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Long-Term Effects of Continuous Subcutaneous Infusion *Versus* Daily Subcutaneous Injections of Growth Hormone (GH) on the Insulin-Like Growth Factor System, Insulin Sensitivity, Body Composition, and Bone and Lipoprotein Metabolism in GH-Deficient Adults*

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ABSTRACT

It remains uncertain whether close imitation of the physiological pulsatile GH pattern determines the effects of GH treatment in humans. However, human studies have reported comparable metabolic responses to short-term constant and intermittent GH exposure. The aim of the study was to compare the metabolic effects of GH after continuous and intermittent sc delivery. In a parallel design, 14 GH-treated GH-deficient patients (mean age, 37 yr; mean body mass index, 27.4 kg/m^2) were studied during steady state at the start of the study and after 6 months. Seven patients received daily injections (inj) in the evening as usual, and 7 received a continuous infusion (inf) of GH by means of a portable pump. The GH dose was kept unchanged before and during the study. Serum levels of insulin-like growth factor I (IGF-I) tended to increase in the patients switched to constant infusion (from 175 ± 36 to 209 ± 50 μg/L), but the differences obtained during the two regimens [+34.3 (inf) *vs.* −11.9 (inj)] were not significant ($P = 0.34$). Serum levels of IGF-II ($P = 0.71$) and IGF-binding protein (IGFBP)-3 ($P = 0.75$) were identical during the two modes of treatment. Serum levels of IGFBP-1 ($P = 0.72$), IGFBP-2 ($P = 0.34$), and GH-binding protein ($P = 0.75$) were unaffected by treatment regimen. Serum levels of free fatty acids, reflecting lipolysis, decreased significantly (16%) in the group switched to GH infusion (difference, −99.8 *vs.* +5 μmol/L; $P < 0.03$). The GH pattern did not influence insulin sensitivity ($P = 0.71$) or glucose effectiveness ($P = 0.15$) derived from Bergman's minimal model. Similarly, the two treatment regimens had no differential impact on lipoprotein levels, bone metabolism, or body composition. In conclusion, continuous and intermittent administrations of GH for 6 months are comparable with respect to the IGF-IGFBP axis, whereas intermittent exposure may be of importance for the lipolytic effect of GH. The data on insulin sensitivity and lipoproteins suggest that constant GH exposure is as safe as intermittent GH administration. (*J Clin Endocrinol Metab* **86:** 1222–1228, 2001)

THE PHYSIOLOGICAL importance of GH pulsatility has been inferred from studies in rats reporting pulsatile GH administration to be superior to continuous delivery in terms of growth stimulation (1) and insulin-like growth factor I (IGF-I) generation (2, 3). By contrast, experimental data in humans have demonstrated that constant GH administration increases serum levels of IGF-I and IGF-binding proteins (IGFBPs) at least as effectively as intermittent delivery (4–8). Markers of GH therapy other than the IGF axis, however, may be dependent on the GH pattern.

Constant GH exposure might in theory down-regulate the GH receptor. Studies in rats, however, have revealed that the hepatic GH receptor is down-regulated by a single GH injection (9) and up-regulated after continuous GH exposure (2, 10), but these results await confirmation in human studies.

In acromegaly, constantly elevated circulating levels of GH and IGF-I are accompanied by reduced glucose tolerance, hyperinsulinemia, and sometimes diabetes mellitus. An early study suggested that even short-term continuous GH infusion might impair glucose tolerance (11).

Disturbances in lipid and lipoprotein metabolism (12) and observation of premature atherosclerotic plaques in vessels of patients with untreated GH deficiency (GHD) (13) may explain the increased cardiovascular mortality reported in hypopituitary patients (14). In animal models, levels of certain lipoproteins are influenced by the pattern of GH exposure (15–18), but similar data are not available in man.

The present study aimed to collect longer term data about the effects on the IGF-IGFBP axis, insulin sensitivity, and bone and lipoprotein metabolism of continuous GH exposure compared with intermittent exposure obtained by daily sc injections of GH.

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Subjects and Methods

Subjects (Table 1)

Fourteen patients with GHD ultimately defined by a peak GH response less than 5 μg/L after two different stimulation tests (insulin-induced hypoglycemia or arginine infusion) were studied. The majority of the patients suffered from additional pituitary insufficiencies and received adequate replacement therapy with hydrocortisone, T_4, and sex steroids, which was unchanged during the entire study period. Female sex steroids were administered by the oral route. All patients had received uninterrupted GH replacement therapy for at least 3 yr.

Experimental protocol

The study was carried out in a parallel design. After a period of at least 3 months of unaltered GH replacement therapy, the 14 participating patients were admitted to the hospital for 28 h for baseline examinations. Seven patients (4 men and 3 women) were allocated to continue their usual treatment schedule of daily sc GH (Norditropin, Novo Nordisk A/S, Bagsvaerd, Denmark) injections in the evening (group I). The remaining 7 patients (4 women and 3 men) were transferred to a regimen of continuous sc infusion by means of a portable pump (Nordic Infuser, Mark II) for the following 6 months (group II). Six months later, all 14 patients repeated the 28-h study program. Furthermore, the patients were seen at 3 months. At the 2 admissions, 24-h profiles of hormonal and metabolic indexes were recorded. Day 1 started with initial blood sampling and bioelectrical impedance followed by a frequently sampled iv glucose tolerance test (FSIVGTT), using the minimal model of glucose and insulin kinetics to analyze the data (19, 20). At the end of each study (day 2) indirect calorimetry and dual energy x-ray absorptiometry (DEXA) scan were performed. Breakfast was not served because the patients were fasting, a standardized hot meal was served at 1200 h, dinner was served at 1730 h, and a snack was provided at 2030 h. Moderate physical activity was allowed.

During the inclusion of patients, a balance with respect to gender, age [34 yr (group I) *vs.* 40 yr (group II)], body mass index [29.4 kg/m^2 (group I) *vs.* 25.4 kg/m^2 (group II)], and GH dose [1.1 IU/m^2 (group I) *vs.* 1.2 IU/m^2 (group II)] was sought. All patients, however, continued to receive their usual GH dose during the entire study period to avoid carry-over effects.

The stability of the GH preparation was evaluated before the start of the study to assure that the hormone was stable for up to 3 days when kept in the pump and carried around at room temperature or higher temperatures during sleep. During that procedure freshly reconstituted GH was placed in the pump system, including infusion catheter and collecting vial, and placed in incubators adjusted to 30 or 35 C to simulate 24-h temperature cycles. The outlet from each pump system was collected and analyzed separately. The stability of GH was assessed by analysis of the assay of GH, dimer, polymer, oxidized and desamido forms of GH, preservative, osmolarity, pH, visual appearance, and relative turbidity. In case of transitory pump failure, the patients were instructed to inject GH to assure administration of the daily dose.

The study protocol was approved by the Danish health authorities and the regional ethics committee and was conducted in accordance with Helsinki Declaration II.

Analytical methods

Serum GH was measured by a double monoclonal immunofluorometric assay (DELFIA, Wallac, Inc., Turku, Finland). The intraassay CV was less than 5% in the range 0.03–200 mU/L, and the lower detection limit was less than 0.06 mU/L. Serum GH-binding protein (GHBP) was assessed by a time-resolved fluorometric immunofunctional assay (21). The interassay coefficient of variation (CV) was 6–12%; the intraassay CV was 3.5%. Serum IGF-I and -II were measured by noncompetitive time-resolved immunofluorometric assays (22). Serum IGFBP-3 was measured by a commercial immunoradiometric assay kit (Diagnostics Systems Laboratories, Inc., Webster, TX). The intra- and interassay CVs for the used assays were less than 5% and 10%, respectively. Serum IGFBP-1 was measured by a commercial immunoenzymometric kit using two monoclonal antibodies (Medix Biochemica AB, Kauniainen, Finland). The interassay CV was less than 7.5%, the intraassay CV was less than 5%, and the lower detection limit was 0.4 μg/L. Serum IGFBP-2 was measured by a RIA kit using a double antibody system to separate free and bound antigen (Diagnostics Systems Laboratories, Inc.). The interassay CV was less than 7.5%, the intraassay CV was less than 8.5%, and the lower detection limit was 0.5 μg/L. Serum levels of insulin were analyzed by RIA as previously described (23). Plasma glucose was measured by a standard glucose oxidase method. Serum nonesterified free fatty acids were measured by an enzymatic colorimetric method (Wako Chemicals, Neuss, Germany). Blood levels of β hydroxy butyrate, glycerol, alanine, and lactate were measured by an automated enzyme fluorometric method (24). Serum concentrations of lipoprotein(a) [Lp(a)] were measured with commercial two-site immunoradiometric assays (Pharmacia Biotech, Uppsala, Sweden) as previously described (25). Serum levels of triglycerides, total cholesterol, and high density lipoprotein cholesterol were measured by a standard enzymatic photometric color reaction (Roche, Mannheim, Germany). Levels of low density lipoprotein cholesterol were calculated using the Friedewald formula (26). Bone metabolism was assessed by resorptive as well as formative bone markers. Markers of resorption in urine, the urinary calcium/urinary creatinine ratio and the urinary ratio between the N-terminal telopeptide cross-links (NTX) and creatinine, reflecting collagen degradation, and in serum, CTX. NTX was measured by an immunometric assay using an automated instrument (Vitros ECI, Ortho Clinical Diagnostics, Amersham, UK). This assay employs a monoclonal antibody against human NTX. Serum CTX was measured by the Crosslaps assay using an automated instrument (Elecsys, Roche). Bone formation was

TABLE 1. Patient characteristics

Patient no.	Gender	Substitution	Age (yr)	Wt (kg)	Ht (m)	BMI (kg/m^2)	Surface area (m^2)
Pump							
1	F	T, C, S	21.6	94.0	1.64	34.9	2.00
2	F	T, C, S, V	49.8	84.7	1.61	32.7	1.89
3	F	T, S	22.0	59.0	1.62	22.5	1.63
4	M	T, C, S	26.3	117.3	1.84	34.6	2.39
5	M	T, S	44.7	55.6	1.63	20.9	1.59
6	F	T, C, S	50.3	91.4	1.68	32.4	2.01
7	M		23.3	78.5	1.69	27.5	1.89
Mean			34.0	82.9	1.67	29.4	1.91
Injections							
1	F	S, V	42.8	71.8	1.68	25.4	1.81
2	M	T, C, S	45.6	83.1	1.78	26.2	2.01
3	M	C	25.5	71.6	1.76	23.1	1.87
4	M	T, C, S, V	29.1	75.8	1.74	25.0	1.90
5	F	T, S	28.1	70.0	1.69	24.5	1.80
6	F	C, S	50.9	63.5	1.69	22.2	1.73
7	M	T, C, S	57.1	92.4	1.73	30.9	2.05
Mean			39.9	75.5	1.72	25.3	1.88

T, thyroid; C, corticosteroid; S, sex steroids; V, vasopressin.

illustrated by serum levels of osteocalcin, alkaline phosphatase (AP), bone-specific AP (S-LAP), the carboxyl-terminal propeptide of type I procollagen (PICP), and the amino-terminal propeptides of type I and III collagen (PINP and PIIINP). Osteocalcin was measured using the N-Mid-Osteocalcin assay (Roche) with the Elecsys automated analyzer. This assay determines intact osteocalcin as well as the large N-midterminal fragment. For the above-mentioned automated immunometric assays, total CVs of 4.3–5.7% were observed. After determination of total AP activity by a commercial kit (Roche), the bone-specific fraction, S-LAP, was measured by precipitation with wheatgerm lectin (Bone-ALP, Roche). PICP, PINP, and PIIINP were measured by commercial RIA kits (Orion Diagnostica, Espoo, Finland). Samples were stored at −20 or −80 C (for bone markers), and samples from an individual patient were analyzed in the same assay.

An FSIVGTT was performed, and the minimal model of glucose and insulin kinetics was used for data analysis. The insulin sensitivity index (Si) is a measure of the effect of an increase in plasma insulin to enhance the disappearance of glucose from the extracellular compartment of glucose distribution and to inhibit hepatic glucose production. The glucose effectiveness index (Sg) is a measure of the mass effect of an increase in glucose on the disappearance of glucose from the extracellular compartment and to inhibit hepatic glucose production. Exogenous insulin was used to accelerate glucose disappearance. One iv catheter was placed in an antecubital vein, and another was placed in an arterialized contralateral hand vein for blood sampling. After baseline sampling of glucose and insulin, glucose (0.3 g/kg; 50%) was administered as a bolus within 90 s, and frequent blood sampling followed. A bolus of insulin (0.02 U/kg Actrapid, Novo Nordisk) was injected at 20 min. The acute insulin response (AIR) to glucose was calculated as the area under the curve, using the trapezoidal rule, during the first 8 min. AIR was used to evaluate β-cell function (27). The disposition index was calculated as the product of Si and AIR (28, 29).

At the end of each study period (0800 h), while the patients were fasting, indirect calorimetry was carried out for 20 min to assess resting energy expenditure and respiratory exchange ratio. The patients remained in bed at least 30 min before each measurement. The gas exchange was measured across a 25-L canopy (Deltatrac, Datex Instrumentarium, Inc., Helsinki, Finland) using an open circuit system.

After bed rest, body composition was assessed by bioelectrical impedance (Animeter, HTS Engineering, Odense, Denmark), employing the formula: fat mass = 41.3 Z × BMI − 30.03, where Z is the total body impedance (30). Furthermore, body composition was assessed by DEXA scan and measurements of waist/hip ratio. The DEXA scan was additionally used for estimation of bone mineral content (BMC).

Statistics

The results are given as the mean ± SEM. Comparisons of the two treatments, based on differences from baseline to 6 months of treatment, were performed by paired Student's *t* test. In addition, the parameters were evaluated by ANOVA for repeated measures. The calculations were performed on normally distributed or $\log_{10}$-transformed data, or, alternatively, nonparametric statistics were employed. $P < 0.05$ was considered significant.

Results

GH and GHBP

The serum profile of GH (Fig. 1) displayed the expected pattern, with elevated levels at night and low levels during the day after sc GH injections (inj) in the evening. In the patients receiving continuous GH infusion (inf), constantly elevated circadian GH levels were seen. The mean integrated levels were not significantly different ($P = 0.79$) in the patients receiving continuous infusion (1.2 μg/L) compared with those in the daily injections group (1.1 μg/L), and levels were also similar at baseline ($P = 0.65$). Circulating GHBP levels (Table 2) were unaffected by treatment regimen ($P = 0.75$)

IGF-I, IGF-II, and IGFBPs (Table 2)

Although mean serum IGF-I levels increased ($P < 0.02$) after switching to constant infusion of GH, similar mean integrated levels [175 ± 36 μg/L (baseline, inf) *vs.* 209 ± 50 (6 months, inf), $P = 0.30$], and differences (Δ) were determined during the two treatment regimens [Δ, +34.3 (inf) *vs.* −11.9 (inj); $P = 0.34$]. Serum IGF-II levels were unaffected by mode of GH administration (Δ, −80 *vs.* −50 μg/L; $P = 0.71$), and IGFBP-3 levels displayed a similar pattern (Δ, −110 *vs.* −196 μg/L; $P = 0.75$). Serum IGFBP-2 levels tended to be higher (44%; $P = 0.12$) during constant GH exposure, but the effects of the two regimens were not significantly different (Δ, +139 *vs.* +14 μg/L; $P = 0.34$). Serum levels of IGFBP-1 were not significantly different at baseline or after daily injections and continuous infusion ($P = 0.72$).

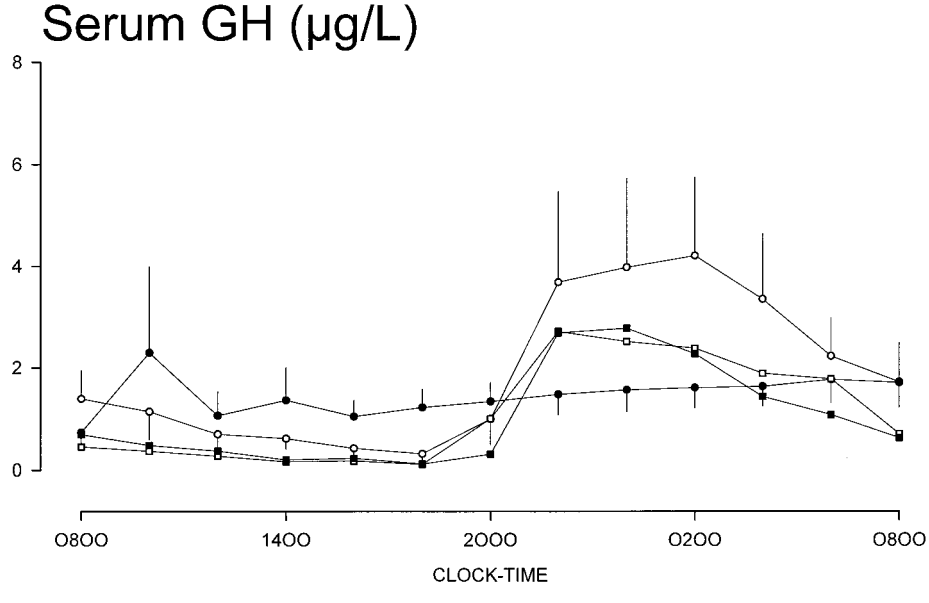

FIG. 1. Serum GH concentrations (micrograms per L) before (○) and after (●) continuous sc infusion and before (□) and after (■) daily sc injections of GH for 6 months.

TABLE 2. GHBP, IGF-I, IGF-II, and IGF-binding protein-1 to 3

Mean integrated conc. ± SEM (μg/L)	Pump		Injections		*P* values (pump *vs.* injection)
	Baseline	6 months	Baseline	6 months	
GHBP	2.52 ± 0.43	2.35 ± 0.38	1.80 ± 0.34	1.73 ± 0.28	0.75
Serum IGF-I	175 ± 36	209 ± 50	217 ± 23	205 ± 30	0.34
Serum IGF-II	912 ± 66	832 ± 51	934 ± 72	884 ± 89	0.71
Serum IGFBP-3	3186 ± 295	3076 ± 362	3342 ± 232	3146 ± 210	0.75
Serum IGFBP-2	316 ± 169	455 ± 92	418 ± 92	433 ± 58	0.12
Serum IGFBP-1	6.9 ± 5.0	5.3 ± 2.9	4.1 ± 1.4	3.4 ± 1.3	0.72

TABLE 3. Mean ± SEM levels of basal metabolic substrates and minimal model-analyzed FIVGT data

	Pump		Injections		*P* values (pump *vs.* injections)
	Baseline	6 months	Baseline	6 months	
FFA (μmol/L)	610.4 ± 71.5	510.6 ± 85.8	388.4 ± 33.9	393.4 ± 38.5	< 0.03
Fasting plasma glucose (mmol/L)	4.90 ± 0.39	4.89 ± 0.37	4.50 ± 0.13	4.71 ± 0.12	0.57
Fasting serum insulin (pmol/L)	87.4 ± 27.9	83.6 ± 42.7	47.1 ± 10.4	36.6 ± 6.8	0.90
Si (10^{-5}(pmol/L)·min)	5.35 ± 1.90	9.55 ± 3.45	5.24 ± 1.49	6.89 ± 1.27	0.71
Fractional SD S_i	6.22 ± 1.10	3.87 ± 0.87	9.89 ± 2.50	5.52 ± 1.19	0.07
Sg (10^{-2} min)	1.16 ± 0.20	1.32 ± 0.24	1.96 ± 0.22	1.40 ± 0.30	0.15
Fractional SD S_g	25.33 ± 4.69	26.01 ± 11.30	14.31 ± 2.01	24.13 ± 5.02	0.47
AIR (mmol/L·8 min)	3083 ± 921	2919 ± 989	2697 ± 425	2207 ± 357	0.71
Disposition index	1.91 ± 1.12	2.66 ± 1.69	1.39 ± 0.51	1.48 ± 0.32	0.38

FFA, Free fatty acids; Si, insulin sensitivity index; Sg, glucose effectiveness; AIR, acute insulin response.

Glucose homeostasis/insulin sensitivity (Table 3)

ANOVA for repeated measurements revealed no significant difference between the 24-h serum profiles of insulin after daily injections and continuous infusion of GH, respectively. A significant increase in the mean levels of insulin (data not shown) was observed in the group who had received GH as a continuous infusion for 6 months ($P < 0.05$). The increase was, however, solely attributed to a single patient who experienced a weight gain of 8.5 kg during the 6 months. The weight gain was not due to water retention. Excluding the patient from data analysis did not change the overall outcomes of the study, except that the increase in mean insulin levels in the pump group disappeared ($P = 0.48$). Moreover, the changes in mean integrated insulin levels were not significantly different during the two modes of GH delivery [from 133.1 ± 83.4 to 220.7 ± 113.7 pmol/L (inf) and from 111.3 ± 32.7 to 118.7 ± 32.7 (inj); $P = 0.49$]. Despite hyperinsulinemia, blood glucose levels were markedly increased ($P < 0.001$) in the above-mentioned patient, whereas levels were similar for the entire group of patients after daily injections compared with those during continuous infusion (data not shown). Similarly, hemoglobin A_{1c} was unaffected by mode of GH administration and even tended to increase in the daily injection group ($P = 0.12$).

The Si derived from minimal model analysis of a FSIVGTT did not change significantly during the two treatment regimens ($P = 0.71$), although a trend ($P = 0.16$) toward improvement [Δ, +0.42 (inf) *vs.* +0.17 (inj)] was observed after 6 months in the group receiving continuous infusion of GH (Table 3). The AIR was also unaffected by the pattern of GH delivery ($P = 0.73$). The Sg was unaffected by the mode of GH administration, but tended to improve after continuous infusion compared with daily injections [Δ, +0.16 (inf) *vs.* −0.56 (inj); $P = 0.15$]. The disposition index, as a combined measure of insulin sensitivity and insulin release, was similar during the two modes of GH administration ($P = 0.38$).

Substrate metabolism

Serum levels of free fatty acids (Fig. 2 and Table 3), reflecting lipolysis, decreased significantly (16%) in the group switched to GH infusion (Δ, −99.8 *vs.* +5 μmol/L; $P < 0.03$). The parallel decrease in glycerol levels (data not shown) did not reach statistical significance ($P = 0.29$). Levels of the gluconeogenic precursors (data not shown) alanine ($P = 0.18$) and lactate ($P = 0.94$) were unaffected by the mode of GH delivery. Indirect calorimetry revealed no changes in energy expenditure [from 1635.7 ± 127.9 to 1570.0 ± 146.4 Cal/24 h (inf), and from 1458.6 ± 77.6 to 1418.6 ± 79.3 Cal/24 h (inj); $P = 0.61$] or the computed predicted value ($P = 0.32$) after a change in the mode GH administration. Similarly, the respiratory exchange ratio (data not shown) was unaffected by GH pattern ($P = 0.37$).

Lipoprotein metabolism (Table 4)

At baseline, lipoprotein levels were similar, although serum triglyceride levels tended to be higher in the group transferred to continuous sc GH infusion ($P = 0.07$). Six months of GH treatment by daily injections and continuous infusion, respectively, resulted in unaltered serum levels of triglycerides, total cholesterol, high density lipoprotein, and low density lipoprotein cholesterol. Levels of Lp(a) were similar at baseline ($P = 0.55$) and were unaffected by the mode of GH administration ($P = 0.59$).

Bone metabolism (Table 5)

Statistical analysis of levels of the measured bone markers at baseline revealed no significant differences before allocation to continuous infusion or daily injections of GH.

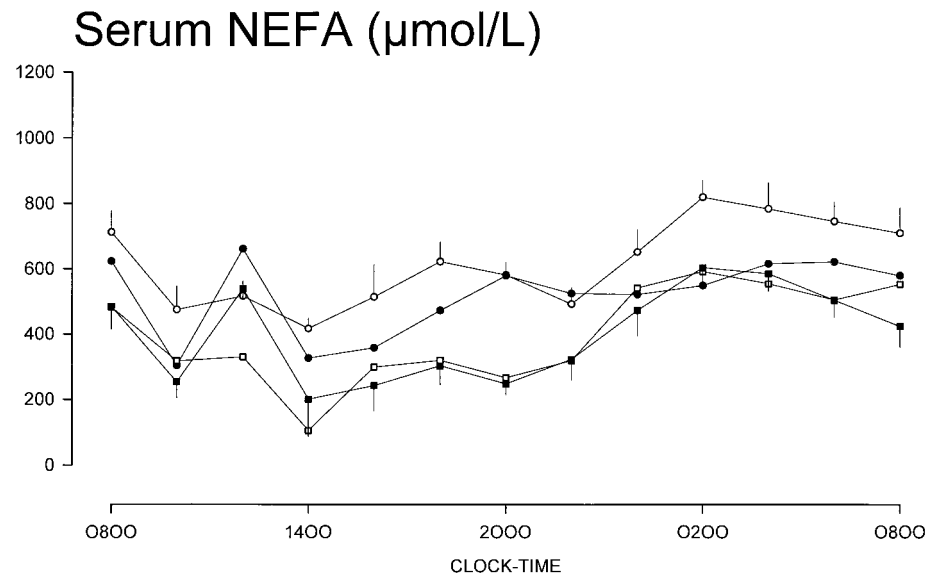

FIG. 2. Serum concentrations (micromoles per L) of nonesterified free fatty acids (NEFA) before (○) and after (●) continuous sc infusion and before (□) and after (■) daily sc injections of GH for 6 months.

TABLE 4. Lipoprotein metabolism

Parameter (±SEM)	Pump		Injections		*P* values (pump *vs.* injections)
	Baseline	6 months	Baseline	6 months	
Serum total cholesterol (mmol/L)	4.84 ± 0.28	4.70 ± 0.20	5.27 ± 0.36	5.57 ± 0.23	0.42
Serum HDL cholesterol (mmol/L)	1.40 ± 0.24	1.19 ± 0.22	1.28 ± 0.11	1.26 ± 0.15	0.56
Serum LDL cholesterol (mmol/L)	2.48 ± 0.24	2.49 ± 0.22	3.40 ± 0.28	3.74 ± 0.21	0.29
Serum triglycerides (mmol/L)	2.05 ± 0.48	2.17 ± 0.61	1.23 ± 0.31	1.22 ± 0.26	0.55
Serum Lp(a) (mg/dL)	14.31 ± 5.02	14.81 ± 5.95	18.56 ± 5.28	20.29 ± 6.33	0.59

HDL, High density lipoprotein; LDL, low density lipoprotein; Lp(a), lipoprotein(a).

Daily injections and continuous infusion of GH resulted in similar and nonsignificant changes in levels of markers of bone resorption in urine, the urinary calcium/creatinine ratio (data not shown), and the NTX/creatinine ratio, and in serum, CTX. Similarly, serum levels of markers of bone formation (osteocalcin, AP, S-LAP, PICP, PINP, and PIIINP) were not significantly different during the two modes of GH administration. Data for PICP, PINP, and PIIINP are not shown.

In accordance with the unaltered levels of bone markers, BMC (Table 5), as measured by DEXA scan, was unchanged ($P = 0.52$) after assessment at different anatomical regions.

Body composition (Table 5)

DEXA scan revealed no effect of mode of GH administration on fat mass ($P = 0.40$) or lean body mass ($P = 0.37$). Alternative calculations based on bioelectrical impedance confirmed these results (data not shown). Finally, the waist/hip ratio displayed similar changes in the two treatment groups.

Discussion

The present study documents the first long-term data on the effects of continuous GH exposure in adult GHD subjects. Our data suggest that generation of IGF-I and IGFBPs is stimulated at least as effectively by constant GH delivery as by daily injections.

Achieving maximal effects with the smallest GH dose is of importance concerning health economics and occurrence of side effects. Only a small number of patients was studied, which to some extent reflects difficulties with recruitment. A reduced power of the study may thus partly explain the negative findings, but data provided no trends toward significantly different efficacy or safety of the two GH regimens. With respect to safety, no inexpedient changes in glucose or lipoprotein metabolism occurred. An impact of mode of administration in patients not previously treated with GH cannot be excluded by these data. A study of such patients might, however, have been complicated by an individually varying response to GH and lack of steady state conditions.

GH receptor status might be evaluated by levels of GHBP, which is identical to the extracellular part of the receptor. Continuous exposure to GH might theoretically down-regulate the receptor, eventually resulting in waning effects of GH therapy. By contrast, continuous infusion of GH to rats up-regulates hepatic GH receptors (2). Short-term studies in humans, however, have revealed no differential effect on circulating GHBP levels of pulsatile and continuously administered GH (31, 32). Similarly, the long-term sustained elevations of serum GH concentrations in the present study neither resulted in down- or up-regulation of GHBP. The reported similar growth responses in children after 6 months of GH administration as continuous infusion and daily injections, respectively (33), speaks in favor of unaltered GH receptor status during continuous exposure to GH.

In accordance with studies in GHD patients measuring serum IGF-I levels the first 24–48 h after GH stimulation and

TABLE 5. Bone metabolism and body composition

Parameter (27SEM)	Pump		Injections		*P* values (pump *vs.* injections)
	Baseline	6 months	Baseline	6 months	
Urine NTX (nmol)/creatinine (mmol) ratio	70.9 ± 11.8	64.3 ± 11.0	62.3 ± 11.5	56.7 ± 9.6	0.77
Serum CTX (pmol/L)	0.60 ± 0.09	0.70 ± 0.08	0.64 ± 0.11	0.63 ± 0.15	0.54
Serum osteocalcin (μg/L)	37.7 ± 3.5	40.6 ± 5.2	37.4 ± 7.9	40.1 ± 7.6	0.97
Serum total alkaline phosphatase (U/L)	156.9 ± 13.7	152.6 ± 9.7	140.6 ± 11.0	149.3 ± 8.4	0.26
Serum LAP (U/L)	54.7 ± 9.8	54.7 ± 8.9	48.0 ± 10.0	48.3 ± 6.7	0.62
Bone mineral content (kg)	2.73 ± 0.22	2.61 ± 0.19	2.56 ± 0.14	2.54 ± 0.14	0.52
Fat mass (kg (%))	23.3 ± 3.9 (28.6)	23.7 ± 3.5 (28.7)	17.3 ± 1.5 (23.6)	18.2 ± 1.5 (24.5)	0.40
Lean body mass (kg)	53.8 ± 5.0	54.7 ± 5.4	54.1 ± 3.6	54.2 ± 3.5	0.37

NTX, N-terminal telopeptide cross-links; CTX, C-terminal telopeptide cross-links; LAP, lectin-percipitating alkaline phosphatase.

studies recording steady state levels after 2–4 weeks of GH administration, it clearly appears from the present data that generation of serum IGF-I can be achieved as effectively with constant GH delivery as with intermittent administration. Similar patterns are displayed by IGF-II and IGFBP-1, -2, and -3. Simulation of the experimental designs of rodent studies (3, 34), reporting that pulsatile GH patterns are superior to continuous delivery with regard to IGF-I generation, have led to almost the opposite results in man (4, 5).

As concerns safety, insulin sensitivity is of particular interest, because constantly elevated GH levels, as seen in acromegaly, are associated with disturbed glucose homeostasis (35). The introduction of sustained release GH preparations emphasizes the need for long-term safety data on, for instance, insulin sensitivity. Results from an early uncontrolled study, reporting hyperinsulinemia and impaired glucose tolerance in pubertal GHD children during short-term continuous GH infusion (11), were not confirmed in subsequent controlled studies of 2- to 4-week duration in GHD adults (7, 8). In the former study GH was administered to previously untreated children, suggesting that the short treatment period may explain the findings. A temporary deterioration of glucose tolerance is often observed immediately after the initiation of GH therapy followed by a gradual normalization in parallel with and perhaps due to the loss of abdominal fat (36). Moreover, hyperinsulinemia may not be of similar concern in pubertal children and adults. In the present study no evidence of impaired glucose tolerance or insulin sensitivity was detected. Continuous administration of GH doses higher than the 1.2 IU/m^2 employed in our study, however, might affect glucose homeostasis inexpediently. It is notable that in both groups of GHD patients reduced insulin sensitivity and glucose effectiveness were apparent during the entire study period compared with those in normal adult males examined in our laboratory (37). These findings are not unexpected in view of the increased BMI and percent fat mass of the patients.

Continuous and pulsatile GH patterns have been reported to affect lipoprotein levels differently in animal studies (15, 18). Two recent studies in GHD patients reported that Lp(a), an independent marker of atherosclerosis (38), attained slightly higher levels after continuous GH infusion compared with daily injections (39, 40). In the present longer-term study serum levels of cholesterol particles and Lp(a) were not influenced by the mode of GH administration.

Changes in BMC or bone structure can only be detected after longer-term GH therapy, and GH-induced improvements have been reported to develop several months after interruption of GH therapy (41). It is therefore not surprising that no changes in BMC were observed after 6 months with a different GH treatment regimen. Bone markers, reflecting even short-term changes in resorption as well as formation (42), were unaffected by the mode of GH administration and also remained unchanged with time.

A central effect of GH is stimulation of lipolysis, which ultimately reduces fat mass (43, 44) and furthermore provides lipid as an alternative to other substrates for fuel metabolism (45). The significance of the reduced nocturnal increase in free fatty acids during continuous GH exposure, which is less physiological than the still unphysiological daily injection, is uncertain.

In a study of the 24-h serum GH profiles of 60- to 70-yr-old male volunteers, it was suggested that the peak values of a GH concentration profile may influence the IGF axis, whereas trough values may influence body composition and metabolic parameters of GH action (46). This suggestion is not supported by the present or other studies of the impact of GH pattern, which have reported that serum IGF-I can be increased at least as effectively with continuous GH delivery as with intermittent administration (4, 6–8). Concerning the suggested regulation of metabolism primarily by GH trough levels, data from an experimental study of the acute effects of a GH pulse in normal subjects, by contrast, indicated that GH pulsatility might be essential for the effects of GH on fuel metabolism (47). In the present study fat mass, as measured by bioelectric impedance and DEXA scan, respectively, and waist/hip ratio were unaffected by the mode of GH administration.

In summary, long-term constant GH exposure exert similar impacts on the IGF-IGFBP axis, GHBP, bone metabolism, body composition, insulin sensitivity, and lipoproteins as daily GH injections. Our data challenge the paradigm that the effects of GH depend strongly on a pulsatile pattern. While daily injections still represent a more physiological regimen, continuous delivery is a safe and efficient alternative for patients, in whom convenience and compliance will be improved by avoiding daily injections, or for patients who may receive GH treatment for indications other than replacement therapy.

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