CLINICAL STUDY

Automated image analysis of hand radiographs reveals widened joint spaces in patients with long-term control of acromegaly: relation to disease activity and symptoms

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Abstract

Objective: Arthropathy is an invalidating complication of acromegaly. Although acromegalic arthropathy shares features with primary osteoarthritis, joint spaces are widened rather than narrowed in patients with long-term cure of acromegaly. The late effects of acromegaly on hand joints have not been characterized. Therefore, the objective of the current study was to assess joint space widths (JSWs) of hand joints in patients with long-term control of acromegaly and to identify factors associated with JSW.

Methods: A cross-sectional study was carried out in 89 patients (age 58 ± 12 years, 49% women) with long-term controlled acromegaly and 471 controls without hand symptoms (age 46 ± 12 years, 42% women). Radiological JSWs of individual hand joints were measured by automated image analysis.

Results: Patients had wider mean joint spaces than controls: metacarpo-phalangeal (MCP) joints were $\sim 24\%$, proximal interphalangeal joints $\sim 21\%$, and distal interphalangeal joints were $\sim 20\%$ wider (patients vs controls; $P < 0.001$ for all joints). Mean JSW exceeded the 95th percentile of the values obtained in controls in 64% of patients. Higher IGF1 and GH concentrations at diagnosis were associated with larger JSWs (adjusted β for pretreatment GH in tertiles: 0.09 (95% confidence interval (CI) 0.03–1.84) and for IGF1 in tertiles: 0.14 (95% CI 0.05–0.23) at the MCP joints in acromegalic patients. In male patients, but not in female patients, increased JSWs were associated with more self-reported pain ($P = 0.02$).

Conclusions: Using a new semi-automated image analysis of hand radiographs, acromegalic patients with long-term disease control appeared to have increased joint spaces of all hand joints. JSWs were positively related to disease activity at diagnosis, but not to duration of follow-up, suggesting irreversible cartilage hypertrophy. Irreversible cartilage hypertrophy may partly explain persisting hand complaints despite long-term disease control.

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Introduction

Acromegaly is a rare disease caused by overproduction of GH from pituitary adenomas (1). It is characterized by a variety of complaints, and increased co-morbidity and mortality. On radiographs, active acromegaly is characterized by increased joint space widths (JSWs) (2). However, the effects of long-term cure or biochemical control of acromegaly on JSW have not been established. Nonetheless, patients with acromegaly have a high prevalence of joint pain and arthropathy even after long-term biochemical cure (3). Although the changes in joints of patients with controlled acromegaly match the criteria of both clinical and radiological osteoarthritis (OA) (4), characteristics of radiological OA

differ between controlled acromegaly and primary OA: patients with acromegaly have more severe osteophytosis, but less joint space narrowing (4). In addition, the joint spaces in acromegaly patients appear to remain abnormally wide, reflecting persistent cartilage hypertrophy despite long-term biochemical control of acromegaly.

At present, there are no quantitative data available on the magnitude of JSWs in patients with acromegaly. Therefore, the aim of the present study was to quantify JSWs in hand radiographs of patients with long-term control of acromegaly in comparison with age- and gender-matched controls. We used semi-automated image analysis software (5) for this purpose. The second aim was to explore the potential factors that are

associated with the size of the joint space in acromegalic patients, such as age at diagnosis, markers of severity, duration of acromegaly, and duration of remission. The third aim was to explore the relation between JSWs and specific joint complaints in these patients with controlled acromegaly.

Materials and methods

Patients

We compared JSW of hand joints in patients with long-term control of acromegaly with that of control subjects.

Acromegalic patients All patients with long-term remission of acromegaly (i.e. more than 2 years), according to a normal insulin-like growth factor 1 (IGF1) concentration for age, were selected from our database. The Leiden Acromegaly Database includes baseline and follow-up results of all patients who have been treated in the Leiden University Medical Center, a tertiary referral center with dedicated pituitary surgeons, from 1977 onward. We invited 126 patients to participate in the present cross-sectional study, of whom 89 (71%) agreed to participate.

The majority of the patients were treated by primary transsphenoidal surgery, if necessary, followed by additional treatment. Control of GH oversecretion was achieved by curative transsphenoidal surgery ($n=49$), surgery and radiotherapy ($n=15$), primary surgery followed by somatostatin analog treatment ($n=15$), all three modes of treatment ($n=3$), and primary somatostatin analog treatment ($n=7$). At the study visit, all patients were in biochemical remission for a mean of 14 years. Biochemical remission was defined as normal glucose, suppressed serum GH concentrations below $0.38 \mu\text{g/l}$ (in patients not treated with somatostatin analogs), serum GH concentrations below $1.9 \mu\text{g/l}$, and normal IGF1 levels for age at yearly follow-up visits (6). Hypopituitarism was defined by the presence of clinically relevant hormonal deficiencies in minimal one pituitary axis and was supplemented with thyroxine (T_4), hydrocortisone, testosterone, or estrogens (in premenopausal women) according to the following definitions. Estrogen deficiency in women was present in the case of LH/FSH deficiency in premenopausal women with prolonged amenorrhea (>1 year) without adequate replacement therapy or with a low serum estradiol concentration of $<70 \text{ nmol/l}$ and in all postmenopausal women. In men, LH/FSH deficiency was defined as testosterone level below the reference range (8.0 nmol/l). Thyroid-stimulating hormone (TSH) deficiency was defined as a thyroxine (free T_4) level below the reference range (absolute value $<10 \text{ pmol/l}$). ACTH deficiency was defined as an insufficient increase in cortisol levels (absolute value $<0.55 \mu\text{mol/l}$) after ACTH test or insulin tolerance test. GH deficiency was not routinely assessed in all patients.

Controls An age- and gender-matched control group was derived from databases of The Leiden Early Arthritis Clinic (EAC, $n=167$) (7) and a prospective study in patients with knee complaints ($n=304$) (8). None of these controls had hand symptoms. EAC is a prospective study that was started in 1993 and includes patients with early arthritis with symptoms for <2 years (7). The goal is to detect inflammatory disorders early in the disease state and to treat these accordingly. All parameters such as medical history and physical diagnostics examination were obtained by trained staff consisting of rheumatologists and research nurses. Conventional radiographs of hands, feet and affected joints were obtained in all patients at baseline. For the purpose of the present study, we selected patients without hand symptoms and used the hand radiographs taken at their inclusion visit. The second study is an epidemiological study which includes patients with traumatic or non-traumatic subacute knee complaints (8). At a follow-up visit 10 years later, routine radiographs of the hands were performed in all patients. Since patients were not included in the study on the basis of hand joint pathology, we assumed that their hand joints are a valid sample of the general population.

The protocols of the studies were approved by the Medical Ethics Committee. Written informed consent was given by all patients and controls who participated in the studies.

OA diagnosis

In all subjects, clinical OA was scored according to the criteria proposed by the American College of Rheumatology (ACR) (9).

Study parameters

Conventional radiographs of the hands From all subjects with acromegaly and the second control group, standardized digital hand radiographs were taken by the same radiological technician with standardized focus-detector distances. Of the EAC controls, 133 radiographs were analog and 39 were digital. For computerized analysis, the analog radiographs were digitized first (VXR-12, VIDAR System Corporation, Herndon, VA, USA). Hand joints were evaluated for the presence of radiological OA using the Kellgren–Lawrence classification system (10, 11). This is a 5-point ranking scale (0, normal OA; 4, severe OA), in which a score of 2 or higher is considered to be (mild) OA.

Image processing for determination of JSW Recently, van 't Klooster *et al.* (5) developed in our institute a semi-automatic quantitative method to measure JSW in hand radiographs with a good correlation with semi-quantitative scoring of joint space narrowing (Fig. 1). Therefore, JSWs of the hands in the current

Figure 1 Example of joint space width assessment in a hand joint of a patient with acromegaly.

study were measured using this semi-automatic image analysis program. First, this program loads the digital/digitized (vide supra) radiographs and the user separates the left and the right hand. Subsequently, in each hand, 12 joints, being four distal interphalangeal (DIP), four proximal interphalangeal (PIP), and second to fifth metacarpophalangeal (MCP) joints, were analyzed semi-automatically in four steps: i) identification of the joint locations, ii) detection of the proximal and distal margins of each joint, iii) measurement of the width of each proximal phalanx, as a reference for the JSW measurement interval, and iv) calculation of the width of the joint space within the determined measurement interval. The automatic results of each step were reviewed by an expert (S H Malm) and corrected if needed. For each subject, 24 measured joint spaces, as well as the thickness of the proximal phalanges, were reported. The joints of the thumb were omitted from the analysis since they were not perpendicular to the imaging plane and could not be assessed reliably. The individual values and the mean results of all joints, the MCP, PIP, and DIP joints were used for analysis. The intra-individual variation between repeat readings ($n=25$) was low ($<5\%$), reflected by a κ value of >0.9 . Within the EAC cohort, we compared digitized analog

and digital radiographs. There was no significant difference between both techniques for any of the mean joint spaces ($P=0.30$).

Pain Self-reported painful joints were recorded on a standard diagram including all 24 hand joints. Pain during structured physical examination was recorded systematically for all 24 joints.

Disease characteristics in acromegaly patients In order to estimate the duration of exposure to previous GH excess, the estimated disease duration before diagnosis and disease duration before remission were carefully assessed. Estimated onset of disease was based on the start of signs and symptoms and changes on photographs. The date of remission was the date of normalization of GH and IGF1 concentrations. The duration of follow-up was the period between diagnosis and study visit. The duration of remission was the period between normalization of GH/IGF1 concentrations and study visit. At the study visit, the actual GH and IGF1 concentrations were measured. Pretreatment GH and IGF1 concentrations were recorded from the database. Since IGF1 analysis was not available in our center before 1986, pretreatment IGF1 levels were not available for all cases (only 67 of 89 patients).

Assays At the study visit, and after 1993, serum GH level was measured with a sensitive immunofluorometric assay (Wallac, Turku, Finland) specific for the 22 kDa GH protein, calibrated against WHO International Reference Preparation (WHO IRP) 80/505 (detection limit: $0.3 \mu\text{g/l}$; intra-assay coefficient of variation (CV) 1.6–8.4% of 0.1 – $15.4 \mu\text{g/l}$). Before 1992, GH was measured by RIA (Biolab, Serona, Coissins, Switzerland) calibrated against WHO IRP 66/21 (detection limit: 0.5 mU/l , inter-assay CV $<5\%$; for the conversion of $\mu\text{g/l}$ to mU/l , multiply by 2). From 1986 to 2005, serum IGF1 concentrations were determined by RIA (Incstar, Stillwater, MN, USA) with a detection limit of 1.5 nmol/l and an inter-assay CV $<11\%$. IGF1 is expressed as SDS for age- and gender-related normal levels determined in the same laboratory (12). From 2005, serum IGF1 concentration (ng/ml) was measured using an immunometric technique on an Immulite 2500 system (Diagnostic Products Corporation, Los Angeles, CA, USA). The intra-assay variation was 5.0 and 7.5% at mean plasma levels of 8 and 75 nmol/l respectively. IGF1 levels were expressed as age- and gender-dependent SDS, using lambda-mu-sigma (LMS) smoothed reference curves based on measurements in 906 healthy individuals (13, 14).

Statistical analysis

For data analysis, PASW 17 for Windows was used (SPSS, Inc., Chicago, IL, USA). We reported the mean

$\pm$ s.d. unless specified otherwise. For comparison of the mean JSWs between patients and controls, we used ANOVA analysis with adjustments for age and gender. For the correlation between JSW and disease characteristics of acromegaly, we used Pearson's correlation and linear regression analysis. Tertiles of serum GH and IGF1 concentrations and sex were used as fixed factors, and age was used as a covariate. (Un)standardized betas (β) were reported with 95% confidence intervals (95% CIs). Mean joint spaces were dichotomized to normal (<95 th percentile of female or male controls per joint site) or increased (>95 th percentile of female or male controls per joint site).

In addition, we studied self-reported pain in relation to the joint space of the individual joints. Individual JSWs were re-coded in deciles for each joint pair (i.e. left and right MCP 2–5, DIP 2–5, and PIP 2–5; $n=12$) per gender within acromegalic patients. The decile score was used as a covariate in a general estimated equation model to take into account the intra-patient effect.

Results

Baseline characteristics

The mean age of the 89 included acromegaly patients was 58.2 ± 11.5 years and there was an equal gender distribution (49% females). Mean body mass index (BMI) was 28.5 ± 4.7 kg/m². At the time of diagnosis, the IGF1 SDS was 7.4 ± 4.7 ($n=67$) and the GH concentration was 44.5 ± 63 μ g/l. The estimated duration of acromegaly before the moment of diagnosis was 8.8 ± 7.4 years. All patients were in biochemical remission of acromegaly and the mean duration of remission was 14 ± 6 years. One or more pituitary hormone deficiencies were present in 33% of patients; ACTH and TSH deficiency was present in 25 and 20% of patients respectively, and the patients were adequately supplemented with hydrocortisone and T₄. LH/FSH deficiency, including natural menopause and hypogonadotropic hypogonadism, was present in 54% of patients. Sex hormone substitution therapy was given to ten patients (nine men used testosterone and one

woman used estrogens). The majority of patients with acromegaly (84%) reported pain and stiffness of the hand at the time of the current evaluation. The prevalence of clinical hand OA in acromegaly according to the ACR criteria was 40%. The mean age of the 470 controls was 46 ± 12 years, which was lower compared with that of the acromegalic patients ($P<0.001$), and 42% were females, which was not different from the gender distribution in the patients ($P=0.178$).

Hand JSW in acromegaly patients and controls

Both among acromegaly patients and controls, men had wider joint spaces and larger proximal phalange widths than women ($P<0.001$). There was a negative correlation between JSW and age for the MCP ($R=-0.31$, $P<0.003$) and DIP joints in acromegalic patients ($R=-0.22$, $P<0.04$), but not for the PIP joints ($R=0.024$, $P=0.825$ (not significant (NS))).

In acromegaly patients, the JSWs of all 24 hand joints were increased compared with those of controls (mean difference adjusted for age and gender was 0.26 mm (95% CI 0.22–0.30), $P<0.001$; Table 1, Fig. 2). Mean MCP joint spaces were increased by 24%, mean PIP joint spaces by 21%, and mean DIP joint spaces by 20% in patients compared with controls (Table 1). The mean width of the proximal phalanx was also increased in acromegaly patients by 7% ($P<0.001$).

Mean joint spaces above the 95th percentile of controls were observed in 53% of the MCP, 45% of the PIP, 27% of the DIP joint sites, and in 64% (all 24 measured joints) of acromegalic patients. Only 9% of the acromegalic patients had mean JSW (all joints) below the 50th percentile of controls.

Influence of (previous) activity of acromegaly on joint space

For both MCP and PIP joints, there was a positive correlation between JSWs and pretreatment serum GH and IGF1 concentrations (both $R=0.35$, $P=0.001$). In contrast to the other hand joints, DIP joints were not significantly associated with parameters of severity of acromegaly disease. A negative correlation

Table 1 Patients with acromegaly have wider mean JSWs than controls. All measurements are expressed in millimeters (s.d.).

Mean JSW (mm)	Acromegalic patients ($n=89$)	Controls ($n=470$)	Mean difference	Adjusted mean difference ^a	P value ^b (two-tailed)
All joints	1.38 ± 0.25	1.15 ± 0.17	0.23 (0.19–0.27)	0.26 (0.22–0.30)	<0.001
MCP	1.95 ± 0.34	1.61 ± 0.23	0.34 (0.28–0.40)	0.38 (0.33–0.44)	<0.001
PIP	1.15 ± 0.23	0.95 ± 0.15	0.20 (0.16–0.24)	0.20 (0.17–0.25)	<0.001
DIP	1.04 ± 0.30	0.89 ± 1.78	0.14 (0.10–0.19)	0.18 (0.14–0.23)	<0.001
Mean width proximal phalanx (mm)	10.19 ± 1.26	9.40 ± 1.04	0.79 (0.54–1.0)	0.72 (0.55–0.90)	<0.001

JSW, joint space width; MCP, metacarpo-phalangeal joint; PIP, proximal interphalangeal joint; DIP, distal interphalangeal joint.

^aAdjustments were made for age and gender.

^bAll mean and adjusted mean differences were significant at the level $P<0.001$.

Figure 2 Increased mean (S.E.M.) of joint space widths of the hands in patients with acromegaly in three age groups compared with controls. Symbols represent the mean of all measured hand joint spaces (MCP, PIP, and DIP joints). Black circles, acromegalic patients; white squares, controls. * $P < 0.001$.

was present between JSWs and age at diagnosis ($R = -0.28$, $P = 0.009$).

On linear regression analysis, pretreatment GH and IGF1 SDS were significantly associated with JSWs (mean of all joints and mean of MCP joints) with and without adjustments for age and gender (adjusted β for pretreatment GH tertiles: 0.07 (0.0–0.14) and for IGF1 tertiles: 0.09 (0.03–0.15); Table 2, Fig. 3). A younger age at diagnosis of acromegaly was associated with larger joint spaces also after adjustments for the duration of follow-up. The mean JSWs were not associated with different treatment modalities in this long-term controlled acromegaly cohort. Furthermore, JSWs were associated neither with current biochemical markers of disease activity in this biochemically controlled population nor with duration of remission or duration of follow-up.

JSW and relation with complaints

In general, there was no gender difference in the number of patients with self-reported pain in any joint of the hands. In individual joints, assessed by the structured diagram of 24 joints, female patients reported pain more frequently, i.e. in 16% of DIP joints, 21% of PIP joints, and 10% of MCP joints, compared with male patients who reported pain in 6.2% of DIP and PIP joints and 11.8% of MCP joints ($P < 0.001$ for both DIP and PIP joints and $P = 0.60$ (NS) for MCP joints). Joint pain was reported more frequently in joints with larger JSWs in male patients, when considering JSW in deciles per joint separately for gender (β for male patient 0.15 (0.05–0.26) $P = 0.004$, especially in the MCP joints, and for female patients β 0.04 (–0.02–0.16) $P = 0.184$ (NS); Fig. 4).

Discussion

The aim of the present study was to compare JSWs of hand joints in patients with long-term controlled acromegaly with a large control group, adjusted for age and gender. The data show that acromegalic patients have increased JSWs of their hand joints, indicating persistent cartilage hypertrophy despite long-term control of the disease. In addition, JSWs were related to GH and IGF1 concentrations at the time of initial diagnosis, but not to current concentrations of GH and IGF1, disease duration, or duration of follow-up. Finally, painful hand joints were wider than asymptomatic hand joints, especially in male patients. These observations characterize the late manifestations of well-controlled acromegaly in hand joints and indicate persistent, possibly irreversible, cartilage hypertrophy in these hand joints.

Arthropathy is an invalidating complication of active and well-controlled acromegaly (14). However, little is known about the clinical characteristics and progression or regression of acromegalic joint disease after induction of biochemical remission. Nonetheless, the prevalence of clinical and radiographic OA is considerably increased in patients with long-term controlled acromegaly (4). A remarkable finding of our previous study was the combination of severe osteophytosis with normal or even widened joint spaces (4). In the present study, we document that the JSWs of the hand joints in acromegaly, especially the PIP and MCP joints, were clearly wider than those of controls. The increased joint spaces of the small hand joints are in accordance with the appearance of wide joint spaces on hip and knee radiographs of patients with long-term cure of acromegaly (4, 15). Therefore, joint space widening is a persistent feature of long-term controlled acromegaly in both small and large, weight- and non-weight-bearing joints.

Table 2 Linear regression analysis of factors influencing joint space width in metacarpo-phalangeal (MCP) joints and all hand joints in acromegaly patients. Data reported are unstandardized β and confidence intervals. GH and IGF1 are categorized in groups according to tertiles. Pretreatment IGF1 S.D. and age are continuous variables. Proximal interphalangeal and distal interphalangeal joints were not influenced by markers of disease severity.

	MCP joints (n=8)	All joints (n=24)
Age (years)	–0.009 (–0.015 to –0.003)	–0.005 (–0.009 to 0.000)
Gender (M/F)	–0.25 (–0.38 to –0.12)	–0.22 (–0.32 to –0.12)
Pretreatment GH tertiles ($\mu\text{g/l}$)	0.09 (0.03–0.184) ^a	0.07 (0.00–0.14) ^a
Preoperative IGF1 (SDS) tertiles	0.14 (0.05–0.23)	0.09 (0.027–0.15)
Pretreatment IGF1 (SDS)	0.018 (0.02–0.035)	0.012 (0.001–0.023)
Age at diagnosis (years)	NS	NS

n, number of joints evaluated; NS, not significant.

^aAdjustments for sex and present age.

Figure 3 Mean joint space width (JSW; S.E.M.) increases with increasing pretreatment GH and IGF1 concentrations. Left, mean JSWs of MCP joints; right, mean JSWs of all 24 measured hand joints; upper panels, GH tertiles; lower panels, IGF1 tertiles.

Both GH and IGF1 act as growth factors for chondrocytes (16). In accordance with this notion, JSWs correlated positively with pretreatment GH and IGF1 concentrations. Age at diagnosis was negatively related to JSW, compatible with biochemically more active acromegaly at young age and/or, alternatively, with cartilage that is more responsive to GH-induced cartilage hypertrophy in younger subjects. JSWs were related to markers of disease severity at the time of initial diagnosis, but not to the duration of remission. This suggests that cartilage hypertrophy, induced during the active phase of the disease, is maintained in the long-term after cure of acromegaly. Apparently, the transient period of active acromegaly has resulted in a higher persistent set point of joint cartilage volume. Some short-term studies have suggested that cartilage hypertrophy may improve upon successful treatment of acromegaly (17, 18). However, in our study, the JSWs were still increased after long-term control of acromegaly, indicating persistent cartilage hypertrophy. In acromegalic patients, before treatment, joint spaces are more widened compared with values after early disease control, as indicated in the ultrasound studies by Colao *et al.* (17, 18). Therefore, in the present cross-sectional study, we cannot differentiate between partial and complete irreversibility because pretreatment radiographs were not available for analysis. Additional follow-up measurements in acromegalic patients and studies in treatment-naïve patients are necessary to establish potential ongoing reversibility in the short term and during additional prolongation of follow-up.

We used a new semi-automated technique to quantify JSWs (5). This method is accurate and fast and can be used to determine joint space narrowing in patients with OA and is in good agreement with a semi-quantitative scoring system of JSW (19). In the

present study, we used a new technique to measure JSWs (5, 20). Previously, there was no validated method to assess joint space widening in the hands. By the use of validated qualitative scoring systems frequently used in primary OA, we experienced an important limitation of these scoring methods (i.e. Osteoarthritis Research Society (OARSI) scoring, Kellgren–Lawrence method), since widened joint spaces, a major feature of acromegalic arthropathy, are not included. With the present, new, and semi-automated method, we are the first to detect quantitative differences in JSWs in acromegalic patients compared with controls.

Moreover, within the group of acromegalic patients, this method was sensitive enough to relate JSWs to markers of disease severity of acromegaly. Further longitudinal studies are needed to assess whether this technique is sensitive enough to be used in clinical practice to detect ongoing GH/IGF1 stimulating effects on cartilage tissue, which would be very useful since we lack reliable biomarkers at present. The large number of abnormally wide joint spaces, which we defined as higher than the 95th percentile of controls, may have even been underestimated because of the somewhat lower age of the controls. Joints with increased JSWs were more frequently painful than joints within the range of normal, especially in male patients. In acromegalic patients, cartilage loss is probably not the main cause of pain, and therefore the reverse, i.e. cartilage hypertrophy, should be recognized as a risk factor for pain. Additional studies are needed to establish which factors are determinants of joint pains in these patients, such as osteophytosis, and instability of joints. Only 10% of the acromegalic patients used pain medication for joint complaints, on a chronic or on demand basis. The mean number of reported painful joints was not different

Figure 4 Bar chart of the distribution of self-reported pain in individual joints in 89 patients with acromegaly. Bars represent the number of painful joints in 89 acromegaly patients in the respective decile, for eight DIP, eight PIP, and eight MCP joints respectively (71.2 joints per decile evaluated). A higher decile reflects a higher joint space width (JSW). White bars, female patients; black bars, male patients. In men, more painful MCP joints are found in higher JSW deciles. * $P < 0.05$.

between users of pain medication and non-users ($P=0.543$). Therefore, we conclude that the use of pain medication does not affect our conclusions.

A limitation of this study is the possibility that the difference in age distribution between the various groups may have confounded the results to some extent. To correct for differences in age between patients and controls, we adjusted for age in all analyses. However, this may not necessarily control for the possible confounding effect of age because of the relatively small sample size. Nonetheless, in the present study, age had an effect on JSWs in patients with long-term control of acromegaly, but not in controls. Therefore, it is unlikely that the difference in age between controls and patients invalidates our conclusion with respect to the long-lasting effects of previous GH excess on JSWs.

In conclusion, the widening of joint spaces is a rather unique feature of acromegaly. Hand JSWs in acromegaly are positively related to GH and IGF1 concentrations at the time of diagnosis and age at diagnosis, but not to the duration of follow-up, suggesting a dose-dependent and irreversible effect of previous GH excess on cartilage hypertrophy.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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