

CLINICAL STUDY

Twelve months of treatment with octreotide-LAR reduces joint thickness in acromegaly

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Abstract

Objective: To evaluate the role of age, gender, duration and control of acromegaly on the reversibility of arthropathy.

Patients and design: 30 *de novo* patients with active acromegaly, 30 cured patients and 30 healthy subjects were studied in a tranverse and an open longitudinal study design.

Methods: Shoulder, wrist and knee thickening was measured by ultrasonography at study entry in all 90 subjects and after 12 months of treatment with octreotide-LAR (OCT-LAR) at a dose of 10–40 mg every 28 days in the 30 *de novo* patients.

Results: Thickness at all joint sites was greater in the active than in the cured patients and controls ($P < 0.001$), and was greater in the cured patients than in the controls ($P < 0.001$). There was no gender difference, but joint thickness was less in the patients with disease duration > 10 years. Age significantly correlated with wrist ($r = -0.55$; $P < 0.001$), right knee ($r = -0.45$; $P = 0.01$), and left knee thickness ($r = -0.42$; $P = 0.02$) in patients with active disease, and with wrist thickness ($r = 0.88$; $P < 0.0001$) in controls. Twelve months of OCT-LAR treatment led to disease control in 18 patients (60%). There was a decrease in the thickness of the shoulder ($15.1 \pm 3.2\%$), wrist ($20.5 \pm 3.1\%$), right knee ($22.2 \pm 3.4\%$) and left knee ($18.2 \pm 2.8\%$) in all patients but the reduction in joint thickness at all sites was greater in the patients with controlled disease after OCT-LAR treatment than in the uncontrolled patients ($P < 0.01$). Shoulder and right knee thickening normalized in respectively 11 (61.1%) and 16 (88.9%) well-controlled patients.

Conclusions: Growth hormone and insulin-like growth factor-I (IGF-I) suppression by 12 months' OCT-LAR treatment is accompanied by a significant decrease in the thickness of both weight-bearing and non-weight-bearing joints (mainly in patients whose disease is controlled) regardless of disease duration. These findings suggest that tissue hypertrophy in the context of the acromegalic arthropathy can be improved by suppressing IGF-I levels.

European Journal of Endocrinology 148 31–38

Introduction

Most patients with acromegaly suffer from arthropathy which is a leading cause of morbidity and functional disability (1–3). The acromegalic arthropathy affects both axial and peripheral sites, is generally non-inflammatory but is manifested as a degenerative disease and in later stages of the disease osteoarthritic features frequently become apparent (1–6). A mild-to-moderate improvement in pain, crepitus, the most common clinical sign, and range of motion has been observed after treatment with the subcutaneous formulation of octreotide (OCT), a somatostatin analogue (7–12). However, due to its degenerative pathogenesis the acromegalic arthropathy seems to be hardly

reversed by normalizing growth hormone (GH) and insulin-like growth factor-I (IGF-I).

Periarticular soft tissue structures such as the joint capsule or tendons, especially in the presence of exudative processes are currently investigated very easily and accurately by ultrasonography (USG) (13). We have previously reported that the thickness of both weight-bearing (knees), and non-weight-bearing joints (shoulder and wrist) is significantly increased in patients with active acromegaly, and significantly decreased after six months of treatment with s.c. OCT in a small group of previously untreated acromegalic patients (14). However, joint thickness in the patients who had been cured for a long time and in those receiving OCT treatment did not return to values comparable

with those of healthy subjects (14). Similar results were obtained in another small cohort of patients treated for 12 months with lanreotide, another somatostatin analogue supplied in a slow-release formulation (15). However, the possibility that joint thickening can only be reversed in patients whose disease is controlled or has lasted for a shorter time could not be investigated because of the small number of patients included in these studies.

The slow-release formulation of OCT (OCT-LAR) was developed in order to allow the once every 28-days administration of doses leading to stable blood drug concentrations and sustained GH and IGF-I suppression (16). It has been found to be superior to lanreotide by some authors (17–20). In a study of 151 patients responsive to s.c. OCT, GH ($\leq 2.5 \mu\text{g/l}$) and IGF-I secretion were controlled in 69.8% and 65.8% of patients respectively (21). We have previously demonstrated that long-term treatment with OCT-LAR was effective in controlling GH and IGF-I hypersecretion in most of quite a large cohort of acromegalic patients, whether it was administered as primary therapy or adjunctive therapy after surgery (22).

In this study, we used USG to investigate the potential reversibility of joint thickening as an expression of the acromegalic arthropathy in a large cohort of *de novo* acromegalic patients receiving OCT-LAR as primary treatment. The results were compared with those obtained in patients cured by means of other therapeutic approaches in order to verify whether there were any differences related to gender, disease duration and disease control.

Patients and methods

Patients

Thirty *de novo* acromegalic patients (15 women and 15 men aged 26–73 years) gave their informed consent to participate in this open study which was approved by the local Ethics Committees and carried out at the

Department of Molecular and Clinical Endocrinology and Oncology of 'Federico II' University of Naples and the Department of Medicine and Pharmacology of the University of Messina. The diagnosis of acromegaly was defined as previously reported (23), by high serum GH levels during a 6-h time course ($36.9 \pm 5 \mu\text{g/l}$), not suppressible $< 1 \mu\text{g/l}$ after glucose load and high plasma IGF-I levels for age ($789.4 \pm 32.5 \mu\text{g/l}$). Four patients (13.3%) had overt diabetes mellitus and did not receive an oral glucose load. None of the patients had ever received a treatment capable of affecting GH/IGF-I secretion or had undergone pituitary tumour surgery or radiotherapy. The presumed duration of acromegaly was assessed by comparing photographs taken over a period of 10–20 years and interviewing the patients as to the date of onset of acral enlargement assumed to be the interval between clinical onset and the time of treatment: in this series, it ranged from three to 30 years. The study also included 30 patients whose acromegaly had been cured for at least one year (range: 1–21 years) by surgery ($n = 25$) or surgery plus radiotherapy ($n = 5$) and 30 healthy subjects; both groups matched the group with active patients in terms of gender and age. None of the 30 patients undergoing octreotide-LAR treatment had previously been included in other studies on the same issue (14, 15), while 12 of the 30 cured patients and 18 of the 30 controls had participated in a preliminary study (14). The profiles of all three groups are shown in Table 1.

Study protocol

The study was divided into two arms: a transverse arm comparing the patients with active disease with the cured patients and healthy subjects and a longitudinal arm to evaluate the decrease in joint thickness after OCT-LAR treatment in the patients with active disease.

At study entry, plasma IGF-I levels of all 90 subjects were assayed twice in a single sample whereas serum GH was calculated as the mean value of samples

Table 1 Results of the transverse study: clinical features, GH and IGF-I levels and ultrasonographic findings in patients with active and cured acromegaly and in controls. Data are shown as means \pm s.d.

	Patients with active acromegaly	Cured patients	Controls	P
No.	30	30	30	
F/M	15/15	15/15	15/15	
Age (years)	45.4 \pm 12.2	47.5 \pm 13.6	47.3 \pm 13.7	0.8
Disease duration (years)	13.0 \pm 7.3	9.2 \pm 3.3	—	0.01
Duration of cure (years)	—	3.6 \pm 4.0	—	
GH levels ($\mu\text{g/l}$)	37.6 \pm 26.2 ^a	1.5 \pm 0.9	0.7 \pm 0.5	< 0.001
IGF-I levels ($\mu\text{g/l}$)	786.0 \pm 179.9 ^a	217.4 \pm 93.9	215.8 \pm 62.5	< 0.001
Right shoulder thickness (mm)	2.89 \pm 0.66 ^a	1.85 \pm 0.61 ^b	1.32 \pm 0.27	< 0.001
Right wrist thickness (mm)	3.08 \pm 0.74 ^a	2.59 \pm 0.651 ^b	1.80 \pm 0.67	< 0.001
Right knee thickness (mm)	4.39 \pm 0.81 ^a	3.60 \pm 0.78 ^b	2.56 \pm 0.63	< 0.001
Left knee thickness (mm)	4.35 \pm 0.93 ^a	3.36 \pm 0.77 ^b	2.52 \pm 0.64	< 0.001

^a $P < 0.001$ vs cured patients and controls; ^b $P < 0.01$ vs controls.

drawn from the acromegalic patients every 30 min over a period of 6 h or the mean value of three blood samples drawn from the healthy subjects at 15-min intervals. The final GH value during the OCT-LAR treatment of the patients with active disease was calculated as the average in at least three blood samples collected at 15-min intervals during the morning preceding the next drug injection. Plasma IGF-I concentrations were assayed in a single sample drawn at the same time. Hormonal measurements were made before starting OCT-LAR treatment, every month for the following three months and then quarterly; the USG examinations were performed quarterly. Acromegaly was considered to be controlled after OCT-LAR treatment when fasting GH levels were $\leq 2.5 \mu\text{g/l}$ and IGF-I levels were within the normal range for age (24). In patients with fasting GH values of $> 2.5 \mu\text{g/l}$ but normal IGF-I levels, GH levels of $\leq 1 \mu\text{g/l}$ after a glucose load were considered indicative of disease control (24). Gall bladder and biliary system USG was performed before treatment and after 6 and 12 months in the 30 patients treated with OCT-LAR.

Treatment protocol

All the patients underwent an acute test with s.c. OCT at a dose of 0.1 mg in order to investigate individual patient tolerability to somatostatin analogues (25). As previously reported (22), OCT-LAR was initially administered i.m. at a dose of 20 mg every 28 days for three months which was increased to 30 mg every 28 days in 15 patients whose GH levels were $> 5 \mu\text{g/l}$. After six months of treatment the dose was further increased to 40 mg every 28 days in four patients and decreased to 10 mg every 28 days in two elderly patients whose fasting GH levels were $\leq 1 \mu\text{g/l}$. All patients were followed up for 12 months.

Ultrasonography imaging

The USG studies were performed using a SONORA LOGIC 500 MD (Naples) or an ALOKA SSD-900 (Messina) both equipped with a 7.5 MHz transducer preliminarily covered with ultrasound transmission gel (Acquasonic, Parker Lab., NJ, USA) or a spacer-pad for curved structures that are usually difficult to measure. The articular cartilage of the right and left knees was measured at the level of the supra-patellar space with the joint bent at 90° , that of the shoulder was measured in transverse sections with the arm adducted to the trunk; and that of the wrist was measured at the radiocarpal joint. As all subjects were right-handed, we only measured the size of the right shoulder and the right wrist. All of the USG measurements in one centre were made by a single operator (G V in Naples and S S in Messina) blinded to treatment response.

Assays

Serum GH levels were measured by IRMA (Sorin, Saluggia, Italy). The sensitivity of the assay was 0.6 mU/l and the intra- and interassay coefficients of variation were respectively 4.5 and 7.9%. The equivalence ratio of mU/l to $\mu\text{g/l}$ was 2 (2 mU/l = $1 \mu\text{g/l}$). Plasma IGF-I was measured by IRMA after ethanol extraction (DSL, Webster, TX, USA). The normal ranges in our laboratories were 110–502 $\mu\text{g/l}$ (at 20–30 years), 100–494 $\mu\text{g/l}$ (at 31–40 years), 100–303 $\mu\text{g/l}$ (at 41–50 years), and 78–258 $\mu\text{g/l}$ (> 50 years). The sensitivity of the assay was 0.8 $\mu\text{g/l}$. The intra-assay coefficients of variation for the low, medium and high points of the curve were respectively 3.4, 3.0 and 1.5%. The interassay coefficients of variation were 8.2, 1.5 and 3.7% for the low, medium and high points of the curve.

Statistical analysis

The data were statistically analysed using SPSS software (SPSS Inc., Cary, NC, USA). The between group differences were compared using the two-way ANOVA followed by the Newman–Keuls test in the entire groups or by the Mann–Whitney U test when only the subgroup of patients and controls younger than 35 or older than 55 were studied. The effect of OCT-LAR treatment was analysed using the paired Student's *t*-test. The χ^2 test was used to evaluate the prevalence of disease cure vs disappearance of joint thickening. Linear correlation analysis by calculating the Pearson or Spearman coefficients was used to investigate the correlation between continuous variables. Data are reported as means \pm S.D..

Results

Transverse study

The patients with active disease had significantly thicker shoulder ($P < 0.001$), wrist ($P < 0.001$), and right and left knee articular cartilage ($P < 0.001$) than the cured patients and healthy controls (Table 1, Fig. 1). The cartilage at all four sites was significantly thicker ($P < 0.01$) in the cured patients than in the controls (Table 1, Fig. 1). The only gender-related difference in the entity of joint thickening was a significant increase in the shoulder thickness of women. The thickness of the shoulder, wrist and right knee was less in the patients with disease duration of > 10 years (Table 2). Among the patients with active disease, age significantly correlated with disease duration ($r = 0.71$; $P < 0.001$), wrist thickness ($r = -0.55$; $P < 0.001$), and right ($r = -0.45$; $P = 0.01$) and left knee thickness ($r = -0.42$; $P = 0.02$). GH and IGF-I levels correlated with each other ($r = 0.43$; $P = 0.02$) but neither with joint thickening. Among the cured

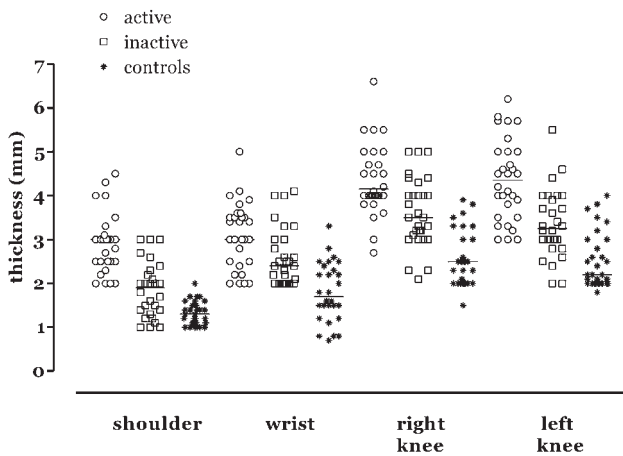


Figure 1 Individual ultrasonographic measurements of right shoulder, right wrist, and right and left knee cartilages in 30 patients with active acromegaly (active), 30 cured patients (inactive) and 30 controls. The median is shown for each column. See Table 1 for levels of significance.

patients, age significantly correlated with cured disease duration ($r = 0.38$; $P = 0.04$) but not with joint thickening, and among the controls age significantly correlated with IGF-I ($r = -0.64$; $P = 0.0002$) and wrist thickening ($r = 0.88$; $P < 0.0001$). This latter result was more evident when active patients and controls were compared according to age ≤ 35 years or ≥ 55 years (Table 3).

Longitudinal study

After three months of OCT-LAR treatment, there was a significant decrease in both GH (from 36.9 ± 27.2 to $5.7 \pm 3.7 \mu\text{g/l}$, $P < 0.001$) and IGF-I levels (from 789 ± 178 to $521 \pm 150 \mu\text{g/l}$, $P < 0.001$). No change in the thickness of the wrist or left knee was observed, but there was a significant decrease in right knee thickness (from 4.48 ± 0.84 to 3.89 ± 0.89 mm, $P < 0.05$). After 12 months of treatment, joint thickening was reduced at all sites: the percentage reductions were $15.1 \pm 17.7\%$ (shoulder), $20.5 \pm 16.9\%$ (wrist), $22.2 \pm 18.5\%$ (right knee) and $18.2 \pm 15.5\%$ (left knee). Disease control was achieved in 18 patients (60%) who also experienced a greater reduction in the thickness of all four joints after three, six and twelve months of treatment (Fig. 2). The maximal percentage decrease after 12 months of treatment is shown in Fig. 3.

In order to investigate whether the patients with a shorter disease duration showed a greater improvement in joint thickening, the controlled patients were divided into those with a disease duration of ≤ 10 or > 10 years. Of the eleven patients with a shorter disease duration and achieving disease control after OCT-LAR treatment, the thickness of the shoulder (taken as an example of a non-weight-bearing joint) did not normalize in four cases (36.4%) and that of the right knee (taken as an example of a weight-bearing joint) did not normalize in two cases (18.2%). Of the seven patients with a longer disease duration and also achieving disease control after OCT-LAR treatment,

Table 2 Transverse study: comparison of ultrasonographic findings by gender, disease activity and disease duration. Data are shown as means \pm S.D.

	Patients with active acromegaly		P	Cured patients		P
	≤ 10 years	> 10 years		≤ 10 years	> 10 years	
No.	14	16		14	16	
F/M	8/6	7/9		7/7	8/8	
Age (years)	35.6 ± 7.6	52.2 ± 10.6	0.001	42.3 ± 12.8	52.1 ± 12.8	0.04
Duration of cure (years)	—	—	—	3.8 ± 5.2	3.4 ± 2.8	0.8
GH levels ($\mu\text{g/l}$)	36.7 ± 31.7	38.4 ± 21.4	0.8	1.7 ± 0.9	1.4 ± 0.9	0.3
IGF-I levels ($\mu\text{g/l}$)	743 ± 157	824 ± 195	0.2	249 ± 103	190 ± 78	0.09
Right shoulder (mm)	3.21 ± 0.76	2.61 ± 0.39	0.009	1.91 ± 0.53	1.79 ± 0.69	0.6
Right wrist (mm)	3.42 ± 0.72	2.77 ± 0.64	0.014	2.51 ± 0.61	2.66 ± 0.69	0.5
Right knee (mm)	4.76 ± 0.93	4.07 ± 0.55	0.02	3.72 ± 0.87	3.49 ± 0.70	0.4
Left knee (mm)	4.60 ± 1.01	4.14 ± 0.82	0.2	3.54 ± 0.87	3.21 ± 0.65	0.2
	Women	Men		Women	Men	
No.	15	15		15	15	
Age (years)	46.3 ± 8.8	44.5 ± 14.5	0.7	42.7 ± 12.8	52.3 ± 12.9	0.049
Disease duration (years)	12.9 ± 6.7	13.2 ± 8.1	0.9	8.1 ± 2.8	10.2 ± 3.6	0.001
Duration of cure (years)	—	—	—	3.7 ± 5.0	3.5 ± 2.9	0.9
GH levels ($\mu\text{g/l}$)	43.2 ± 31.9	32.0 ± 18.5	0.2	1.6 ± 0.8	1.4 ± 1.1	0.6
IGF-I levels ($\mu\text{g/l}$)	711 ± 165	861 ± 167	0.02	227 ± 97	207 ± 83	0.6
Right shoulder (mm)	3.23 ± 0.73	2.55 ± 0.35	0.003	1.87 ± 0.59	1.82 ± 0.66	0.8
Right wrist (mm)	3.10 ± 0.66	3.05 ± 0.84	0.8	2.57 ± 0.74	2.61 ± 0.58	0.8
Right knee (mm)	4.46 ± 0.71	4.32 ± 0.93	0.6	3.59 ± 0.75	3.61 ± 0.83	0.6
Left knee (mm)	4.33 ± 0.94	4.38 ± 0.94	0.6	3.48 ± 0.61	3.25 ± 0.91	0.4

Table 3 Transverse study: comparison of ultrasonographic findings by age in patients with active disease and in controls. Data are shown as means±s.d.

	Patients with active acromegaly		P	Controls		P
	≤35 years	≥55 years		≤35 years	≥55 years	
No.	8	9		8	16	
F/M	2/6	5/4		2/6	8/8	
GH levels (µg/l)	41.4±41.0	34.2±23.3	0.9	0.7±0.6	0.6±0.4	0.9
IGF-I levels (µg/l)	883±223	809±138	0.9	284±54	182±39	0.0003
Right shoulder (mm)	2.85±0.76	2.73±0.35	0.9	1.26±0.24	1.52±0.28	0.06
Right wrist (mm)	3.49±0.86	2.78±0.74	0.07	1.09±0.39	2.56±0.33	<0.001
Right knee (mm)	4.87±0.93	3.94±0.63	0.04	2.45±0.41	2.40±0.40	0.8
Left knee (mm)	4.73±1.08	3.89±0.83	0.09	2.37±0.44	2.22±0.34	0.6

the corresponding figures were three cases (42.8%) and one case (14.3%) ($\chi^2 = 0.14$; $P = 0.7$). Individual data in the 18 patients achieving disease control and grouped according to the estimated disease duration is shown in Fig. 4.

After 12 months of OCT-LAR treatment, age still significantly correlated with wrist ($r = -0.41$; $P = 0.02$), but not with shoulder, or right or left knee thickness, or with the percentage decrease in GH and IGF-I levels or joint thickness. The percentage decrease in GH significantly correlated with that in IGF-I ($r = 0.77$; $P < 0.0001$) and wrist thickness ($r = 0.47$; $P = 0.008$)

and the percentage decrease in IGF-I significantly correlated with that in both right ($r = 0.42$; $P = 0.02$) and left knee thickness ($r = 0.8$; $P = 0.005$).

OCT-LAR treatment was well tolerated: abdominal discomfort was reported by eight patients (26.7%), steatorrhoea by three (10%), flatulence by 13 (43.3%) and hair loss by three patients. Side effects disappeared without any treatment in five cases and after pancreatic enzymes in the others. Hair loss stopped in two cases and was reduced in one after 3–6 months. Three patients developed asymptomatic gallstones.

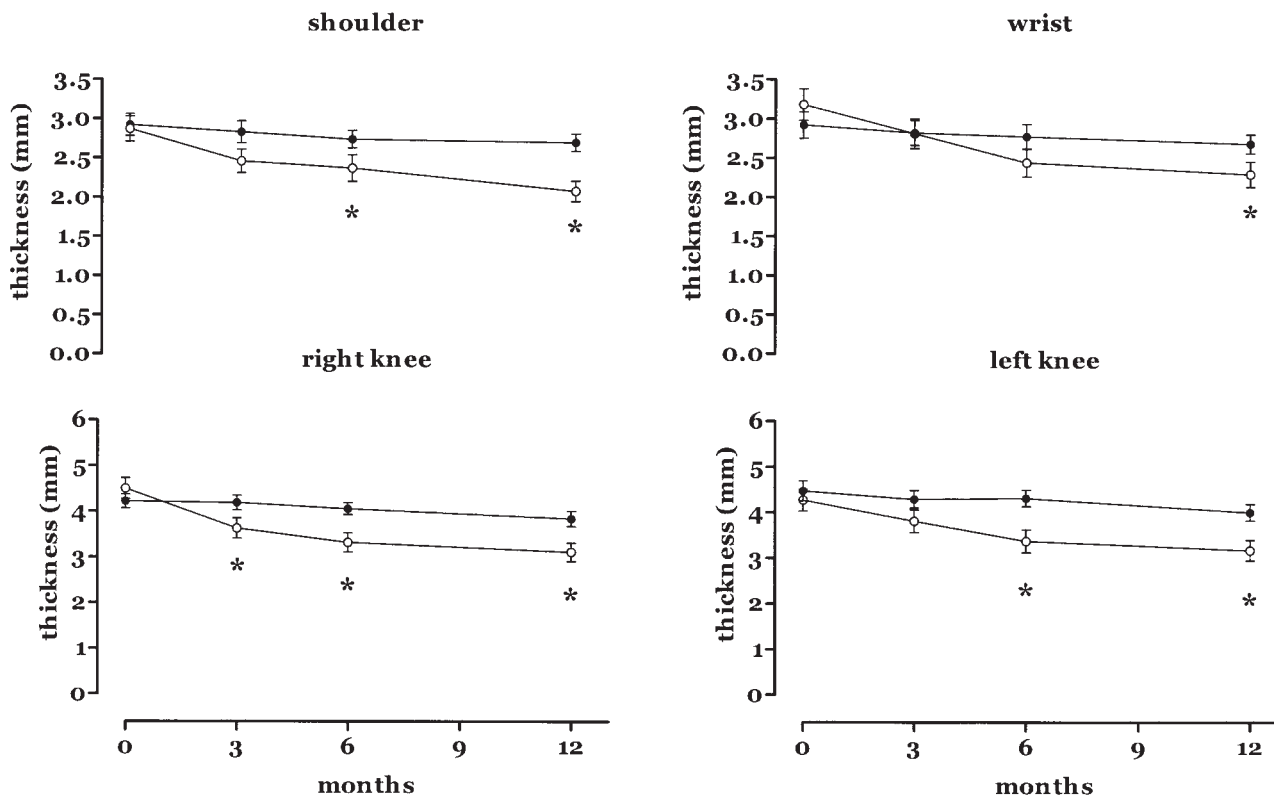


Figure 2 Effect of 12 months octreotide-LAR treatment on joint thickening in 18 patients with controlled disease (○) and 12 with uncontrolled disease (●). * $P < 0.05$ vs uncontrolled patients.

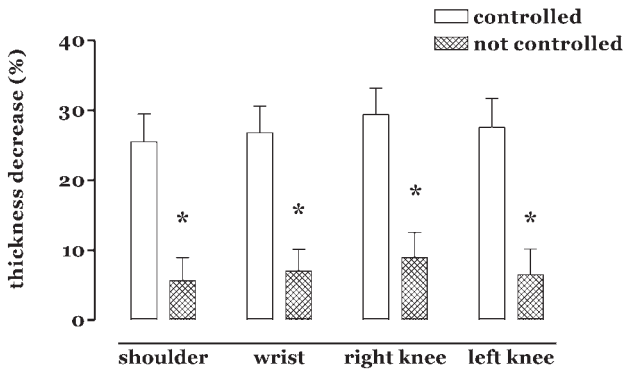


Figure 3 Percentage decrease in joint thickening at different sites after 12 months' octreotide-LAR treatment in patients with controlled and uncontrolled disease. * $P < 0.01$ vs controlled patients.

Discussion

The results of this study show that: (1) articular and peri-articular soft tissue hypertrophy can be measured by USG in patients with active acromegaly; (2) patients who have been cured for at least one year still present thicker joints than healthy controls; (3) the suppression of circulating GH and IGF-I levels induced by 12 months' OCT-LAR treatment is accompanied by a significant decrease in the thickness of both weight-bearing and non-weight-bearing joints (mainly in patients whose disease is controlled) regardless of disease duration; and (4) the percentage reduction in GH and IGF-I levels correlates with that in wrist and knee thickness. These findings suggest that acromegalic arthropathy is characterized by a tissue hypertrophy that negatively correlates with age and whose early manifestations might be reversed by suppressing IGF-I levels.

Arthropathy is a major cause of morbidity in acromegalic patients (9–11). Two-thirds of the patients

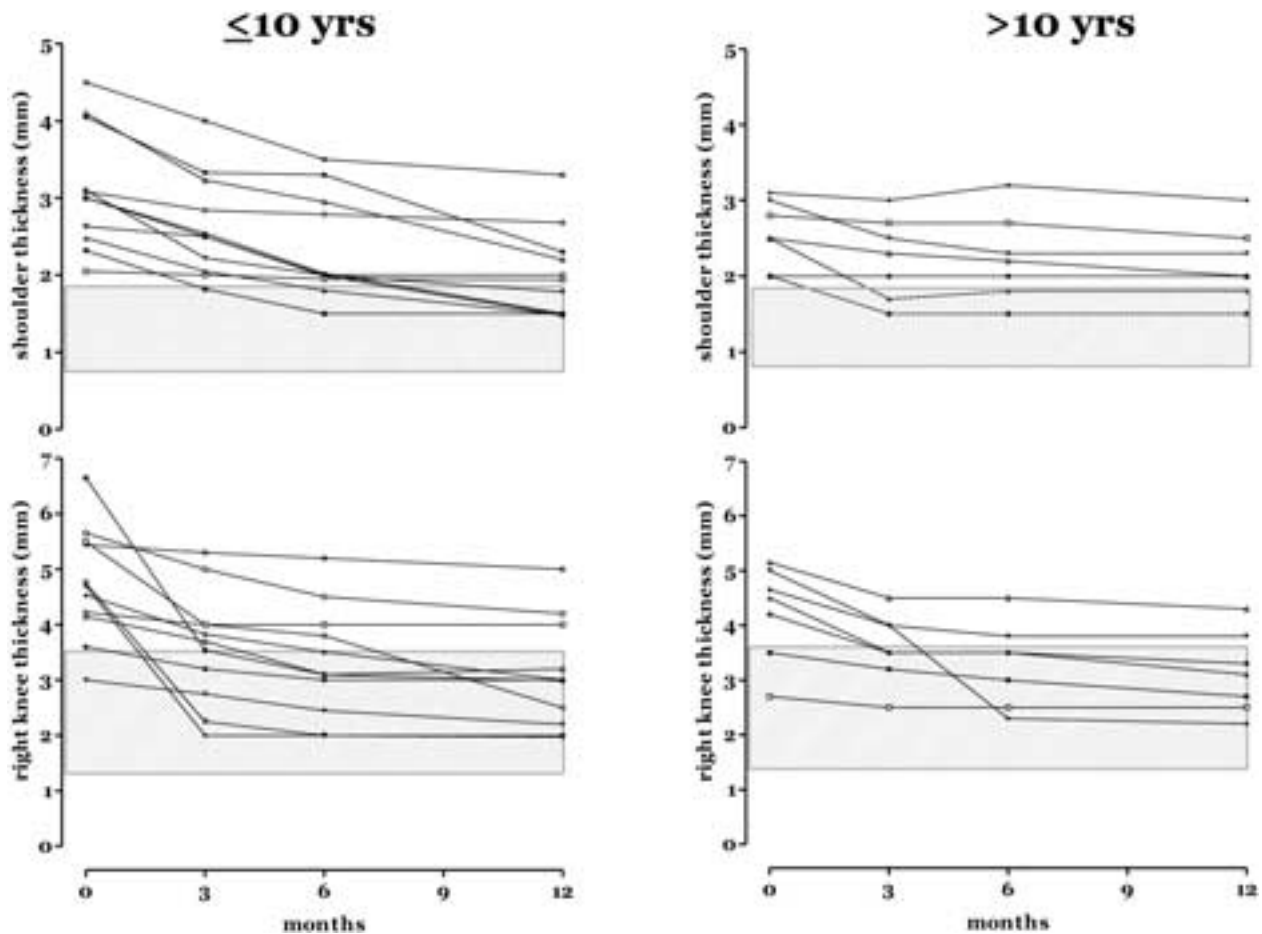


Figure 4 Effect of 12 months' octreotide-LAR treatment on shoulder (top panels) and right knee thickening (bottom panels) in patients with controlled disease. On the left, patients with disease duration less than 10 years; on the right, patients with disease duration greater than 10 years. The shaded area indicates the mean values ± 2 s.d. of the healthy controls.

report minor joint complaints at diagnosis and approximately 16% report severe articular problems (4). The pathogenesis of arthropathy in acromegaly is complex and involves both excess GH/IGF-I levels and secondary degenerative changes. Circulating and locally produced IGF-I stimulates DNA synthesis, cell replication, and proteoglycan and glycosaminoglycan synthesis in articular chondrocytes (9). Like acromegaly-specific cardiomyopathy (26, 27), arthropathy develops during the natural history of acromegaly: the early standard radiology signs are widened joint spaces and peri-articular soft tissue hypertrophy, whereas osteoarthritis is frequently found in acromegalic patients with a long history of untreated disease (9) and is considered to be due to the premature degeneration of hypertrophied hyaline cartilage as a result of poor perfusion and micro traumas, despite the fact that growth and cartilage repair are stimulated *in vivo* by GH and IGF-I (28, 29).

However, standard X-rays are not sensitive enough to reveal an improvement in acromegalic arthropathy. We have shown previously that patients with active acromegaly present a significant increase in the thickness of both weight-bearing and non-weight-bearing joints at diagnosis in comparison with cured patients and sex-, age- and body mass index-matched healthy subjects. In contrast with the evidence that GH/IGF-I hypersecretion for more than 10 years causes a narrowing of articular spaces (9), no difference was found in shoulder, wrist and knee thickness of patients with a disease duration more or less than 10 years before or during treatment with s.c. OCT (14) or lanreotide (15). However, the small number of patients included in these two studies prevented any evaluation of role of gender, disease duration or disease control under pharmacological treatment.

Such an evaluation is essential if an investigation into the still questioned potential reversibility of acromegalic arthropathy is needed. Anecdotal reports suggest that it is at least clinically improved by the suppression of GH secretion (7, 8, 30, 31) but, once a significant build-up of abnormal cartilage has occurred, the control of hormone hypersecretion by any form of treatment is considered unable to arrest the evolution of the disease (30). This may explain the negative findings at the articular or periarticular level reported by some authors (2, 4). We have previously found by means of USG, that s.c. OCT at a dose of 0.3–0.6 mg/day for six months significantly reduced the thickness of the shoulder, wrist and left knee but it did not modify the size of the right knee (14), and that 12 months' treatment with lanreotide led to a significant decrease in the thickness of both weight-bearing and non-weight-bearing joints (15). However, no complete reversal of joint thickening was observed in either study.

OCT-LAR successfully suppresses IGF-I levels (16–22, 32) and some authors have found that it is more effective than lanreotide (17–20). The results of the

present study not only confirm that 12 months' treatment with OCT-LAR reduces the thickness of both weight-bearing and non-weight-bearing joints in *de novo* patients with active acromegaly (as has previously been observed with lanreotide) but also show that the patients in whom disease was controlled experienced a greater reduction in joint thickening at all of the investigated sites. As further confirmation, the percentage decrease in GH and IGF-I levels significantly correlated with that in the thickness of the wrist and the right and left knees. Finally, among the 18 patients whose disease was controlled, no difference was found between those with a shorter or a longer disease duration and, in contrast with previous data (14, 15), 11 patients (61.1%) recovered from shoulder thickening and 16 (88.9%) from right knee thickening.

In conclusion, our results show that high GH and IGF-I levels induce joint abnormalities in acromegaly by demonstrating that their suppression as a result of 12 months' OCT-LAR treatment improves articular and periarticular soft tissue hypertrophy of both weight-bearing (knees) and non-weight-bearing joints (shoulder and wrist). They also demonstrate for the first time that joint thickening can be completely reversed, as was observed in most of the patients whose disease was controlled by the same treatment.

Acknowledgements

This study was partially supported by Italfarmaco (Italy).

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Received 7 May 2002

Accepted 18 September 2002