CLINICAL STUDY

Effect of a six-month treatment with lanreotide on cardiovascular risk factors and arterial intima–media thickness in patients with acromegaly

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Abstract

Objective: To evaluate the effect of a 6-month treatment with slow-release lanreotide (LAN) on cardiovascular risk and atherosclerosis in 24 normotensive patients with active acromegaly (GH = 67.4 ± 12.6 mU/l, IGF-I = 866.0 ± 55.8 µg/l) and 24 healthy subjects sex-, age- and body mass index-matched with the patients (as controls).

Design: Open, prospective, multicenter.

Methods: The following were measured before and after 6 months of LAN treatment (dose 60–90 mg/month): fasting GH, IGF-I, LDL, HDL and total cholesterol, triglyceride, glucose, glycosylated hemoglobin, insulin and fibrinogen levels, intima–media thickness (IMT) and blood systolic and diastolic peak velocity (SPV and DPV respectively) in both common carotids.

Results: At study entry, insulin, total and LDL cholesterol, triglyceride and fibrinogen levels were higher while HDL cholesterol levels were lower in patients than in controls. At the right (0.88 ± 0.04 vs 0.77 ± 0.03 mm, $P = 0.05$) and left (0.93 ± 0.03 vs 0.78 ± 0.02 mm, $P = 0.01$) common carotid IMT was significantly higher in patients than in controls; 12 patients and two controls showed an IMT of ≥ 1 mm ($\chi^2 = 8.2$, $P = 0.004$). After 6 months of LAN treatment, disease control was achieved in 15 patients (62.5%). Insulin, triglyceride and fibrinogen levels were significantly decreased, and a trend toward a decrease of IMT in the right (from 0.90 ± 0.05 to 0.78 ± 0.04 mm, $P = 0.06$) and left (from 0.95 ± 0.04 to 0.84 ± 0.04 mm, $P = 0.06$) common carotid arteries was observed only in patients with disease control, while SPV and DPV did not change.

Conclusions: LAN treatment for 6 months significantly lowered GH, IGF-I, insulin and fibrinogen levels and reduced IMT of both common carotid arteries in normotensive patients with acromegaly.

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Introduction

Patients with acromegaly have an increased mortality from atherosclerosis and cardiovascular and cerebrovascular diseases when compared with the healthy population, mainly after the age of 45 years (1–4). The poor prognosis of these patients is not only due to an increased frequency of cardiovascular disease, such as systemic arterial hypertension and premature coronary artery disease, but is also due to a specific cardiomyopathy (5).

The vascular consequences of long-term growth hormone (GH) and insulin-like growth factor (IGF-I) hypersecretion have been poorly investigated. Increased intima–media thickness (IMT) in both common carotid arteries without an increased prevalence of atherosclerotic plaques has recently been reported, both in patients with active acromegaly and in those cured from the disease (6, 7). Furthermore, a decreased blood flow at the brachial artery (8) and alterations of the microcirculation (9) have been reported in acromegaly. Other independent risk factors such as high glucose, insulin, cholesterol,

triglyceride and fibrinogen levels may further aggravate cardiovascular risk in acromegaly (10, 11).

Pharmacotherapy with somatostatin analogs that suppress GH and IGF-I levels has been shown to partially reverse the abnormalities of cardiac muscle structure and function (12–19), also markedly improving cardiovascular risk parameters. No data are currently available on the effect of long-term treatment with somatostatin analogs, such as slow-release lanreotide (LAN), on vascular disease in acromegaly.

The current study was designed to investigate the cardiovascular risk and vascular consequences of a 6-month treatment with LAN in active, normotensive patients with acromegaly.

Patients and methods

Patients

Twenty-four normotensive patients with acromegaly (12 men, 12 women, aged 20–58 years) and never

before treated with somatostatin analogs entered this open prospective study. Thirteen patients were enrolled in a multicenter Italian study while 11 patients were studied at the Department of Molecular and Clinical Endocrinology and Oncology of the University 'Federico II' of Naples. Nine of the 24 patients had previously undergone unsuccessful surgery. Acromegaly was diagnosed in keeping with typical clinical features, high serum GH levels during an 8 h time course, not suppressible below 2 mU/l (1 µg/l) after a 75 g oral glucose load, and high plasma IGF-I levels for age (11, 20, 21). Within this group disease duration ranged between 2 and 20 years (9.0 ± 1.0 , median 9 years). Twenty-four healthy subjects, among the medical and paramedical personnel of the Department of Molecular and Clinical Endocrinology and Oncology of Naples, sex-, age-, and body mass index (BMI)-matched with the patients, agreed to participate in this study and were used as controls. Exclusion criteria were: familial or personal history of cardiovascular diseases, previous treatment with drugs known to interfere with glucose or lipid metabolism or influence blood pressure, and previous treatment with somatostatin analogs or dopamine agonists. Eighteen patients (75%) and 17 controls (71%) were non-smokers, two patients and four controls were ex-smokers, two patients and three controls were mild smokers (<15 cigarettes/day); all had a sedentary lifestyle. All subjects gave their informed consent to participate in this study and the study protocol was approved by the ethical committees of all centers. Patient and control profiles at study entry are shown in Table 1.

Study protocol

Serum GH and IGF-I, fasting glucose, insulin, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and total cholesterol, fibrinogen and glycosylated hemoglobin (gHb) levels were measured in all patients and controls at study entry using standard procedures. In the acromegalics, they were repeated after 1, 3 and 6 months of LAN treatment; this study shows only baseline and 6 month follow-up results. Hypertriglyceridemia was diagnosed when triglyceride levels were >150 mg/dl (1.69 mmol/l) (22), while hypercholesterolemia was diagnosed when total cholesterol levels were >200 mg/dl (5.17 mmol/l) (23). Diabetes mellitus was diagnosed when fasting glucose was >126 mg/dl at two consecutive measurements or when 2 h after the oral glucose tolerance test (OGTT) glucose was ≥ 200 mg/dl. Impaired glucose tolerance was diagnosed when glucose was between 126 and 200 mg/dl 2 h after the oral glucose tolerance test (OGTT) with an additional value of ≥ 200 mg/dl between 0 and 2 h after glucose load (24).

Ultrasound imaging of common and internal carotid arteries was carried out using Vingmed Sound CMF 725 equipment (Horten, Norway) by means of a 7.5 MHz annular phased array transducer. Details of the technique have been reported elsewhere (25). Right and left carotid arteries were scanned longitudinally, 2.5 cm proximal and 1 cm distal to the bifurcation. When satisfactory B-mode imaging of the common carotid artery wall was achieved, M-mode images were taken for several cardiac cycles to obtain

Table 1 Clinical, biochemical, hormonal and ultrasonographic features in patients with acromegaly before and after 6 months of treatment with SR-lanreotide at the dose of 60–90 mg/month and in controls.

Parameters	Controls (n = 24)	Patients (n = 24)		P
		Before	After	
Body mass index (kg/m ²)	22.5 ± 1.3	23.7 ± 0.5	23.1 ± 1.3	0.4
Fasting GH levels (mU/l)	1.42 ± 0.1 ^{AB}	54.6 ± 12.4	7.3 ± 2.2	0.008
Plasma IGF-I levels (µg/l)	244.9 ± 19.8 ^{AB}	858 ± 58	487 ± 47	<0.0001
Blood glucose levels (mmol/l)	5.3 ± 0.5 ^{AB}	5.6 ± 0.3	5.5 ± 0.3	0.5
Glycosylated hemoglobin (%)	2.5 ± 0.2 ^{AB}	5.1 ± 0.1	5.4 ± 0.2	0.007
Serum insulin levels (mU/l)	10.3 ± 0.5 ^A	18.9 ± 3.0	8.9 ± 1.1	<0.001
Total cholesterol levels (mmol/l)	4.84 ± 0.15	5.15 ± 0.24	4.59 ± 0.16	0.006
LDL-cholesterol levels (mmol/l)	2.22 ± 0.9 ^{AB}	3.56 ± 0.23	3.41 ± 0.19	0.45
HDL-cholesterol levels (mmol/l)	1.57 ± 0.06 ^{AB}	1.00 ± 0.05	1.27 ± 0.10	0.03
Serum triglycerides levels (mmol/l)	1.06 ± 0.03 ^{AB}	1.86 ± 0.16	1.28 ± 0.12	0.005
Serum fibrinogen levels (mg/dl)	198.3 ± 9.4 ^{AB}	334.7 ± 16.4	263.7 ± 13.1	<0.001
Intima-media thickness (mm)				
Right	0.77 ± 0.03 ^C	0.88 ± 0.04	0.84 ± 0.04	0.029
Left	0.78 ± 0.02 ^{AB}	0.93 ± 0.03	0.87 ± 0.04	0.027
Systolic peak velocity (cm/s)				
Right	76.3 ± 3.2	79.9 ± 5.3	77.4 ± 4.5	0.63
Left	73.8 ± 2.9	79.9 ± 4.4	79.5 ± 4.4	0.39
Diastolic peak velocity (cm/s)				
Right	15.4 ± 0.6 ^D	30.2 ± 2.4	30.8 ± 2.6	0.85
Left	19.1 ± 0.4 ^D	30.9 ± 2.3	32.4 ± 2.1	0.63

^AP < 0.01 vs. patients before LAN treatment; ^BP < 0.01 vs. patients after LAN treatment; ^CP < 0.05 vs. patients before LAN treatment; ^DP < 0.0001 vs. patients before and after LAN treatment.

the best quality measurements of IMT. Quantitative and semi-quantitative indices were evaluated by echo-Doppler ultrasonography (US) placing the sample volume (set at 75% of lumen caliber) in the middle of the vessel lumen. US imaging studies were performed by operators blind with respect to the patients' response to treatment; each patient was studied by one investigator using one machine. Each measurement was repeated three times and the mean of the six evaluations taken into consideration. The variability in IMT measurements for the equipment used was 0.03 mm. Flow indices of both carotids were investigated by measuring blood systolic and diastolic peak velocities (SPV and DPV respectively), and the transversal diameter (TD). The IMT of both common carotid arteries was measured and was considered normal when <1 mm (26–28). The presence, location and size of plaques were also evaluated in the common carotid arteries. A type IV plaque, as shown by thickening of the vascular wall and increased density of all US-detectable layers without any hemodynamic alteration, was classed as a well-defined plaque (29). The vascular study was performed at study entry and after 6 months of LAN treatment.

Treatment protocol

At study entry, plasma IGF-I levels were assayed twice for each sample from all patients and controls. The value of serum GH was calculated as the mean of three blood samplings (0800–0830 h with 15 min sampling) in the controls and as the mean of a 6-h blood sampling (0800–1400 h with 30 min sampling) in the acromegalics. LAN treatment was initially administered i.m. at a dose of 30 mg every 14 days for 3 months. Thereafter, the frequency of LAN injections was increased to 10 day intervals on the basis of GH levels ≥ 10 mU/l (30, 31). At the end of the study, the frequency of LAN injections was every 14 days in 13 patients (54.2%) and 10 days in 11 patients (45.8%). Patients were considered cured when safe hormone levels were achieved, i.e. fasting or glucose-suppressed GH levels were below 5 and 2 mU/l (equal to 2.5 and 1 μ g/l) respectively, together with normal IGF-I levels for age (11, 21). During treatment, the final GH level was calculated as the average value from at least three blood samples collected at 15 min intervals the day before LAN injection. At this time point, plasma IGF-I concentrations were assayed in a single sampling.

Assays

GH and IGF-I assays were centralized in one laboratory; samples from each patient were measured in duplicate in the same assay. Serum GH levels were measured by IRMA using commercially available kits (HGH-CTK-IRMA, Sorin, Saluggia, Italy). The sensitivity of the

assay was 0.4 mU/l. The intra- and interassay coefficients of variation (CV) were 4.5 and 7.9% respectively. Plasma IGF-I was measured by IRMA after ethanol extraction using DSL kits (Webster, TX, USA). The sensitivity of the assay was 0.8 μ g/l. The normal IGF-I range was 110–450 μ g/l and 100–300 μ g/l for patients aged 20–40 and 41–60 yrs respectively. The intra-assay CV values were 3.4, 3.0 and 1.5% for the low, medium and high points respectively on the standard curve. The interassay CV values were 8.2, 1.5 and 3.7% for the low, medium and high points respectively on the standard curve.

Statistical analysis

The statistical analysis was performed by means of the SPSS Inc. package (Cary, NC, USA). Data are reported as mean $\pm$ S.E.M. The comparison between patients and controls was performed by a Mann–Whitney U test. The effect of LAN treatment on ultrasonographic variables was analysed by the Wilcoxon–Rank test, while effects on GH, IGF-I, glucose and lipid metabolism were analysed by the Kruskal–Wallis test followed by the Wilcoxon–Rank test in cases of significance. The χ^2 test was used where appropriate. Significance was set at 5%.

Results

At study entry, LDL cholesterol and triglyceride levels were higher, while HDL cholesterol levels were lower in patients than in controls (Table 1). Hypercholesterolemia was found in 12 patients (50%) and in two controls (4.2%) ($\chi^2 = 8.2$, $P = 0.004$). Hypertriglyceridemia was found in 14 patients (58.3%) and none of the controls ($\chi^2 = 17$, $P < 0.0001$). At both common carotid arteries IMT was significantly higher in patients with acromegaly than in controls (Table 1), 12 patients and two controls showed IMT ≥ 1 (Fig. 1) ($\chi^2 = 8.9$, $P < 0.01$). Two patients (8.3%) had two well-defined plaques, both at the proximal inner right and left common carotid causing a 50% stenosis.

After 6 months of treatment with increasing doses of LAN, a decrease in GH ($P < 0.001$) and IGF-I levels ($P < 0.001$) was observed in most patients. The percent GH decrease was $81.5 \pm 4.6\%$ (range 9.5%–98.9%) while the percent IGF-I decrease was $46.4 \pm 4.0\%$ (range 0%–89.5%). Controlled GH secretion was achieved in 18 patients (75%) and normal IGF-I levels for age were achieved in 15 patients (62.5%) (Table 2). Insulin ($P = 0.0004$), triglyceride ($P = 0.0006$) and fibrinogen ($P = 0.0089$) levels decreased significantly, while glucose, gHb, total cholesterol and HDL-cholesterol did not change (Table 1). After treatment, HDL levels remained lower ($P < 0.001$) and insulin and fibrinogen levels remained higher

Figure 1 Individual measures of intima-media thickness (IMT) measured from the right and left common carotid arteries (CCAs) in 24 patients with acromegaly and 24 controls. The interrupted line indicates the threshold of normal values.

($P < 0.01$) than for controls. A trend toward a decrease of IMT was observed in patients achieving disease control but not in those who did not (Table 2). Eight patients (66.7%) achieved normal cholesterol levels while nine patients (64.3%) achieved normal triglyceride levels; two patients with increased IMT achieved normal values after 6 months of treatment (Fig. 2). No difference was found in systolic or diastolic blood pressure before and after treatment, although a trend toward an increase in systolic (122.3 ± 4.1 vs 128.5 ± 4.1 mmHg) and diastolic (78.5 ± 2.7 vs 82.9 ± 2.5 mmHg) blood pressure was observed in patients with controlled disease but not in those with uncontrolled disease (128.0 ± 7.2 vs 135.1 ± 9.6 and 79.0 ± 5.1 vs 80.0 ± 4.8 mmHg respectively).

No changes were found in SPV or DPV in the right or left common carotid arteries, either as a whole or when data were analyzed separately for disease-controlled and disease-uncontrolled patients (Table 2).

Discussion

The results of the current study demonstrate that normotensive patients with active acromegaly had increased IMT both in the right and left common carotid arteries. Treatment with LAN for 6 months, beyond suppressing GH and IGF-I levels in most patients, reduces insulin, triglyceride and fibrinogen levels and tends to reduce IMT to the same level as that of the controls. However, after treatment insulin

Table 2 Effect of a six-month treatment with lanreotide at the dose of 60–90 mg/month on hormonal and vascular features in 24 patients with acromegaly in line with treatment response.

Parameters	Patients with controlled disease ($n = 15$)			Patients with uncontrolled disease ($n = 9$)		
	Before	After	<i>P</i>	Before	After	<i>P</i>
Fasting GH levels (mU/l)	56.7 ± 14.9	2.1 ± 0.3	<0.0001	85.2 ± 22.5	18.4 ± 5.5	0.02
Plasma IGF-I levels ($\mu\text{g/l}$)	822.7 ± 75.9	306.4 ± 20.2	<0.001	1005.0 ± 115	639.6 ± 60.8	0.003
Blood glucose levels (mmol/l)	5.6 ± 0.28	5.5 ± 0.3	0.57	5.7 ± 0.2	5.5 ± 0.4	0.55
Glycosylated hemoglobin (%)	5.0 ± 0.2	5.3 ± 0.2	0.42	5.0 ± 0.3	5.4 ± 0.2	0.31
Serum insulin levels (mU/l)	21.4 ± 2.8	9.4 ± 0.9	0.0058	18.2 ± 4.3	8.1 ± 0.7	0.02
Total cholesterol levels (mmol/l)	5.41 ± 0.32	4.67 ± 0.2	0.045	4.72 ± 0.32	4.46 ± 0.28	0.85
LDL-cholesterol levels (mmol/l)	3.89 ± 0.27	3.46 ± 0.22	0.39	3.03 ± 0.35	3.32 ± 0.35	0.91
HDL-cholesterol levels (mmol/l)	1.05 ± 0.06	1.37 ± 0.15	0.13	0.93 ± 0.07	1.09 ± 0.09	0.55
Serum triglycerides levels (mmol/l)	1.59 ± 0.15	1.20 ± 0.12	0.029	2.29 ± 0.33	1.42 ± 0.23	0.01
Serum fibrinogen levels (mg/dl)	330.0 ± 20.4	256.7 ± 16.8	0.028	342.4 ± 28.8	275.3 ± 21.3	0.31
Intima-media thickness (mm)						
Right	0.90 ± 0.05	0.78 ± 0.04	0.07	0.84 ± 0.09	0.86 ± 0.07	0.86
Left	0.95 ± 0.04	0.84 ± 0.04	0.08	0.88 ± 0.07	0.91 ± 0.06	0.73
Systolic peak velocity (cm/s)						
Right	74.1 ± 7.6	69.6 ± 5.8	0.85	89.6 ± 5.5	90.4 ± 4.7	0.86
Left	73.3 ± 5.6	73.5 ± 5.6	0.96	89.6 ± 6.3	90.7 ± 5.9	1
Diastolic peak velocity (cm/s)						
Right	27.4 ± 3.2	28.6 ± 3.4	0.78	34.9 ± 3.2	34.4 ± 3.5	0.66
Left	26.4 ± 2.4	29.9 ± 2.8	0.43	38.6 ± 3.4	36.4 ± 2.9	0.43

Figure 2 Individual measures of intima-media thickness (IMT) from the right (top) and left (bottom) common carotid arteries in 15 patients with controlled, and in 9 patients with uncontrolled, acromegaly before (●) and after (○) 6 months of treatment with SR-lanreotide. The shaded area indicates normal values. The interrupted line separates controlled from not-controlled patients.

and fibrinogen levels remained higher while HDL-cholesterol levels remained lower than normal.

Recently, evidence has been provided on the negative effect of chronic GH and IGF-I excess on cardiac function in patients with acromegaly (32). The detrimental cardiac effect of GH/IGF-I excess was demonstrated both in patients with uncomplicated acromegaly (33, 34) and in those with concomitant hypertension and glucose tolerance abnormalities which further worsened cardiac function (35, 36). However, to date, the vascular component of the cardiac complications of acromegaly has been poorly investigated. IGF-I has been shown to contribute to the regulation of vascular tone (37–39). Endothelial cells possess high-affinity binding sites for IGF-I (40) and IGF-I has been shown to increase endothelial nitric oxide (NO) formation

(41, 42). Decreased NO activity is associated with impaired arterial vasodilator capacity, increased platelet aggregability and intimal thickening (41). An inverse relationship between free IGF-I levels and IMT has been recently reported in healthy elderly subjects (43). Altogether these findings indicate a parietal effect of GH/IGF-I on the arterial wall (44). In patients with active acromegaly, a heterogeneous distribution of cardiac output has been recently demonstrated by directly measuring brachial artery hemodynamics which showed lower regional blood flow and increased local resistance (8). Morphological alterations in the peripheral microcirculation have also been documented (9).

We recently found a significant increase in the IMT in both common carotid arteries, both in active patients

and in those cured from acromegaly (10). However, the prevalence of well-defined atherosclerotic plaques was not higher than in control subjects (10). The patients included in the present study similarly presented an increase in IMT in the common carotid arteries and seven of them (29.2%) had abnormal IMT levels. A mild increase in carotid IMT was also reported by Otsuki *et al.* (7). Other factors such as glucose tolerance alterations, hypertension, unfavorable lipid profiles and increased fibrinogen levels can be relevant concomitant causes of vascular disease. Furthermore, patients with acromegaly have increased insulin levels which are known to be directly correlated with IMT (45–47). Hyperinsulinemia has been suggested to act as a risk factor for myocardial infarction in adults (48). The 24 patients with acromegaly had hyperinsulinemia at study entry which dramatically improved after treatment, with a likely favourable effect on vascular parameters.

In acromegaly the increase in circulating IGF-I together with locally produced IGF-I (40, 42) could, however, protect from the formation of atherosclerotic plaques despite the presence of high insulin levels and an unfavorable lipid profile. However, IGF-I may potentially be a more important regulator of regional blood flow than insulin: IGF-I was demonstrated to possess a direct impact on the vasculature and to attenuate the contractility in rat arteries, an effect related to NO production (47, 49). Infusion of recombinant human IGF-I into both humans and rats increases renal blood flow and decreases vascular resistance in that organ (38, 39). Since IGF-I is not only secreted by vascular smooth muscle cells but also stimulates vascular NO production, it was suggested that this hormone plays a significant paracrine/autocrine role in the regulation of local blood flow (40). In the current study, IGF-I levels were normalized in 15 of 24 patients, IMT was decreased in the majority of them with two patients showing abnormally high IMT at study entry normalizing their values. Even taking into consideration that the current study measured only rather crude parameters of the vascular system, it is worth noting that the DPV was high in the patients' group and remained high after LAN treatment. In patients not achieving disease control, IMT did not significantly change, even if in some patients a different degree of IMT decrease was found.

In conclusion, treatment with LAN for 6 months significantly inhibited GH and IGF-I secretion, lowered insulin, triglyceride and fibrinogen levels, and tended to reduce IMT in both common carotid arteries in most normotensive patients with acromegaly.

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