Assessment of Functional Liver Mass and Plasma Flow in Acromegaly Before and After Long-Term Treatment With Octreotide

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Functional liver mass and functional liver plasma flow (FLPF) were assessed in 11 patients with clinical features of acromegaly by determining galactose elimination capacity (GEC) and extrarenal clearance of sorbitol, before and 5 to 7 months after treatment with the long-acting somatostatin analog, octreotide (150 to 600 μg/d in three subcutaneous injections). Growth hormone (GH) and insulin-like growth factor-I (IGF-I) levels, as well as liver size by ultrasound, were also recorded. Baseline GEC was increased in every patient but one, for a mean of 0.78 ± 0.10 g/min (normal, 0.53 ± 0.07; $P < .01$). At reevaluation after 5 to 7 months of octreotide treatment, a significant reduction of GEC was observed (0.62 ± 0.08 g/min, $P < .001$). Changes of GEC paralleled those of GH (38.6 ± 34.4 *v* 11.7 ± 15.2 μg/L, $P < .01$) and IGF-I (5.0 ± 1.7 *v* 2.7 ± 2.2 U/ml, $P < .001$). Significant correlations were found between GEC and GH ($r = .50$, $P < .05$) and between GEC and IGF-I ($r = .55$, $P < .01$). FLPF, assessed by extrarenal clearance of sorbitol, was within the normal limit in all cases (0.98 ± 0.19 *v* 0.97 ± 0.12 L/min, NS) and remained normal after 5 to 7 months of octreotide treatment (0.99 ± 0.11 L/min). Hepatic structure determined with ultrasonic scanning and conventional liver-function tests were basally normal in all patients, with a slight increase of liver volume in three cases. No change of biochemical and/or morphological features occurred during follow-up evaluation. The results support the hypothesis that GH and especially IGF-I enhance liver metabolic capacity; conversely, functional liver perfusion is largely independent of their actions. Our data also suggest that octreotide is unable to produce well-structured changes of liver circulation when administered long-term.

IN ACROMEGALY, prolonged growth hormone (GH) hypersecretion leads to generalized visceromegaly, involving the heart, liver, spleen, and kidneys.[1]

Comprehensive autopsy studies of visceromegaly have focused on the kidney,[2,3] heart,[4,5] and thyroid gland.[6] Besides anatomical enlargement, the liver was found to be changed functionally in acromegalics; an increased excretory capacity for sulfobromophthalein and a relative reduction in parenchymal perfusion have been reported.[7] However, little is known about the mechanisms responsible for such effects, and their pathophysiological meaning has not been fully investigated.

The present study was designed to evaluate in acromegalic patients the effects of GH hypersecretion on functional liver mass and functional liver plasma flow (FLPF) before and during long-term treatment with the long-acting somatostatin analog, octreotide.

Functional liver mass was estimated by calculating galactose elimination capacity (GEC)[8,9] and FLPF by measuring extrarenal clearance of sorbitol.[10-12]

SUBJECTS AND METHODS

Subjects

Eleven patients (four men aged 28 to 48 years [mean, 39.7] and seven women aged 40 to 66 years [mean, 55.2]) with active acromegaly were studied. In all subjects, the diagnosis was established clinically and confirmed by serum GH concentrations greater than 5 μg/L, which failed to suppress to less than 2 μg/L after an oral glucose load (100 g), insulin-like growth factor-I (IGF-I) levels greater than 2.3 U/mL, and computed tomographic demonstration of a pituitary tumor. Eight patients were previously untreated, and the remaining three underwent noncurative transphenoidal surgery. Pertinent clinical information is summarized in Table 1. In all cases, physical examination, conventional blood chemistry values, and medical history, as well as hepatic ultrasound morphology, excluded liver disease. None of the patients were taking any vasoactive drug or had a history of alcohol consumption. Furthermore, none of them had clinical or baseline biochemical findings of either hyperprolactinemia or anterior pituitary insufficiency. Five cases showed mild diabetes mellitus with a positive family history (case no. 3) or secondary to acromegaly (cases no. 5, 7, 9, and 11), and cases no. 4, 5, 8, and 9 had mild arterial hypertension. Controls were eight normal healthy volunteers (four men and four women aged 25 to 58 years [mean, 42]) participating in studies at our institution to establish a normal range for evaluations. Patients were informed of the nature, purpose, and requirements of the study before giving oral consent. The study was performed according to the principles of the Helsinki Declaration for research in human subjects, and was approved by the Ethics and Research Committee of our Hospital.

Study Design

All subjects underwent assessment of hormonal pattern, functional liver mass, FLPF, and hepatic volume by ultrasonography on 4 consecutive days.

Assessment of hormonal pattern (first day). Fasting blood samples were taken at 8 AM for estimation of plasma GH and IGF-I levels. Serum GH values were determined as the mean of 15-minute interval determinations up to 3 hours; for IGF-I, a single measurement was assumed as a reliable index of disease activity.[13] Blood samples were immediately centrifuged and stored at −20°C until assay. Analysis was performed using commercially available kits purchased from Sorin (Saluggia, Italy) for GH (immunoradiometric assay) and Nichols Institute (San Juan Capistrano, CA) for IGF-I (radioimmunoassay after ethanolic extraction).

Assessment of functional liver mass (second day). The determination of GEC, according to Tygstrup,[8,9] was established as a safe and

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Table 1. Clinical Characteristics of Subjects With Acromegaly

Patient No.	Sex/Age (yr)	Duration (yr)	Previous Therapy	SMS Dose (μg/d)	Follow-up (mo)
1	M/47	15	None	450	5
2	F/66*	17	TSS	300	6
3	M/36	15	TSS	150	7
4	F/45	4	None	300	6
5	F/65*	18	None	150	5
6	F/51	2	None	300	7
7	F/40	11	None	300	7
8	F/57*	6	None	400	5
9	M/28	7	None	600	6
10	M/48	5	None	300	5
11	F/63*	15	TSS	300	7

Abbreviations: TSS, transsphenoidal surgery; SMS, octreotide.
*Postmenopausal women.

physiologically meaningful method for estimation of functional liver mass. After an overnight fast in the supine position, galactose (500 mg/kg body weight of a 40% water solution) was injected intravenously over 5 minutes into an antecubital vein, and plasma concentrations were measured from the 20th to 60th minute following the injection. The analytical procedure was performed with an enzymatic-spectrophotometric method using a commercially available kit (Galactose Test Combination; Boehringer-Biochemia, Mannheim, Germany).

GEC was calculated as follows: $(I - U)/(t + 7)$, where I corresponds to the amount of galactose injected and U to galactose urinary excretion, t is the extrapolated time (in minutes) when the concentration would decrease to 0 if galactose kept following a zero-order kinetic, and 7 refers to a temporal correction to be added because of uneven distribution observed between the intravascular and extravascular compartments.[9]

Assessment of FLPF (third day). Measurement of extrarenal clearance of sorbitol was assumed as a noninvasive, simple, and safe method to evaluate functional (parenchymal) liver plasma flow.[10-12] The test was performed at rest after an overnight fast. Steady-state sorbitol concentrations in peripheral blood (mean value of three consecutive samples) after a 180-minute intravenous infusion (50 mg/min of a 5% D-sorbitol water solution) were used for calculation of total clearance, and urinary sorbitol elimination (from 120 to 180 minutes) was used to compute renal clearance. The analytical procedures were based on an enzymatic spectrophotometric method[14] using commercial preparations of sorbitol dehydrogenase and NAD purchased from Boehringer-Biochemia. The assay was reliable between 1 and 10 mg/dL, with a mean coefficient of variation of ±6% (10 determinations for 10 levels), and estimation errors for plasma and urine concentrations were found to be proportional to the true values.[10] Calculations were performed according to the following equations: total sorbitol clearance = I/Css, renal sorbitol clearance = U/Css, and extrarenal sorbitol clearance = total minus renal sorbitol clearance, where I represents the infusion rate of sorbitol in milligrams per minute, *Css* is the sorbitol plasma concentration at steady-state regimen in milligrams per deciliter, and U corresponds to the urinary output of sorbitol in milligrams per minute.

Assessment of liver volume (fourth day). Liver volume was assessed in each patient by means of serial sagittal ultrasonic scanning sections. Single measurements were performed by a single experienced ultrasonographer at baseline and after 5 to 7 months of octreotide treatment. This procedure allows a fairly accurate measure of hepatic size and has been shown to be superior to the transverse-scanning technique required by the computed tomography scanner.[15]

At completion of baseline study, patients started octreotide treatment with a standard dose of 300 μg/d in three subcutaneous injections. Reduced or increased doses (range, 150 to 600 μg/d) were subsequently administered depending on clinical and laboratory response to treatment. From 5 to 7 months later, all patients underwent the above protocol while fasting and at least 12 hours after the last administration of the drug.

Statistical Analysis

The Statistix PC DOS package (version 2.0; NH Analytical Software, 1987, Roseville, MN) was used for statistical analysis. When the data did not fulfill the criteria of normal distribution by the Wilk-Shapiro test (ie, GH and IGF-I), statistical analysis was performed with nonparametric methods (two-tailed Wilcoxon rank-sum test for paired and unpaired data and Kruskal-Wallis one-way ANOVA). Other variables (ie, GEC and FLPF) were analyzed by Student's t test for paired and unpaired data. The product-moment correlation coefficient was calculated after logarithmic transformation of the data. Limits of statistical significance were set at $P \leq .05$. Values are expressed as the mean ± SD and range.

RESULTS

Baseline GEC values were found to be significantly higher in acromegalic patients than in healthy subjects (0.78 ± 0.1 [range, 0.62 to 0.96] *v* 0.53 ± 0.07 [range, 0.47 to 0.64] g/min, $P < .002$; Table 2). At reevaluation after 5 to 7 months of octreotide treatment, a significant reduction of GEC was observed (0.62 ± 0.08 [range, 0.53 to 0.79] *v* 0.78 ± 0.1 [range, 0.62 to 0.96] g/min, $P < .001$). Changes of GEC paralleled those of GH (from 38.6 ± 34.4 [range, 6.4 to 106] to 11.7 ± 15.2 [range, 2.2 to 42] μg/L, $P < .01$) and IGF-I (from 5.0 ± 1.7 [range, 3.0 to 8.3] to 2.7 ± 2.2 [range, 0.8 to 7.2] U/mL, $P < .001$; Table 3 and Fig 1). Plotting the whole set of log-transformed data, obtained before and during octreotide treatment, significant correlations were found between GH and GEC values ($r = .50$, $P < .05$), and a higher level of significance was found between IGF-I and GEC ($r = .55$, $P < .01$; Figs 3 and 4).

FLPF values were in the normal range in all patients at baseline (0.98 ± 0.19 [range, 0.81 to 1.15] *v* 0.97 ± 0.12 [range, 0.75 to 1.17] L/min, NS; Table 2), as well as after 5 to 7 months of octreotide treatment (0.99 ± 0.11 [range, 0.82 to 1.3] L/min; Table 3 and Fig 2).

Baseline liver ultrasound evaluation showed normal hepatic structure in all cases, with a slight increase of liver volume in patients no. 1, 2, and 4. No change in ultrasound morphology or liver biochemical patterns occurred during follow-up study (data not shown).

DISCUSSION

This study demonstrates a significant increase of functional liver cell mass in active acromegaly. In our series, we

Table 2. Basal Values (mean ± SD) of GEC and FLPF in Controls and Subjects With Acromegaly

Group	GEC (g/min)	FLPF (L/min)
Controls (n = 8)	0.53 ± 0.07	0.97 ± 0.10
Patients (n = 11)	0.78 ± 0.12*	0.98 ± 0.19†

*$P < .002$, †$P > .05$ (NS): *v* controls.

Table 3. Hormonal Pattern and Liver-Function Tests in Acromegalic Patients Before and After 5 to 7 Months of Octreotide Treatment

Patient No.	GH (μg/L)		IGF-I (U/mL)		GEC (g/min)		FLPF (L/min)	
	Before	After	Before	After	Before	After	Before	After
1	83.1	11.0	6.0	1.9	0.90	0.67	0.96	0.99
2	26.0	6.0	4.8	2.9	0.83	0.56	1.12	0.92
3	28.9	3.7	5.8	4.0	0.96	0.78	0.96	0.96
4	19.9	3.5	4.0	0.8	0.86	0.70	0.82	1.00
5	6.4	2.8	3.0	1.3	0.78	0.59	0.97	0.95
6	10.1	3.9	3.9	2.2	0.73	0.60	0.86	1.30
7	13.6	5.8	3.6	1.5	0.72	0.64	1.16	1.05
8	52.4	6.0	4.8	0.9	0.69	0.53	1.11	1.03
9	106.0	42.0	8.3	7.2	0.88	0.68	1.06	0.99
10	71.0	42.0	7.5	6.0	0.69	0.54	0.93	0.95
11	6.8	2.2	3.4	1.0	0.63	0.54	0.81	0.82
Mean	38.6	11.7	5.0	2.7	0.78	0.62	0.98	0.99
± SD	±34.4	±15.2*	±1.7	±2.2†	±0.10	±0.08†	±0.19	±0.11‡

*$P < .01$, †$P < .001$, ‡$P > .05$ (NS): *v* before.

did not find consistent anatomical enlargement; also FLPF was within the normal range. Long-term octreotide treatment (5 to 7 months) suppressed hormonal hypersecretion and markedly reduced functional liver mass without affecting hepatic perfusion.

Liver enlargement in acromegaly is debated. Visceromegaly was reported as a common finding on autopsy examination[1] and was confirmed in vivo with hepatic photoscan.[7] However, other studies failed to detect clinically apparent hepatomegaly,[16] and a more recent investigation found normal liver size in patients with active acromegaly, as estimated by an experienced ultrasonographer. It was suggested that an alternative diagnosis should be

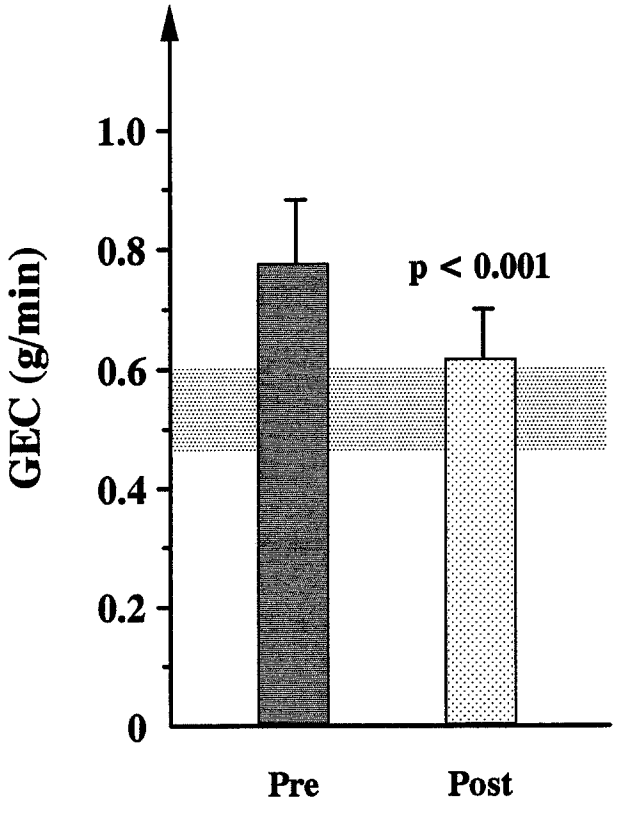

Fig 1. Time course of GEC in acromegalic patients (mean ± SD) in relation to octreotide treatment (5 to 7 months at 150 to 600 μg/d). Shaded area represents the normal range. Pre, before treatment; Post, after treatment.

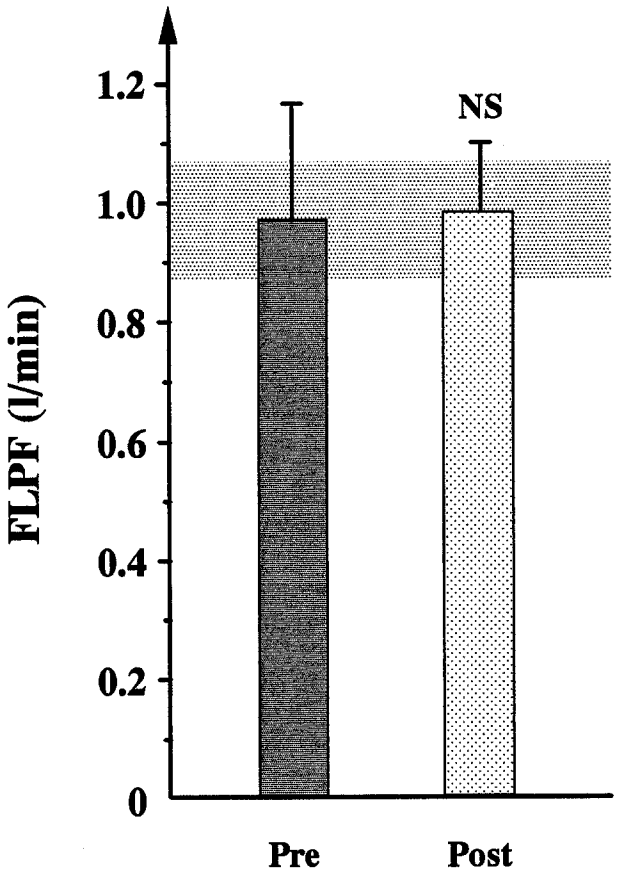

Fig 2. Time course of FLPF in acromegalic patients (mean ± SD) in relation to octreotide treatment (5 to 7 months at 150 to 600 μg/d). Shaded area represents the normal range. Pre, before treatment; Post, after treatment; NS, $P > .05$.

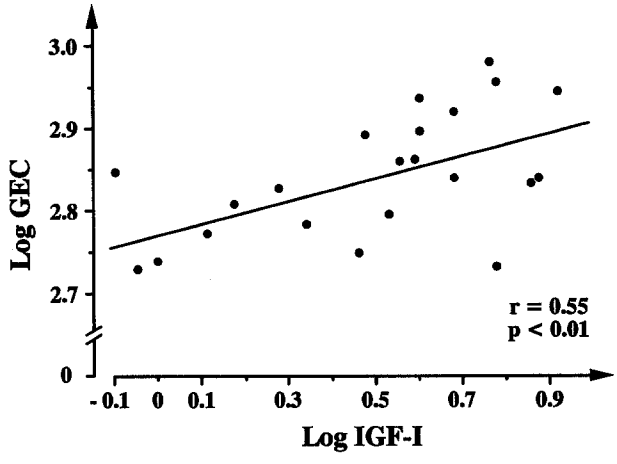

Fig 3. Relation between IGF-I and GEC in acromegalic patients. Log-transformed data were used for the calculation.

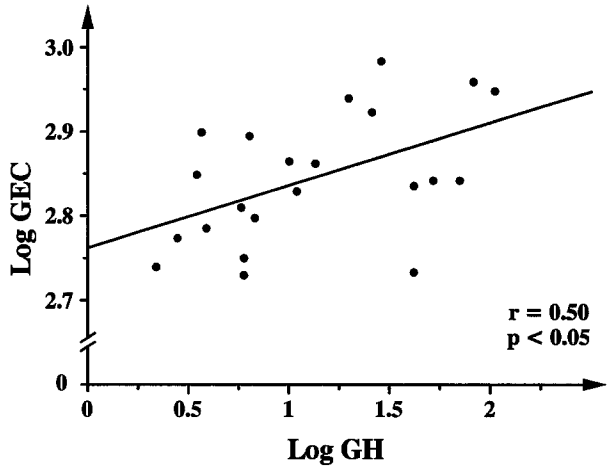

Fig 4. Relation between GH and GEC in acromegalic patients. Log-transformed data were used for the calculation.

sought for in the acromegalic patient with evidence of liver enlargement.[17]

In the present study, three of 11 cases showed slight hepatomegaly at baseline ultrasonic serial sagittal scans without clinical signs of hepatomegaly or biochemical features of hepatic disease. This finding is unlikely to represent a direct consequence of GH and/or IGF-I hypersecretion, since treatment with octreotide, although markedly decreasing the hormonal excess, failed to reduce liver volume in such patients. On the other hand, it was reported that heart hypertrophy, also referred to as acromegalic cardiomegaly, subsides in a remarkable number of patients treated with octreotide.[18]

In the face of these inconstant morphometric data, functional liver cell mass, as estimated by measuring GEC, was found to be significantly increased in all patients studied, without relationship to liver volume. The overlap with controls was minimal. Only one patient (case no. 11) had a GEC value at the upper limit of the normal range, and GEC was remarkably higher in the remainder.

The capacity of the liver to remove galactose primarily depends on hepatocellular galactokinase activity, conceivably enhanced by sustained elevation of GH and/or IGF-I. In this study, we found a correlation between IGF-I and GEC slightly closer than that between GH and GEC. The finding agrees with previous data suggesting a role for IGF-I as a driving factor for many GH actions. Such an effect was demonstrated for other enzymatic activities involved in carbohydrate metabolism[19] and for transcription of the 2C11, 2C12, and 2C13 hepatic cytochrome P-450 genes,[20] in accordance with the initial observations of Preisig et al,[7] who first suggested that changes in enzymatic processes within parenchymal cells could explain the increase of excretory capacity for sulfobromophthalein in acromegalic liver.

The enhanced hepatic metabolic capacity in active acromegaly suggests the possibility of a parallel increase of liver perfusion. To ascertain this possibility, we evaluated liver plasma flow by measuring the extrarenal clearance of sorbitol, a reliable estimate of the blood supply coming into functional contact with intact hepatocytes.[10,11] In subjects without liver disease and blood shunting (as in the selected acromegalic patients), extraction of sorbitol is close to 1.0, and according to Fick's principle, functional flow equals total (parenchymal) flow.[12]

Liver plasma flow was normal in all patients tested. This was not surprising, since wedged hepatic venous pressure and splanchnic blood volume were also normal in patients with active acromegaly.[7] Yet clinically apparent splanchnomegaly is uncommon in acromegalics apart from associated disease.[16]

After long-term octreotide administration, GEC significantly decreased in all patients together with serum levels of GH and IGF-I. The effect also occurred in the two cases showing GH plasma levels that were still high, albeit reduced in comparison to basal levels. This finding requires further comment. Existing evidence argues against a direct octreotide effect on parenchymal liver cell function. No somatostatin receptors have been demonstrated on hepatocytes, and the drug is not hepatotoxic in any experimental condition.[21] Although liver metabolic activity is reduced in cirrhotic patients by short-term octreotide, this effect is explained as being dependent on changes of blood flow in these particular patients.[22,23] Our data are in agreement with this evidence; however, they cannot prove a causal relationship, and therefore suggest further investigation.

At variance with the consistent effects on hepatic metabolism, we did not find any change of FLPF after long-term octreotide in acromegalic patients. Short-term octreotide has well-established effects on splanchnic circulation in healthy persons. Liver blood flow diminishes by 25% to 35% independently of the given dose and route of administration[24,25]; the reduction lasts up to 6 hours after subcutaneous injection, and subsequently, liver flow recovers.[25] In the present study, FLPF was measured at least 12 hours after the last subcutaneous administration of octreotide, to avoid detection of any short-term hemodynamic effect. Our data suggest that octreotide is unable to produce well-structured changes of liver circulation when administered long-term. This assumption is in agreement with reports showing a marked improvement in both hepatic and Kupffer-cell function in cirrhotic patients after long-term management of portal hypertension by octreotide.[26]

Results of the present study also support the hypothesis that GH and especially IGF-I enhance liver metabolic capacity; the clinical relevance and application of this property has to be further ascertained. It could be that GH and/or IGF-I administration improve liver function in patients with advanced chronic liver disease.

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