Exercise-Induced Microalbuminuria in Patients With Active Acromegaly: Acute Effects of Slow-Release Lanreotide, a Long-Acting Somatostatin Analog

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Recent clinical studies have demonstrated an increase of urinary albumin excretion (UAE) at rest in acromegalic patients and, on the other hand, a reduced UAE in patients with growth hormone (GH) deficiency. Physical exercise is known to induce abnormal UAE in patients with diabetes, probably unmasking early glomerular alterations. The effect of exercise on UAE in acromegaly is not known. Moreover, the effect of acute but sustained GH inhibition in acromegaly on UAE at rest and after exercise has never been studied. The aim of our study was to evaluate the acute short-term effects of slow-release lanreotide (SR-L), a long-acting somatostatin analog, on UAE and α1-microglobulinuria (A-1-M), a marker of renal tubular damage, at rest and after exercise in 7 normotensive patients with active acromegaly and normal renal function (4 males and 3 females; mean age, 53 ± 3.1 years; body mass index [BMI], 27.3 ± 1.1 kg/m^2) at baseline and 7 and 14 days after SR-L injection (30 mg). Two of the acromegalic patients were microalbuminuric at rest, and in other 3 cases, UAE was in the borderline range (10 to 20 μg/min). At baseline in the acromegalic subjects, we found a significant increase in UAE at rest with respect to 7 normal subjects considered as a control group. GH and insulin-like growth factor-1 (IGF-1) were also reduced compared with baseline 7 and 14 days after SR-L injection (GH, 13.4 ± 7.3 and 13.61 ± 7 *v* 18.5 ± 9.3 μg/L, $P < .05$; IGF-1, 230 ± 53 and 255 ± 54 *v* 275 ± 64 μg/L). Concomitantly, we observed a significant decrease of UAE at rest and after exercise and 7 and 14 days after SR-L injection as compared with baseline values (27.3 ± 20.5 and 18.2 ± 13.7 *v* 35.3 ± 12.8 μg/min, $P < .05$; exercise, 48.5 ± 24.1 and 18.6 ± 6.8 *v* 68.3 ± 39.7 μg/min, $P < .05$). A-1-M always remained in the normal range (<12 mg/L) both at rest and after exercise. We can thus conclude that in acromegaly, submaximal exercise induces abnormal increases in microalbuminuria. We hypothesize that this phenomenon may be due to the functional glomeruler involvement. SR-L can significantly reduce UAE at rest and after exercise in the short-term in acromegaly, probably via a decrease in circulating GH levels.

THE PRESENCE OF glomerular hyperfiltration in patients with acromegaly is well known.[1,2] Growth hormone (GH) administration to healthy subjects increases the glomerular filtration rate (GFR) and effective renal plasma flow.[3,4] GH is hypothesized to stimulate renal function either directly or by enhancing the release of insulin-like growth factor-1 (IGF-1), which in turn has been shown to have immediate effects on renal hemodynamics.[5,6] Subclinical elevation of urinary albumin excretion (UAE), microalbuminuria (ie, UAE between 20 and 200 μg/min), is a prognostic marker of glomerular damage in diabetes mellitus.[7,8] Recent clinical studies have suggested an increase in UAE at rest in acromegalic patients and, on the other hand, reduced UAE levels in patients with GH deficiency.[9] Microalbuminuria after exercise has been proposed both as an early marker for identifying normoalbuminuric diabetic patients susceptible to later development of microalbuminuria at rest[10,11] and as a sensitive tool for evaluating the effects of various treatments on UAE.[7,12,13] It has been hypothesized that the increase in systemic blood pressure during exercise and, consequently, the higher intraglomerular filtration pressure in patients who may already have either structural or functional microvascular or macrovascular changes in the glomerulus, may induce increased urinary excretion of albumin as compared with normal subjects.[10] To date, no data are available on the effect of exercise on microalbuminuria in acromegalic patients. Renal tubular proteinuria can be quantified by determining α_1-microglobulinuria ([A-1-M] normal value, <12 mg/L).[14] Little is known on the effect of the treatment of acromegaly on the course of kidney dysfunction. A 3-month treatment with the somatostatin analog octreotide has been able to reduce glomerular hyperfiltration in a group of diabetic acromegalic patients.[15] The positive correlation between GH, IGF-1, and UAE in those subjects has suggested that GH and IGF-1 may play a role in the pathogenesis of enhanced urinary protein excretion, probably via vasodilatation of the afferent glomerular vessels.

We have recently shown that an acute but sustained GH reduction obtained through 24-hour continuous infusion of octreotide caused significant improvement in the work capacity at both the anaerobic threshold and during maximal exercise in acromegalic patients.[16] Lanreotide is a long-acting somatostatin analog recently introduced into clinical practice as a treatment of acromegaly.[17] In a sequential open study, octreotide and slow-release lanreotide (SR-L) induced a similar control of GH hypersecretion.[18] However, no data are available on microalbuminuria at rest and after exercise in acromegalic patients treated with either SR-L or other somatostatin analogs.

The aim of our study was to evaluate (1) the effect of exercise on microalbuminuria in acromegaly, and (2) the acute effect of SR-L on UAE and A-1-M at rest and after exercise in patients with active acromegaly and glomerular hyperfiltration.

SUBJECTS AND METHODS

SR-L

SR-L (D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-hN$_2$) was provided by Ipsen-Biotech (Milano, Italy) in vials for intramuscular (IM) injection containing 30 mg of the peptide in microspheres.

Subjects

We studied 7 nondiabetic normotensive patients with active acromegaly and glomerular hyperfiltration (4 men and 3 women; mean age,

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53.3 ± 3.1 years; body mass index [BMI], 27.3 ± 1.1 kg/m^2; blood pressure, 149 ± 7.6/81 ± 3.6 mm Hg; creatinine clearance, 149 ± 4 mL/min; duration of disease, 13.3 ± 1.8 years) on medical treatment with octreotide (100 μg subcutaneous × 3 injection/d). They were not previously medically treated. No patients had clinical signs of cardiac and pulmonary disease; everyone also had Doppler echocardiographic tracings adequate for analysis, and sinus rhythm. Control values for UAE and A-1-M at rest and after exercise were obtained from 7 normal subjects (4 males and 3 females; mean age, 47 ± 3.2 years; BMI, 26.1 ± 2.1; blood pressure, <140/90 mm Hg; creatinine clearance, 122 ± 5 mL/min) matched for sex, age, and BMI with the acromegalic patients (Table 1).

Study Design

Acromegalic patients were studied over a 2-week period, at baseline (T + 0) and 7 (T + 7) and 14 (T + 14) days after the IM injection of SR-L (30 mg). These time points were chosen based on previous pharmacokinetic and pharmacodynamic studies. In fact, it has been shown that the maximal or "plateau" inhibitory effect of SR-L on serum GH is generally obtained 1 week after administration, and the effect may start decreasing 2 weeks after administration.[8,19] At each time of the study, the patients underwent hematochemical routine and endocrine examinations; blood samples for IGF-1 were taken at 8 AM and for GH assay every hour from 8 AM until 12 noon. At 9 AM of each day of the study, each patient underwent a submaximal cycloergometric test (Mijnardt, Kein, Holland) to evaluate UAE and A-1-M after exercise.

The study was approved by the Institutional Ethics Committee, and informed consent was obtained from each patient before hospitalization.

Hormone Assays

Serum GH was measured using a commercial immunoradiometric kit (Nichols Institute, San Juan Capistrano, CA). The IGF-1 assay was performed with a commercially available radioimmunoassay kit after acid-ethanol extraction of the samples (Nichols Institute). All samples were assayed in duplicate.

UAE and A-1-M Assays

UAE and A-1-M were assayed by an immunonephelometric method (nephelometer BNA 100; Behring, Scoppito, Italy). For UAE, the intraassay coefficient of variation (CV) was 4.3% and interassay CV 4.4% (sensitivity limit of the assay, 1.7 mg/L). For A-1-M, the intraassay CV was 2.9% and interassay CV 7.4% (sensitivity limit of the assay, 12 mg/L).

Assessment of UAE and A-1-M Variability at Rest

To assess the variability of UAE and A-1-M at rest, both patients and controls were asked to perform 3 24-hour urine collections over 1 month before entering the study. Only subjects with values within the ±20% average UAE were admitted to the study.

UAE and A-1-M After Exercise

The acromegalic patients performed 3 physical exercise tests during the study (at baseline and 7 and 14 days after SR-L injection). The normal subjects performed only 1 physical exercise. For each test, all subjects came to the outpatient department at 8 AM with a sample from the urine collected during the 24 hours preceding the test for UAE and A-1-M measurements. During the 24-hour period of urine collection, the subjects were asked to avoid heavy or unusual physical exercise. Patients and controls were included in the study if their UAE and A-1-M at rest measured on this single 24-hour collection were in the range of ±20% of the average value for the month preceding the study. Subjects underwent blood sampling for hematochemical routine tests and then remained recumbent for 1 hour and drank 500 mL water. At 9 AM, each subject performed a submaximal exercise test (90% of maximal theoretical heart rate) on a cycle ergometer according to a protocol previously described.[12] The average duration of the exercise period was 10 minutes. The blood pressure, heart rate, and electrocardiogram were monitored constantly during the exercise and recovery period. When the heart rate and blood pressure returned to basal values (after 10 to 20 minutes), the subjects provided a sample of urine for assay of UAE. Each subject again remained recumbent for 1 hour and drank 500 mL of water, and then provided another urine sample for UAE and A-1-M measurement. Therefore, urinary collections for the assessment of the effect of exercise on urinary protein excretion were timed: 24 hours for UAE and A-1-M at rest, 20- to 30-minute period for the assessment of UAE and A-1-M immediately after exercise, and 1 hour for the postexercise values. Postexercise UAE was always expressed as the maximal value obtained after exercise regardless of the timing of the peak (either immediately or 1 hour after exercise).

Statistical Analysis

All data are reported as the mean ± SEM. Results at baseline and during SR-L treatment, as well as UAE and A-1-M at rest and after exercise, were compared with the paired Wilcoxon tests. Differences between urinary indices in acromegalic patients and controls were obtained with the *t* test. Linear regression analysis was used to search for correlations between exercise and hormonal parameters. A P value .05 was considered significant.

Table 1. Clinical Characteristics of the Patients (mean ± SEM)

Patient No.	Age (yr)	Sex	BMI (kg/m^2)	Duration of Disease (yr)	Previous Treatment	Concomitant Disease	Concomitant Treatments (dose/day)
1	44	M	23.9	11	NS	—	—
2	53	M	28.2	7	NS	Gallstones	—
3	51	M	27.2	14	NS + RT	Gallstones, adrenal insufficiency	Cortisone acetate 35 mg
4	69	F	25.3	20	NS + RT	Hypothyroidism, adrenal insufficiency	Thyroxine 75 μg Cortisone acetate 40 mg
5	55	M	32.4	10	NS	Hypogonadism	Testosterone enanthate 200 mg/15 d
6	55	F	25.4	19	NS	—	—
7	46	F	28.9	11	NS	—	—
Mean	53.3	—	27.3	13.1	—	—	—
SEM	3.1	—	1.1	1.8	—	—	—

Abbreviations: NS, neurosurgery; RT, radiotherapy.

RESULTS

Endocrine Data

At baseline, serum GH (mean of the individual profile from 8 AM to 12 noon) and IGF-1 were, respectively, 18.5 ± 9.3 μg/L and 275 ± 64 μg/L (Table 2). SR-L administration decreased GH levels in all acromegalic patients from 18.5 ± 9.3 to 13.4 ± 7.3 μg/L ($P < .05$) 7 days after the injection, and to 13.6 ± 7 μg/L ($P < .05$) at 14 days. Slight but nonsignificant decreases in IGF-1 were observed during the 2-week study period (7 days, 230 ± 53 μg/L; 14 days, 255 ± 54 μg/L) (Table 2).

Cardiovascular Data

At baseline, 2 of the acromegalic patients (no. 4 and 6 in Table 1) were not able to reach the 90% theoretical maximal heart rate and sustained a workload of 60 W. The other 5 patients and the 7 normal subjects did reach their submaximal endpoint, sustaining a workload of 90 W. Patient no. 6, but not no. 4, was able, after SR-L injection, to reach the 90% theoretical maximal heart rate at both the seventh and 14th day of exercise. The remaining patients performed after SR-L similarly to baseline conditions. SR-L injection slightly but significantly decreased systolic blood pressure at days 7 (140.7 ± 7.9 *v* 148.6 ± 7.6 mm Hg, $P < .05$) and 14 (143.6 ± 7.8 mm Hg, $P < .01$) of the study (Table 2). Conversely, no significant variations in diastolic blood pressure were observed throughout the study. We also found a decrease in heart rate on both day 7 (70 ± 2.7 *v* 76 ± 2.8 bpm, $P < .01$) and day 14 (74 ± 2.3 bpm, P = NS) of the study (Table 2).

UAE and A-1-M at Rest and After Exercise

Pretreatment levels. At baseline, acromegalic patients had higher creatinine clearance with respect to the control group (149 ± 4 *v* 122 ± 5 mL/min, $P < .05$). Two acromegalic subjects entered the study at rest with an abnormally elevated UAE (>20 μg/min), ie, microalbuminuria, and in the other 3 patients UAE was in the borderline range (10 to 20 μg/min). Moreover, none of them had a baseline A-1-M in the pathologic range (>12 mg/L). In the control group, UAE and A-1-M were in the normal range both at rest and after exercise (9.58 ± 0.68 and 11.8 ± 1.7 μg/min, P = NS for UAE; 5.4 ± 0.5 and 7.3 ± 1.2 mg/L, P = NS for A-1-M). In the whole group of acromegalic patients, UAE at rest was significantly higher with respect to the control group (35.3 ± 12.8 *v* 9.6 ± 0.7 μg/min, $P < .05$) (Fig 1 and Table 2). Submaximal exercise did not significantly change UAE and A-1-M levels in control subjects (peak, 11.8 ± 1.7 μg/min and 7.28 ± 1.23 mg/L, respectively), whereas it significantly and excessively increased UAE (baseline, 35.3 ± 12.8 *v* 68.3 ± 29.7 μg/min, $P < .05$) in acromegalic patients (Fig 1), with no significant changes in A-1-M. In the whole group of acromegalic patients, peak UAE was also higher as compared with controls (68.3 ± 29.7 *v* 11.8 ± 1.7 μg/min) (Fig 1 and Table 2).

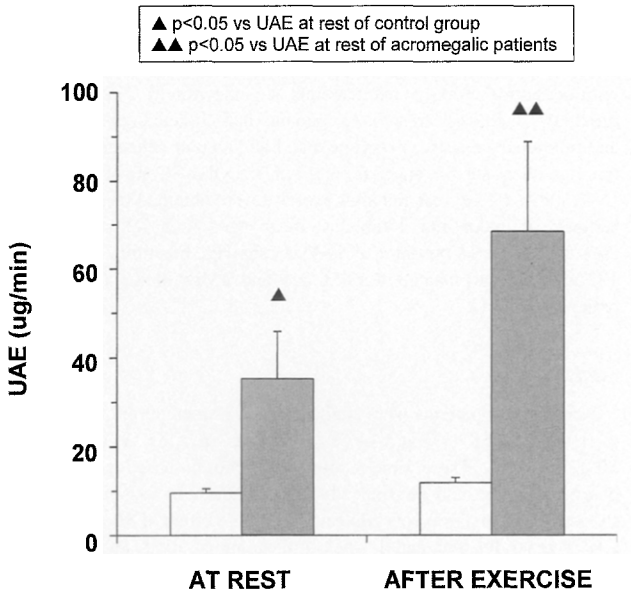

Fig 1. Basal UAE at rest and after exercise in the control group (□) and acromegalic patients (■).

Posttreatment levels. In the acromegalic patients, we observed a decrease in UAE at rest 7 days (27.3 ± 10.5 μg/min, $P < .05$) and 14 days (18.2 ± 13.7 μg/min, $P < .05$) after SR-L injection as compared with baseline levels (35.3 ± 12.8 μg/min). A-1-M at rest always remained in the normal range (<12 mg/L) (Table 1). After exercise at the same times, UAE also decreased after SR-L injection from 68.3 ± 39.7 to 48.5 ± 24 μg/min after 7 days ($P < .05$) and 18.6 ± 6.8 μg/min after 14 days ($P < .05$); A-1-M after exercise always remained in the

Table 2. Changes in Vital Signs, Circulating GH and IGF-1 Levels, UAE, and A-1-M at Baseline and 7 and 14 Days After SR-L Injection (30 mg) (mean ± SEM)

Parameter	Baseline	Day 7	Day 14	*P v* Baseline	
				Day 7	Day 14
Heart rate (bpm)	76 ± 2.8	70 ± 2.71	73.7 ± 2.3	<.01	NS
Systolic blood pressure (mm Hg)	148.6 ± 7.6	140.7 ± 7.9	143.6 ± 7.8	<.05	<.01
Diastolic blood pressure (mm Hg)	81.4 ± 3.6	81.4 ± 4	82.9 ± 3.2	NS	NS
GH (μg/L)	18.5 ± 9.3	13.4 ± 7.3	13.6 ± 7	<.05	<.05
IGF-1 (μg/L)	275 ± 64	230 ± 53	255 ± 54	NS	NS
Creatinine clearance (mL/min)	149 ± 4	139 ± 3.5	138 ± 3.4	<.05	<.05
UAE at rest (μg/min)	35.3 ± 12.8	27.3 ± 10.5	18.2 ± 13.7	<.05	<.05
UAE after exercise (μg/min)	68.3 ± 29.7	48.5 ± 24.1	18.6 ± 6.8	<.05	<.05
A-1-M at rest (mg/L)	6.7 ± 0.5	6.9 ± 0.4	6.8 ± 0.9	NS	NS
A-1-M after exercise (mg/L)	8.1 ± 1.1	7.9 ± 1.4	8 ± 0.8	NS	NS

*Peak value.

normal range (<12 mg/L). At both day 7 and particularly day 14 after SR-L injection, the decrease in UAE was still significant even when UAE was corrected for urinary creatinine excretion.

Correlations

We found significant correlations between the modifications (Δ) in GH (ΔGH) and IGF-1 (ΔIGF-1) at T + 7 and T + 14 (ΔGH (0-7) *v* ΔIGF-1 (0-7), $r = .84$ and $P < .05$; ΔGH (0-14) *v* ΔIGF-1 (0-14), $r = .694$ and $P < .05$). No correlations between ΔGH, ΔIGF-1, and changes in microalbuminuria at rest and after exercise both 7 and 14 days after SR-L injection were observed. ΔUAE from T + 0 to T + 7 significantly correlated with the creatinine clearance (rest, $r = .898$, $P < .01$; exercise, $r = .966$, $P < .001$). In this period (0-7), we also found a weak correlation between systolic arterial pressure, creatinine clearance ($r = .646$, $P = .117$), and UAE at rest ($r = .522$, $P = .130$).

Side Effects

Minor gastrointestinal problems (nausea, mild abdominal pain, and softened stools) in the 24 hours after IM injection were reported by 3 patients. Moderate discomfort at the injection site lasting less than 24 hours was reported in 4 cases. Three patients had transient headache within 12 hours after SR-L injection.

DISCUSSION

The use of slow-release formulations of somatostatin analogs such as SR-L[18] could overcome the scarce compliance associated with either repeated subcutaneous injections or continuous administration of these analogs for the treatment of patients with acromegaly.[17] Recently, it has been demonstrated that long-term SR-L administration is effective in suppressing GH and IGF-1 levels in active acromegaly.[19]

Microalbuminuria at rest (UAE, between 20 and 200 μg/min) in both type 1 and type 2 diabetic patients is a marker of early glomerular damage and predicts the onset of overt diabetic nephropathy, which may lead to chronic renal failure. In type 1 and particularly in type 2 diabetic subjects and in normal elderly subjects, microalbuminuria is also a marker of cardiovascular disease and is strictly correlated with an increased cardiovascular mortality rate.

Exercise can induce abnormal increases in UAE in patients with early glomerular changes (functional and/or reversible).[7,8] Hoogenberg et al[9] demonstrated that UAE was elevated in acromegaly and tended to be reduced in GH deficiency. Furthermore, UAE was consistently reduced after GH and IGF-1 decreases in acromegaly. The positive correlation between GH, IGF-1, and albuminuria supports the fact that these hormonal factors were somewhat involved in the regulation of urinary protein excretion. However, the elevations in UAE that have been reported in patients with GH excess were minor and only one of 14 patients had microalbuminuria according to the cutoff level of 20 μg/min, proposed to define incipient nephropathy in type 1 diabetes mellitus.[20] In our study, we found an elevated UAE at rest in a group of acromegalic patients with renal hyperfiltration as compared with control subjects. Moreover, 2 of 7 had microalbuminuria at rest and the other 3 presented a borderline UAE (10 to 20 μg/min). These data suggest that the prevalence of abnormal UAE at rest and of microalbuminuria in acromegalic patients with hyperfiltration is larger than expected based on previous studies. We have shown for the first time that after physical exercise, UAE is higher in patients with acromegaly as compared with normal subjects. In fact, after submaximal exercise, virtually all patients in our study became microalbuminuric. Therefore, our results suggest that in these patients, the increase in systemic blood pressure during exercise and the consequent higher intraglomerular filtration pressure may induce increased urinary excretion of albumin. The pathogenesis and clinical significance of microalbuminuria at rest and after exercise in acromegaly remain to be established. Hemodynamic factors and permeability-selectivity properties of the glomerular filtration barrier control the glomerular passage of albumin.[21] The impaired renal vasodilatory response to amino acid infusion in already hyperfiltering patients corroborates the presence of abnormal glomerular vasodilation in acromegaly.[15] Interestingly, the GH hypersecretion of type 1 diabetes mellitus has been implicated in the pathogenesis of diabetic retinopathy and nephropathy. Particularly in experimental diabetes, a GH-mediated thickening at the glomerular membrane has been reported.[22] Our study also evidences that in acromegalic patients kidney dysfunction is only at the glomerular level without tubular involvement, due to the normal level of resting and postexercise tubular protein A-1-M in the urine. These data are in agreement with previous studies demonstrating a normal β_2-microglobulin excretion in acromegaly.

Our data demonstrate that microalbuminuria in acromegaly can be caused and, if present, enhanced by a submaximal exercise test. Our group used this test to detect UAE in diabetic patients.[7,8] We and others showed that this stimulatory test may reveal patients with early diabetic nephropathy. It can be hypothesized that also in acromegaly, this submaximal exercise test can demonstrate, via detection of UAE, a functional reversible alteration at the glomerular level, giving us a new early marker for the follow-up of kidney involvement in this disease. The presence and consistency of the phenomenon of exercise-induced microalbuminuria in acromegaly suggests that even in patients with apparently normal UAE at rest, subtle functional (hemodynamic) glomerular abnormalities may exist. This finding is reinforced by the observation that despite a reduced exercise workload in 2 of 7 acromegalics as compared with controls, UAE after exercise was significantly higher in acromegalic versus normal subjects. This hypothesis is confirmed by the observation that even if acromegaly is a chronic disease with a considerable delay in diagnosis and effective treatment, renal insufficiency is not listed as a cause of death in a large cohort of acromegalic patients.[23] Conversely, renal insufficiency develops in 30% to 40% of type 1 diabetic patients.[24] Therefore, it can be suggested that microalbuminuria in acromegaly is linked more to primary hemodynamic changes, while in diabetes it probably reveals early structural lesions of the glomerulus. Our data demonstrate that the long-acting somatostatin analog SR-L can acutely reduce UAE at rest and after exercise. In a recent study, the acute but sustained GH reduction via 24-hour continuous infusion of octreotide in acromegalic patients caused significant improvement in the work capacity at both the anaerobic threshold and during maximal exercise. Interestingly, a single SR-L injection causes

only an acute decrease of GH without significant changes, just a trend for a decrease in serum IGF-1. This may be explained based on the half-life and physiological regulation of the 2 hormones. In fact, serum GH levels are likely to be influenced by a single injection of the somatostatin analog, whereas only longer periods of sustained GH inhibition may lead to a decrease in circulating IGF-1.[25] It can be hypothesized that in our acromegalic patients with elevated circulating GH levels, the acute SR-L–mediated GH decrease could be the key factor in the improvement of exercise-induced microalbuminuria in our acromegalic patients.[16] In fact, acute GH infusion has been shown to increase the GFR[3,4] and cardiac output[26] in normal subjects, as well as to increase cardiac output and decrease peripheral resistance[27,28] in patients with heart failure. However, we did not find any correlations between the SR-L–mediated GH decrease and the decrease in exercise-induced UAE. Alternatively, it can be hypothesized that microalbuminuria may also be an important marker to detect the direct effects of somatostatin at the hemodynamic level in patients with active acromegaly and could be useful to rapidly and effectively evaluate vascular responses to this treatment. In fact, somatostatin and its analogs are known to have significant hemodynamic effects leading to vasoconstriction of the splanchnic circulation and to significant influences on renal hemodynamics in normal subjects[29] and diabetic patients.[30] Moreover, the acute effects of SR-L or other somatostatin analogs on microalbuminuria at rest and after exercise may be useful to predict other vascular positive effects of these agents.[15]

Cardiovascular complications are the first cause of death in acromegalic patients.[31] Microalbuminuria has been positively correlated with the cardiovascular risk in the general population.[32] Therefore, the SR-L–mediated reduction of microalbuminuria (if maintained in the long-term) may have theoretical implications as a marker of the positive cardiovascular effect of the treatment, as well as in predicting a potential SR-L–mediated increase in the life expectancy of acromegalic patients.

In conclusion, we have demonstrated for the first time that patients with acromegaly have elevated UAE after exercise, which can be reversed by short-term lanreotide treatment. It is likely that the pathogenesis of this phenomenon is hemodynamic, and the acute effects of lanreotide demonstrate positive hemodynamic effects of this somatostatin analog at the glomerular level. These effects may be mediated via a reduction of circulating GH levels and/or via the intrinsic hemodynamic properties of this molecule.

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