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Acromegaly : irreversible clinical consequences

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Chapter 6.

WIDE JOINT SPACES IN HAND RADIOGRAPHS OF LONG-TERM CONTROLLED ACROMEGALY PATIENTS ASSESSED BY AUTOMATED IMAGE ANALYSIS IN COMPARISON WITH HEALTHY CONTROLS; IN RELATION TO DISEASE ACTIVITY AND SYMPTOMS.

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Article submitted

ABSTRACT

Background: Acromegalic arthropathy is an invalidating complication of acromegaly and although it shares features with primary osteoarthritis, joint space narrowing is infrequently seen in acromegalic patients. The late effects of acromegaly on hand joints have not been characterized.

Aim: Three aims of the present study were 1) comparing joint space width of hand joints between patients with long-term controlled acromegaly and age- and gender-matched controls, 2) identification of factors associated with joint space width, and 3) assessment of the relation between joint space abnormalities and complaints of joint pain in acromegaly patients.

Methods: Cross-sectional study in 89 patients (age 58 ± 12 yr, 49% women) with long-term controlled acromegaly and 471 controls without hand symptoms (age 46 ± 12 , 42% women). Radiological joint space width of hand joints were measured by automated image analysis.

Results: Patients with long-term remission of acromegaly had 20-24% wider mean joint spaces at the MCP, PIP and DIP-joints ($p < 0.001$). Mean joint space width of all hand joints exceeded the 95th percentile of controls in 64% of patients. Only 9% of patients had mean joint spaces below the 50th percentile of controls. Higher GH and IGF-I concentrations at the time of diagnosis were associated with larger joint space width at the MCP-joints. Duration of follow-up of acromegaly was not related to joint space. In males, not in females, increased joint spaces were associated with more self-reported pain ($P=0.02$).

Conclusion: The increased joint spaces of the hand joints in long-term controlled acromegaly patients characterize an aspect of the late manifestations of well-controlled acromegaly and indicate persistent, possibly irreversible, cartilage hypertrophy.

INTRODUCTION

Acromegaly is a rare disease caused by overproduction of growth hormone (GH) from a pituitary adenoma¹. This syndrome is characterized by a variety of complaints, increased co-morbidity and mortality. On radiographs, active acromegaly is characterized by increased joint space width, amongst other features². However, the effects of cure or biochemical control of the disease on joint space width has not been fully elucidated. Nonetheless, patients with acromegaly have a high prevalence of joint pain and arthropathy even after long-term successful biochemical cure³. Although the changes in joints of patients with controlled acromegaly match the criteria of both radiological and clinical osteoarthritis (OA)⁴, radiological characteristics differ between controlled acromegaly and primary OA: patients with acromegaly have more severe osteophytosis, but less joint space narrowing⁴. In addition, despite long-term control of acromegaly, the joint spaces appear to remain abnormally wide, reflecting irreversible cartilage hypertrophy. There are no quantitative data available on the magnitude of joint space width in patients with acromegaly compared with healthy controls.

The aim of the present study is to quantify joint spaces in hand radiographs of patients with long-term controlled acromegaly in comparison to age and gender related controls by means of semi-automated image analysis software⁵. The second aim was to explore potential factors that are associated with the size of the joint space in acromegaly 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 joint space width and specific joint complaints in these patients with controlled acromegaly.

PATIENT AND METHODS

Patients

In this case-control study we compared joint space width in hand radiographs between patients with long-term controlled acromegaly and controls derived from two epidemiological studies performed in our institution.

Acromegalic patients

All patients with long-term remission of acromegaly (i.e. more than 2 yr), according to a normal IGF-I concentration for age, were selected from our database. The Leiden Acromegaly Database includes baseline and follow-up results of all patients that have been treated in the Leiden University Medical Center, a tertial referral center with a dedicated pituitary surgeon, from 1977 onwards. They were invited to participate in a cross-sectional study aimed at evaluating the extent of joint disease in long-term controlled acromegaly patients⁴. We invited 126 patients. Eighty-nine patients (71%) agreed to participate.

The majority of patients was 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 mcg/L (in patients not treated with somatostatin analogs), serum GH concentrations below 1.9 µg/liter and normal IGF-I levels for age at yearly follow-up visits⁶.

Controls

To compare the hand joint space width in acromegaly patients with normative data from control subjects, we composed an age- and gender matched control group from the database of The Leiden Early Arthritis Clinic (EAC, n=167)⁷ and patients from a follow-up visit of the so called KART study (*vide infra*) (n=304). None of these controls had hand-symptoms. The EAC is a prospective study started in 1993 and includes patients with early arthritis with symptoms for less than 2 years⁷. 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 and feet and affected joints were obtained in all patients at baseline. For the purpose of the present study, we made a selection of patients without hand symptoms and used the hand radiographs of their inclusion visit. The KART study is an epidemiological study, which includes patients with traumatic or non-traumatic knee complaints. At a baseline and follow-up visit 10 years later, routine radiographs of the hands were obtained

in all patients. Since patients were not included in the KART study on the basis of hand joint pathology, we assumed that their hand joints are a valid sample of the general population.

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

Diagnosis of osteoarthritis

In all subjects clinical OA was scored according to the criteria proposed by the American College of Rheumatology (ACR)⁸.

Study parameters

Conventional radiographs of the hands

From all subjects with acromegaly and all KART controls, 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. To analyze the analog radiographs, they were digitized (VXR-12, VIDAR System Corporation, Herndon, VA). Hand joints were evaluated for presence of radiological OA using the Kellgren and Lawrence classification system^{9,10}. This is a 5-point ranking scale (0 = normal, 4 = severe OA). A score of 2 or higher is considered (mild) OA.

Image processing for determination of joint space width

Recently, at our institute, van 't Klooster *et al.* developed a semi-automatic quantitative method to measure joint space width in hand radiographs with a good correlation with semi-quantitative scoring of joint space narrowing^{5,8}. Therefore, joint space width of the hands in the current study were measured using this semi-automatic image analysis program. First, this program loads the digital/digitized 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: 1) identification of the joint locations; 2) detection of the proximal and distal margins of each joint; 3) measurement of the width of each proximal phalanx, as a reference for the joint space width measurement interval; and 4) 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.M) and corrected

if needed. For each subject, 24 measured joint spaces were reported, as well as the thickness of the proximal phalanges. 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 kappa of >0.9. Within the EAC cohort we compared digitized analog and digital radiographs. There was no significant difference between both techniques in 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 at structural physical examination was recorded systematically for all 24 joints.

Disease characteristics in acromegaly patients

In order to estimate the duration of exposure to GH excess, the estimated disease duration prior to diagnosis and disease duration prior to 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 IGF-I 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/ IGF-I concentrations and study visit. During the study visit actual GH and IGF-I concentrations were measured. Pretreatment IGF-I / GH concentrations were recorded from the database. Due to the unavailability of IGF-I assays in our center prior to 1986, pretreatment IGF-I levels were available in 67 of 89 patients. The product of the duration of disease and the severity reflected by the logarithmically transformed GH/ IGF-I concentrations were used as a marker of exposure to GH excess.

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 World Health Organisation International Reference Preparation (WHO IRP) 80/505 (detection limit 0.3 µg/L; intra-assay coefficient of variation (CV) 1.6-8.4% of 0.1-15.4 µg/L). Before 1992, GH was measured by RIA (Biolab, Serona, Coissins, Switzerland) calibrated against

WHO IRP 66/21 (detection limit: 0.5 mU/l, interassay CV: < 5%; for the conversion of mg/l to mU/l, multiply by 2). From 1986 to 2005, serum IGF-I concentrations were determined by RIA (Incstar, Stillwater, MN) with a detection limit of 1.5 nmol/liter and an interassay CV less than 11%. IGF-I is expressed as SD scores for age- and gender-related normal levels determined in the same laboratory¹¹. From 2005, serum IGF-I concentration (ng/ml) was measured using an immunometric technique on an Immulite 2500 system (Diagnostic Products Corporation, Los Angeles, CA). The intra-assay variation was 5.0 and 7.5% at mean plasma levels of 8 and 75 nmol/l, respectively. IGF-I levels were expressed as age and gender dependent standard deviation (SD) score, using lambda-mu-sigma (LMS) smoothed reference curves based on measurements in 906 healthy individuals^{12,13}.

Statistical analysis

For data analysis, PASW 17 for Windows was used (SPSS Inc. Chicago IL). We reported the mean $\pm$ SD unless specified otherwise. For the comparison of the mean joint space width between the patients and the controls we used ANOVA analysis with adjustments for age and gender. For the correlation between the joint space width and the disease characteristics of acromegaly we used Pearson's correlation and linear regression analysis. Tertiles of serum GH and IGF-I concentrations and sex were used as fixed factors, age was used as a covariate. (Un)-standardized beta's (β) were reported with 95% confidence intervals (95%CI). Mean joints spaces were dichotomized to normal (< 95th percentile of female or male controls per joint site) or increased (>95th 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. Within acromegaly patients, individual joint space width was re-coded in tentiles per joint (n=12), separately for males and females. The tentile-score was used as a covariate in a general estimated equations model to take into account the intra-patient effect.

Results

Baseline characteristics (*Table 1*)

The mean age of the 89 included acromegaly patients was 58.2 ± 11.5 years and there was an equal gender distribution (49% females). At diagnosis, the mean IGF-I SD score was 7.4 ± 4.7

(n=67) and mean GH concentrations were 44.5 ± 63 mcg/L. The estimated mean duration of acromegaly prior to 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. The majority of the patients with acromegaly (84%) reported complaints of pain and stiffness of the hand at the time of the current evaluation. The prevalence of clinical OA of the hand in acromegaly according to the ACR criteria was 40%. The mean age of the 470 controls was 46 ± 12 years and 42% were females.

Table 1. Baseline characteristics

	Acromegaly	Controls
N	89	470
Age (yr)	58 ± 12	$46 \pm 12^*$
Gender (% female)	49	42
BMI (kg/m ²)	28.5 ± 4.7	NA
Pre-treatment IGF-I SD score	7.4 ± 4.7	NA
Disease duration (yr)	8.8 ± 7.4	NA
Duration of remission (yr)	14.1 ± 6.2	NA
Age at diagnosis (yr)	41 ± 12	NA
Clinical hand osteoarthritis(%)	40	NA

Data are shown as mean $\pm$ SD, NA: not assessed, yr: years, *p<0.01

Hand joint space width in acromegaly and controls (*Table 2, Figure 1*)

In patients and in controls, males had wider joint spaces and larger proximal phalanx widths than females ($P<0.001$). There was a negative correlation between joint space width and age for the MCP ($R -0.31$, $P<0.003$) and DIP joints in acromegalic patients, ($R 0.22$, $P<0.04$).

The mean joint space width of all 24 joints measured in the hands of acromegaly patients was increased compared with controls (mean difference adjusted for age and gender 0.26 mm (95% CI 0.22-0.30), $P<0.001$). 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 2*). 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 joint space width (all joints) below the 50th percentile of controls.

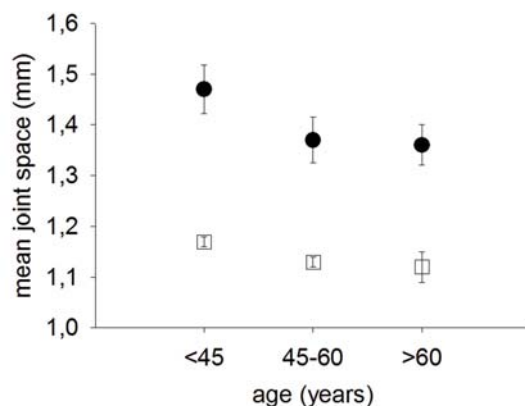


Figure 1. Increased mean joint space width in MCP joints in patients with acromegaly in comparison with controls. Dots are patients, squares are controls. Error bars represent means of 3 age groups.

Table 2. Difference in mean joint space width between acromegaly patients and controls.

Mean joint space width (mm)	Acromegaly patients N=89	Controls N=470	Mean difference	Adjusted mean difference*	P-value ** (2-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

All measurements are expressed in millimeters ± SD. JSW= joint space width, MCP= metacarpophalangeal joint, PIP= proximal interphalangeal joint, DIP=distal interphalangeal joint. *Adjustments were made for age and gender. **All mean and adjusted mean differences were significant at the level P <0.001.

Influence of (previous) activity of acromegaly on joint space (Table 3)

For both MCP and PIP joints, there was a positive correlation between joint space width and pre-treatment serum GH and IGF-I concentrations (both R = 0.35, P=0.001). In contrast with the other hand joints, DIP joints were not significantly associated with parameters of acromegalic disease severity. A negative correlation was present between joint space width and age

at diagnosis ($R = 0.28$, $P = 0.009$).

Using linear regression analysis, tertiles of pre-treatment GH and IGF-I SD concentrations were significantly associated with joint space width (mean of MCP joints and mean of all joints) with and without adjustments for age and gender (*Figure 2*).

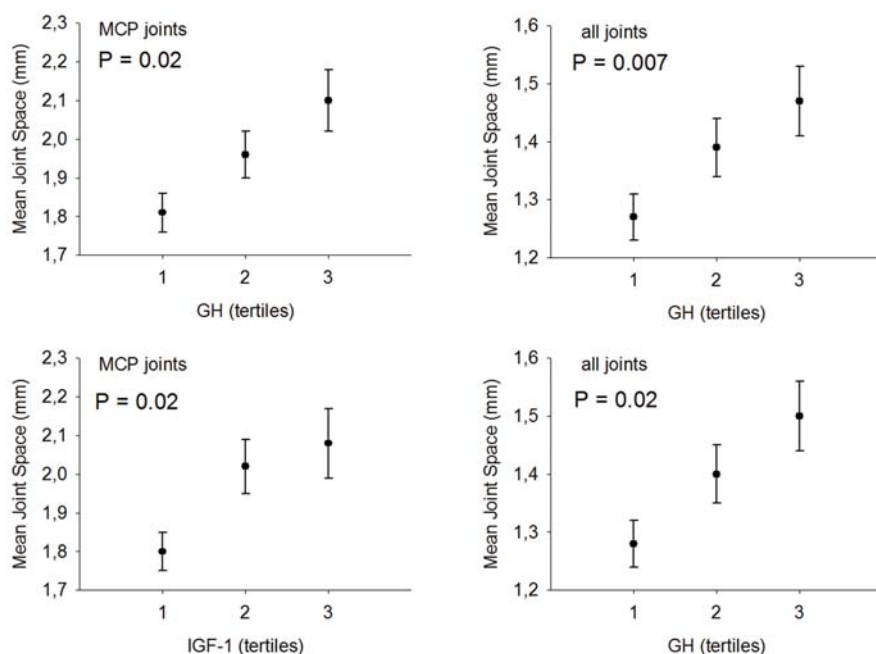


Figure 2. Mean joint space ($\pm$ 95% CI) increases with increasing pre-treatment GH and IGF-I concentrations (left: mean joint space of MCP joints, right: mean joint space of all 24 measured hand joints, upper panels: tertiles of GH concentrations; lower panels: tertiles of IGF-I SD scores,)

A younger age at diagnosis of acromegaly was associated with larger joint spaces also after adjustments for the duration of follow-up. The mean joint space was not associated with different treatment modalities in this long-term well-controlled cohort of acromegaly patients. Joint space width was not associated with current biochemical markers of disease activity in this biochemically controlled population, neither was it associated with duration of remission or duration of follow-up.

Table 3. Linear regression analysis of factors influencing joint space width in MCP joints and all hand joints in acromegaly patients.

	MCP joints (N=8)	All joints (N=24)
Tertiles of pre-treatment GH	0.09 (0.03-0.184)	0.07(0.00 – 0.14)
Tertiles of pre-treatment IGF-I SD	0.14 (0.05-0.23)	0.09 (0.027-0.15)
Pre-treatment IGF-I SD score	0.018(0.02-0.035)	0.012(0.001-0.023)
Age at diagnosis (yr)	NS	NS

Data reported are unstandardized B (95% confidence interval) with adjustments for sex and present age. GH and IGF-I is categorized in groups according to three percentiles (GH 1st <12.5 mcg/L, 2nd 12.5-40 mcg/L, 3rd >40 mcg/L and IGF-I SD 1st <5.5, 2nd 5.5-9, 3rd >9). PIP and DIP joints were not influenced by markers of disease severity. NS = not significant.

Joint space width and relation with complaints

In general, there was no gender difference between the number of patients with self-reported pain in any joint of the hands. At individual joint level, as assessed with the structured diagram of 24 joints, pain was reported significantly more frequently by females in 16% of DIP joints, 21% of PIP joints and 10% of MCP joints in contrast with male patients who reported pain in 6.2% of DIP and PIP joints and 11.8% of MCP joints.

Joint pain was reported more frequently in joints with larger joint space width, when considering joint space width in tentiles per joint separately for gender within acromegaly patients (β for male patient 0.15 (0.05-0.26) $P = 0.004$ and for female patients β 0.04 (-0.02 – 0.16) $p = ns$) (Figure 3).

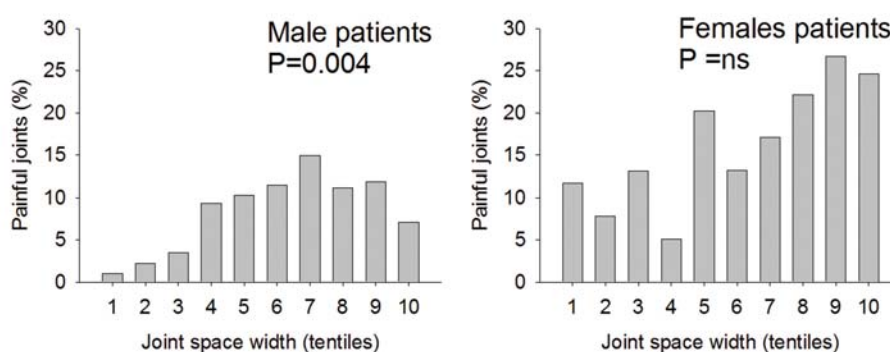


Figure 3. Distribution of self-reported pain in patients with increasing joint space width (in tentiles).

DISCUSSION

The aim of the present study was to quantify joint space width of hand joints in patients with long-term controlled acromegaly compared with age and gender matched controls. The data indicate that acromegaly patients have increased mean joint spaces in their hand joints, indicating persistent cartilage hypertrophy despite long-term control of the disease. In addition, joint space width was related to GH and IGF-I concentrations at the time of initial diagnosis, but not to current concentrations of GH and IGF-I, disease duration, or duration of follow-up. Finally, hand joints in which patients reported pain, were wider than asymptomatic hand joints. 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 acromegaly¹⁴. However, little is known about the clinical characteristics and progression or regression of acromegalic joint disease after induction of biochemical remission. We recently reported an increased prevalence of clinical and radiological osteoarthritis in patients with long-term controlled acromegaly⁴. A remarkable finding of that study was the combination of severe osteophytosis with normal or even widened joint spaces. In the present study, we document that the joint space width 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, which we measured in the present study, are in accordance with the appearance of wide joint spaces on hip and knee radiographs of long-term cured acromegalic patients⁴. Therefore, joint space widening appears to be a persistent feature of long-term controlled acromegaly in both small and large, weight- and non-weight bearing joints.

GH and IGF-I act both as growth factors for chondrocytes¹⁴. In accordance with this notion, joint space width correlated positively with pre-treatment GH and IGF-I concentrations. Age at diagnosis was negatively related to joint space width, compatible with biochemically more active acromegaly at young age or alternatively, with cartilage that is more responsive to GH induced cartilage hypertrophy in younger subjects. Joint spaces width was related to markers of disease severity at the time of initial diagnosis, but not to the duration of remission. This may suggest 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 after successful treatment of acromegaly^{15,16}. However, in our study mean joint space width was increased despite long-term control of acromegaly. Follow-up studies are required to determine whether this cartilage hypertrophy is stable or whether it progresses or regresses during controlled disease.

We used a new, semi-automated technique to quantify joint space width⁵. This method is accurate and efficient and can be used to determine joint space narrowing in patients with OA and has a good agreement with a semi-quantitative scoring system of joint space¹⁷. This method was able to detect quantitative differences in large joint space width in acromegaly patients compared with controls. Moreover, within the group of acromegalic patients, this method was sensitive enough to relate joint space width to markers of disease severity of acromegaly. The large number of abnormally wide joint spaces, which we defined as higher than the 95th percentile of controls, may even be underestimated because of the lower age of the controls. Joints with increased joint space width were more frequently painful than joints within the range of normal, especially in male patients. In this patients group, 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. Further study is needed to assess which factors determine pain, such as osteophytosis, or instability of joints.

In conclusion, long-term biochemical control of acromegaly is associated with wider joint spaces of the hand joints. The increased joint spaces characterize an aspect of the late manifestations of well-controlled acromegaly and indicate persistent, possibly irreversible, cartilage hypertrophy.

REFERENCES

- (1) Melmed S. Medical progress: Acromegaly. *N Engl J Med* 2006; 355(24):2558-2573.
- (2) Layton MW, Fudman EJ, Barkan A, Braunstein EM, Fox IH. Acromegalic arthropathy. Characteristics and response to therapy. *Arthritis Rheum* 1988; 31(8):1022-1027.
- (3) Biermasz NR, Pereira AM, Smit JW, Romijn JA, Roelfsema F. Morbidity after long-term remission for acromegaly: persisting joint-related complaints cause reduced quality of life. *J Clin Endocrinol Metab* 2005; 90(5):2731-2739.
- (4) Wassenaar MJ, Biermasz NR, van DN, van der Klaauw AA, Pereira AM, Roelfsema F *et al.* High prevalence of arthropathy, according to the definitions of radiological and clinical osteoarthritis, in patients with long-term cure of acromegaly: a case-control study. *Eur J Endocrinol* 2009; 160(3):357-365.
- (5) van 't Klooster R, Hendriks EA, Watt I, Kloppenburg M, Reiber JH, Stoel BC. Automatic quantification of osteoarthritis in hand radiographs: validation of a new method to measure joint space width. *Osteoarthritis Cartilage* 2008; 16(1):18-25.
- (6) Biermasz NR, Dekker FW, Pereira AM, van Thiel SW, Schutte PJ, van DH *et al.* Determinants of survival in treated acromegaly in a single center: predictive value of serial insulin-like growth factor I measurements. *J Clin Endocrinol Metab* 2004; 89(6):2789-2796.
- (7) van Aken J, van Bilsen JH, Allaart CF, Huizinga TW, Breedveld FC. The Leiden Early Arthritis Clinic. *Clin Exp Rheumatol* 2003; 21(5 Suppl 31):S100-S105.
- (8) Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K *et al.* The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990; 33(11):1601-1610.
- (9) Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthritis. *Ann Rheum Dis* 1957; 16(4):494-502.
- (10) Kellgren JH, Lawrence JS. Osteo-arthritis and disk degeneration in an urban population. *Ann Rheum Dis* 1958; 17(4):388-397.
- (11) Janssen YJ, Frolich M, Roelfsema F. A low starting dose of genotropin in growth hormone-deficient adults. *J Clin Endocrinol Metab* 1997; 82(1):129-135.
- (12) Cole TJ. The LMS method for constructing normalized growth standards. *Eur J Clin Nutr* 1990; 44(1):45-60.
- (13) Rikken B, van DJ, Ringeling A, Van den Brande JL, Massa G, Wit JM. Plasma levels of insulin-like growth factor (IGF)-I, IGF-II and IGF-binding protein-3 in the evaluation of childhood growth hormone deficiency. *Horm Res* 1998; 50(3):166-176.
- (14) Giustina A, Mazziotti G, Canalis E. Growth hormone, insulin-like growth factors, and the skeleton. *Endocr Rev* 2008; 29(5):535-559.
- (15) Colao A, Marzullo P, Vallone G, Marino V, Annecchino M, Ferone D *et al.* Reversibility of joint thickening in acromegalic patients: an ultrasonography study. *J Clin Endocrinol Metab* 1998; 83(6):2121-2125.
- (16) Colao A, Marzullo P, Vallone G, Giaccio A, Ferone D, Rossi E *et al.* Ultrasonographic evidence of joint thickening reversibility in acromegalic patients treated with lanreotide for 12 months. *Clin Endocrinol (Oxf)* 1999; 51(5):611-618.

- (17) Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage* 2007; 15 Suppl A:A1-56.

