a) during both GH and estrogen treatment. In uncontrolled diabetes mellitus, Lp(a) levels have been shown to be high,[59] and improved glycemic control has been shown to decrease Lp(a) concentrations.[60] It is therefore conceivable that the elevation of basal GH concentrations in uncontrolled diabetes[10] may cause increased serum Lp(a) concentrations, in a similar manner to that demonstrated in the present study. The mechanism for the effect of GH treatment on Lp(a) levels is unclear. It has been suggested that subjects with the same apo(a) phenotype differ in serum Lp(a) concentrations primarily as a result of differences in production rate.[61] In addition, Lp(a) binds to the LDL receptor, although the extent to which it occurs is controversial. GH-treated subjects have been shown to have higher hepatic LDL receptor expression.[18] In the present study and others,[17-19,45] decreased LDL cholesterol levels were observed. This militates against the possibility that Lp(a) levels were elevated as a result of a decrease in the uptake of Lp(a) via LDL receptors. However, since the effects of continuous and intermittent administration of GH on serum LDL cholesterol levels were different, indicating a more marked increase in LDL turnover when GH was given as daily injections, it is possible that Lp(a) levels increased to a greater degree during continuous infusion of GH because of less upregulated LDL receptor activity.

It has been suggested that the increase in basal GH levels during pregnancy may be of importance for metabolic adjustments.[8] The present results argue against the possibility that increased basal GH concentrations during late pregnancy are involved in the regulation of serum triglyceride, apo B, and cholesterol concentrations, since they have been shown to increase from the beginning of the second trimester.[62,63] However, increased basal GH concentrations during pregnancy might be involved in the regulation of Lp(a) concentrations, since Lp(a) concentrations increase significantly from the second trimester.[64]

In conclusion, the present study demonstrates for the first time that GH treatment in GH-deficient adults has an effect on adipose tissue LPL activity, postheparin plasma HL activity, and serum apo E concentrations. Moreover, small differences in the effects produced by different modes of GH administration on LDL, VLDL, apo E, apo B, and Lp(a) concentrations were observed. The clinical significance of these small differences remains to be established in long-term trials.

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