Acromegaly : irreversible clinical consequences

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Chapter 3.

PRE-TREATMENT IGF-I CONCENTRATIONS PREDICT RADIOGRAPHIC OSTEOARTHRITIS IN ACROMEGALIC PATIENTS WITH LONG-TERM CURED DISEASE.

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The Journal of Clinical Endocrinology and Metabolism. 2009 Jul; 94 (7):2374-9.

ABSTRACT

Objective: To identify factors influencing the development of osteoarthritis during long-term control of acromegaly, focusing on disease specific parameters, growth hormone (GH) and insulin-like growth factor I (IGF-I) concentrations and duration of disease, adjusted for the well-known determinants of primary osteoarthritis.

Design: Follow-up study.

Methods: We studied 67 patients, with adequate biochemical control of acromegaly for a mean of almost 13 years. Study parameters were the results of radiological assessment of the spine, hip, knee, and hand. Osteoarthritis was defined as radiological osteoarthritis using the scoring system developed by Kellgren and Lawrence (K&L). Correlations between potential factors of influence and osteoarthritis were performed by analysis of covariance and adjusted for age, gender and body mass index (BMI).

Results: Patients with pre-treatment IGF-I standard deviation (SD) scores in the highest tertile had an almost four-fold increased risk for radiological osteoarthritis of the hip when compared with patients in the lowest tertile. After adjustment for age, gender, BMI, and disease duration, pre-treatment IGF-I SD scores predicted radiographic osteoarthritis in all joint sites. Osteoarthritis was not predicted by other factors including pre-treatment GH levels, type of treatment, and duration of follow-up.

Conclusion: This is the first study to document pre-treatment IGF-I concentration as a predictor of radiographic osteoarthritis in acromegalic patients with long-term disease control.

INTRODUCTION

Acromegaly is a chronic disease with insidious onset caused by hypersecretion of growth hormone (GH) from a pituitary adenoma[1-7]. Joint disease is highly prevalent in active acromegaly and is characterized by wide joint spaces due to cartilage hypertrophy in combination with osteophyte formation[4;8;9]. Moreover, after long-term cure of acromegaly joint related complaints were reported by almost 80% of patients[10], and it is assumed that these complaints are based on degenerative joint disease[4-11].

In the general population, degenerative joint disease, like primary osteoarthritis, is a common disease with an estimated prevalence up to 30 to 78% for different joint groups in subjects above 70 years of age[12]. Although the pathogenesis of osteoarthritis is not completely elucidated, it is likely to be a multifactorial disease. Age, gender, body mass index (BMI), genetic factors and biochemical factors, including occupational factors, play a more or less prominent role in the development of primary osteoarthritis[13]. The effects of risk factors may differ between various joint sites. For example, BMI is most strongly associated with knee osteoarthritis and genetic factors with hip and hand osteoarthritis. Hormonal factors may also play a role, but the exact mechanism is not quite clear[13].

It is likely that activation of the GH-IGF-I axis is a key-factor in the development of the degenerative joint disease in acromegaly, since acromegaly is associated with a very early onset of arthropathy[4-10]. However, previous studies with a relatively short period of follow-up during adequate control of acromegaly did not identify disease specific factors predicting arthropathy [4;9;28-30]. Therefore, the aim of the present study was to identify factors influencing the development of degenerative joint disease in patients during long term control of acromegaly, focusing on disease specific parameters, especially on IGF-I and GH concentrations and duration of active disease adjusting for the known predictors of primary osteoarthritis.

PATIENTS AND METHODS

Patients

For the present study, 126 consecutive patients in long-term remission were invited to par-

ticipate. Thirty-seven patients (29%) preferred not to participate in the study for various reasons, including co-morbidities, long travel distance to the outpatient clinic, lack of time, or no willingness to participate because of psychological reasons. Another 22 patients diagnosed before 1986, prior to the introduction of the IGF-I assay were excluded for the present analysis because no IGF-I level at diagnosis was available. Thus, 67 patients were included in the present analysis. The 59 non-included patients were not different from the study population in age, gender, body mass index (BMI), duration of disease, pre-treatment GH/IGF-I, type of primary treatment, duration of follow-up, and self-reported joint complaints, derived from an earlier study[10].

Detailed yearly biochemical and clinical follow-up had been performed from the onset of treatment of acromegaly. The first treatment option in the majority of patients was transsphenoidal surgery performed by a single specialist neurosurgeon. If necessary, adjuvant treatment was given by radiotherapy (prior to 1985) or predominantly somatostatin (SMS) analogs (from 1985 onwards). From 1998, in some patients primary treatment was given in the form of depot formulations of long-acting SMS analogs. Since 2003, pegvisomant is available for treatment-resistant acromegaly.

Disease activity was assessed yearly by oral glucose tolerance tests (except in medically treated patients), measurement of serum GH/IGF-I concentrations, and evaluation of other pituitary functions. Remission of acromegaly was defined as a normal glucose suppressed serum GH less than 0.38 μg/liter, serum GH levels less than 1.9 μg/liter and normal IGF-I levels for age[14]. Patients not meeting these criteria were offered additional treatment.

Eugonadism was defined as normal testosterone concentration in men and by the presence of a normal menstrual cycle at pre-operative and all post-operative evaluations in premenopausal women. Hypogonadism was defined by a testosterone concentration below 8 nmol/l in males, and in females by a low serum oestradiol concentration of less than 70 nmol/L or by the absence of a normal menstrual cycle in premenopausal women. For the purpose of this study, no distinction was made between hypergonadotrophic or hypogonadotrophic hypogonadism in women. Adequately treated hypogonadism was defined as gonadal hormone replacement therapy instituted within a year of onset of hypogonadism, and these patients were not considered hypogonadal in terms of this study. Thyroid stimulating hormone (TSH) deficiency was defined as a thyroxine (free T4) level below the reference range (absolute value <10 pmol/L). Adrenocorticotrophic hormone (ACTH) deficiency was defined as an insuf-

ficient increase in cortisol levels (absolute value <0.55 umol/l) after a corticotrophin releasing hormone test or insulin tolerance test. Hypopituitarism was present in case of clinically relevant hormonal deficiencies in minimal one axis and was treated promptly with thyroxine, hydrocortisone, testosterone or estrogens (in pre-menopausal women).

The study protocol was approved by the Medical Ethics Committee, and all subjects gave written consent for their participation.

Protocol

Sixty-seven patients were seen at the outpatient clinic for a single visit. Physical examination was performed by a single physician (MW) trained in structured joint assessment. Blood samples were taken in the fasting state to assess actual GH and IGF-I concentrations. Other relevant details of treatment and patients characteristics were derived from the patient records. Conventional radiographs were obtained in all patients, according to a standardized protocol (*vide infra)*.

Study parameters

Radiological investigation and radiological scoring

Conventional radiographs of the hands (dorso-volar), knees (Posterior-Anterior (PA) in weight-bearing / fixed flexion[15] and lateral), hips (PA), lumbar (PA and lateral), and cervical spine (Anterior-Posterior (AP) overview, AP transbuccal, and lateral) were obtained from all participating patients, following a standardized manner with a fixed film-focus distance and fixed joint position. All radiographs were performed by a single experienced radiology technician. Radiographs were scored by a single experienced musculoskeletal radiologist (HK) according to the Kellgren and Lawrence (K&L) scale with the help of the original atlas[16-18]. This is a four-point scale scoring system with increasing severity based on the presence of osteophytes, joint space narrowing, sclerosis and degenerative cysts. The intra-reader variability, scored by the K&L method, assessed by the intra-class correlation coefficient (ICC) was 19% for the hands, 11% for the knees (femorotibial), 0% for the hips, 5% for the cervical spine (intervertebral discs and apophyseal joints), and 12% for the lumbar spine (intervertebral discs and apophyseal joints). The intra-reader variability was based on the repeated scoring of 10 radiographs, which were selected randomly. The radiographs were blinded for any patient characteristics.

Parameters of acromegalic disease

Disease duration was calculated from the estimated date of onset, using start of signs and symptoms, and facial changes on photographs to the date of normalization of serum IGF-I concentration after transsphenoidal surgery, or additional treatment. Duration of remission was calculated from the date of normalization of serum IGF-I concentration after treatment until start of the study. Both surgically and/or irradiated cured patients and patients with controlled disease during SMS analog treatment were collectively referred to as 'in remission'.

Biochemical parameters

Serum GH was measured with a sensitive immunofluorometric assay (IFMA) (Wallac, Turku, Finland), specific for the 22 kDA GH protein, calibrated against World Health Organisation International Reference Preparation (WHO IRP) 80/505 (detection limit 0.01 μg/l; inter-assay coefficient of variation (CV) 2.0-9.0% of 0.1-15.4 μg/l) from 1992 onwards, and previously with the RIA assay (Biolab/Serono, Coinsins, Switzerland) calibrated against WHO-IRP 66/21, with an inter-assay CV below 5% and a detection limit of 0.19 μg/l. Pretreatment GH concentrations were available from all patients.

From 1986 up till 2005, serum IGF-I concentrations were determined by a radioimmunoassay (RIA) (Incstar; Stillwater, MN, USA) with a detection limit of 1.5 nmol/l and an inter-assay CV below 11%. IGF-I is expressed as SD scores (SD score) for age- and gender-related normal levels determined in the same laboratory[19]. From 2005 onwards serum IGF-I concentration (ng/ml) was measured using an immunometric technique on an Immulite 2500 system (Diagnostic Products Corporation, Los Angeles, CA, USA). The intra-assay CV was 5.0 and 7.5% at mean plasma levels of 8 and 75 nmol/l, respectively. IGF-I levels were expressed as SD score, using lambda-mu-sigma (LMS) smoothed reference curves based on measurements in 906 healthy individuals[20;21].

The diagnosis of osteoarthritis

For radiographic signs of osteoarthritis we defined a cumulative score indicating severity, for each joint location on the basis of the number of joints with radiographic osteoarthritis based on a K&L score ≥2[16]. Osteoarthritis on the left and right site of the distal interphalangeal (DIP), proximal interphalangeal (PIP), metacarpophalangeal (MCP) and first carpometacarpal (CMC1) joints of the hand, knee, and hip joints respectively, were summarized. The specific

radiographic osteoarthritis score for the hip and knee (range 0-2) represented no, unilateral or bilateral radiographic osteoarthritis. For radiographic hand osteoarthritis a sum score was derived for DIP joints (range 0-8), PIP joints (range 0-8), and CMC1 joints (range 0-2) separately and a sum score for all affected hand joints together (range 0-20). For the cervical and lumbar spine a sum score was derived which was based on the cervical intervertebral discs (0-6; that is, C1/C2-C6/C7) and lumbar intervertebral discs (0-5; that is, L1/L2-L5/S1), respectively.

Statistical analysis

SPSS for windows version 14.0 (SPSS inc., Chicago, IL, USA) was used for data analysis. Data are presented as mean (SEM), unless mentioned otherwise. Radiographic osteoarthritis was scored for each joint at the separate joint sites.

Multinomial logistic regression with adjustments for age, gender, BMI, and disease duration was used to compare the risk on osteoarthritis according to tertiles of pre-treatment IGF-I SD scores. The adjusted ORs and 95% CIs were subsequently transformed to risk ratios (RRs) and corresponding 95% CIs using the approximation formulae described by Zhang *et al.*[22]. Analysis of variance and binary logistic regression analysis with varying adjustments were used when appropriate.

RESULTS

Clinical characteristics (*Table 1*)

We studied 67 patients, 34 male and 33 female with a mean age of 56.8 (1.5) years. BMI and age were comparable in males and females. All patients were in remission for acromegaly or had medically controlled disease for a mean of 12 years after (multimodality) treatment. Sustained biochemical control was maintained since remission, at least for 2 years. Sixteen (23%) patients were still on long-acting SMS analogs.

At the time of diagnosis of acromegaly mean IGF-I SD scores were 7.3 (0.6) SD, and the mean estimated duration of active disease prior to remission was 8.2 (0.8) yrs (range 1 to 45 yrs).

At the time of the current evaluation, the mean estimated duration since diagnosis was 18.5 (1.0) yrs, mean GH level was 0.96 (0.2) μg/l, and mean IGF-I SD was 0.6 (0.2) SD. There

was no gender difference in duration of active disease or duration of remission, serum GH levels, or in IGF-I SD-scores. More female than male patients were hypogonadal, i.e. estrogen deficient, due to natural menopause. There were no gender differences for the other pituitary hormone deficiencies.

Table 1. Clinical characteristics

	Patients (n=67)
Gender (n(%))	
Males	34 (51 %)
Females	33 (49 %)
Age (yr)	56.8 (1.5)
BMI (kg/m^2)	28.3 (0.6)
Height (m)	1.75 (1.3)
Weight (kg)	87.5 (2.2)
Treatment: (n(%))	
Surgery	39 (58 %)
Surgery + RT	6 (9 %)
Surgery + SMS	14 (21 %)
Surgery + RT + SMS	2 (3 %)
Primary SMS	7 (10 %)
Age at diagnosis	43.2 (1.7)
Disease duration (yrs)	8.2 (0.8)
Duration of remission (yrs)	12.4 (0.6)
GH (μg/L)	
Pre-treatment	31.2 (5.2)*
Current	0.96 (0.2)
IGF-I SD scores	
Pre-treatment	7.3 (0.6)
Current	0.6 (0.2)
Hypopituitarism (n(%))	
Hypothyroidism	11 (16 %)
GH deficiency	7 (10 %)
Hypogonadism	31 (46 %)
Hypocortisolism	15 (22 %)

Data are shown as mean and standard error of the mean (SEM), unless mentioned otherwise. N: number, BMI: body mass index, GH: growth hormone, IGF-I: insulin-like growth factor I, SD: standard deviation, RT: radiotherapy (pituitary irradiation), SMS: somatostatin analogs. Mean respective pretreatment GH for IFMA assay (n=49):32.8 (7.7) μg/L and mean GH for RIA assay (n=18): 28.6 (4.1) μg/L.

Risk of developing osteoarthritis according to pre-treatment IGF-I levels

There was a high prevalence of radiographic osteoarthritis (*Table 2)*. This table also shows the relative risks (RR) for having osteoarthritis according to tertiles of pre-treatment IGF-I SD scores. Patients in the highest tertile of IGF-I SD scores had a ~30% increased risk for developing osteoarthritis of the cervical spine (adjusted RR 1.28, 95% confidence interval (CI) 1.01 to 1.31), a four-fold increased risk of developing osteoarthritis of the hip (adjusted RR 3.98, 95% CI 1.69 to 5.01) and a two to almost five-fold increased risk for developing osteoarthritis of the

Table 2. Risk of having osteoarthritis in relation to tertiles of baseline IGF-I levels, expressed in SD scores

Joint site	Tertiles IGF-I SD	Patients with osteoarthritis (%)	Adjusted RR (95% CI)	P-value
Cervical spine	1.69-4.83	76	1	
	4.84-7.39	86	1.23 (0.78 – 1.31)	0.19
	7.40-23.91	91	1.29 (1.07 – 1.31)	0.03
Lumbar spine	1.69-4.83	76	1	
	4.84-7.39	77	0.77 (0.33 – 1.21)	0.61
	7.40-23.91	91	1.22 (0.78 – 1.31)	0.21
Hip	1.69-4.83	19	1	
	4.84-7.39	32	1.72 (0.53 – 3.57)	0.33
	7.40-23.91	57	3.98 (1.69 – 5.01)	<0.01
Knee	1.69-4.83	38	1	
	4.84-7.39	32	1.37 (0.47 – 2.22)	0.49
	7.40-23.91	52	2.15 (1.14 – 2.55)	0.04
DIP	1.69-4.83	45	1	
	4.84-7.39	55	1.53 (0.50 – 2.10)	0.34
	7.40-23.91	60	2.07 (1.09 – 2.21)	0.04
PIP	1.69-4.83	28	1	
	4.84-7.39	46	3.25 (0.89 – 3.56)	0.06
	7.40-23.91	50	3.49 (1.46 – 3.57)	0.02
IP	1.69-4.83	43	1	
	4.84-7.39	43	0.54 (0.11 – 1.52)	0.33
	7.40-23.91	50	1.37 (0.46 – 2.07)	0.47
CMC	1.69-4.83	19	1	
	4.84-7.39	9	0.48 (0.08 – 2.11)	0.38
	7.40-23.91	38	4.76 (1.13 – 5.25)	0.04

N= 67. Tertiles of pre-treatment IGF-I SD scores based on pre-treatment IGF-I SD scores in the whole population. The risks ratios are adjusted for age, sex, BMI, and duration of active disease. Data were analyzed by multinomial logistic regression analysis. DIP: distal interphalangeal (joints), PIP: proximal interphalangeal (joints), IP: interphalangeal (joints), CMC: carpometacarpal (joints), IGF-I; insulin-like-growth factor I, SD: standard deviation, RR: relative risk, CI: confidence interval.

DIP, PIP, and CMC joints, all in comparison to those patients in the lowest tertile of IGF-I SD scores.

There were no significant associations between IGF-I SD scores and osteoarthritis of the knee and lumbar spine, although there was a tendency for an increased risk for osteoarthritis in the higher tertiles.

Pre-treatment IGF-I scores in patients with and without osteoarthritis

The effect of pre-treatment IGF-I SD scores on the degree of radiographic osteoarthritis in separate joint sites is visualized in *Figure 1.*

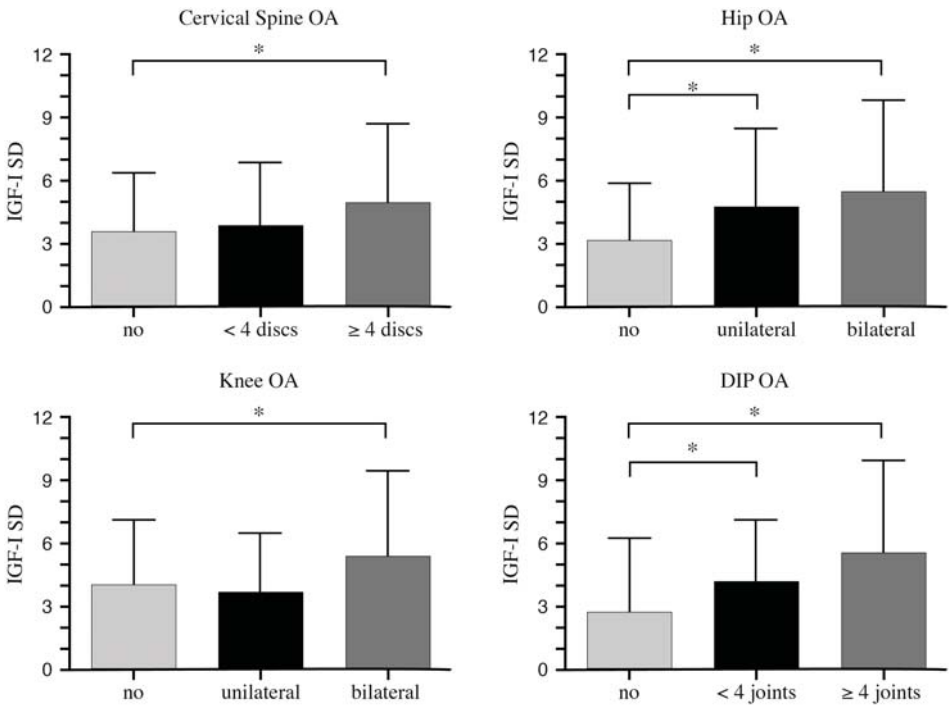

Figure 1. IGF-I SD represent the pre-treatment IGF-I SD scores. * = P<0.05. OA: osteoarthritis, IGF-I: insulin-like growth factor I, SD: standard deviation.

The bars in this figure represent crude values, unadjusted for age, gender, BMI, pre-treatment GH levels, or duration of active disease. The pre-treatment IGF-I SD scores were different in patients with bilateral, but not with unilateral, osteoarthritis of the hip when compared with the IGF-I SD scores of patients without hip osteoarthritis, the mean differences

were 4.78 SD (95% CI 1.89 to 7.67), and 1.49 SD (95% CI -0.03 to 6.03), respectively. Accordingly, bilateral, but not unilateral, osteoarthritis of the knee was significantly associated with higher pre-treatment IGF-I SD scores when compared with patients without knee osteoarthritis, the mean difference was 3.78 SD (95% CI 0.16 to 7.39).

Osteoarthritis in ≥4 intervertebral discs of the cervical spine was associated with higher pre-treatment IGF-I SD scores when compared with patients without osteoarthritis of the spine, the mean difference was 6.16 SD (95% CI 1.03 to 11.28). Patients with osteoarthritis in <4 or ≥4 DIP joints showed higher IGF-I SD scores when compared with patients without osteoarthritis of the DIP joints, the mean differences were respectively 4.47 SD (95% CI 1.21 to 7.73) and 5.36 SD (95% CI 0.39 to 10.32). All mean differences were adjusted for age, gender, BMI, and disease duration. Similar results were seen for PIP, IP and CMC1 joints as well as for the lumbar spine (data not shown).

Development of extensiveness of osteoarthritis in association to pre-treatment IGF-I SD scores

As shown in *Table 3* there was a positive correlation between IGF-I SD scores at the time of diagnosis (pre-treatment IGF-I SD score) and the degree of radiographic osteoarthritis of the hip during long term follow-up. After adjustment for age, gender, and BMI there was a positive correlation between pre-treatment IGF-I SD scores and osteoarthritis of the hip, DIP, IP, and Total Body. In addition, after adjustment for disease duration, age, gender, BMI, pre-treatment IGF-I SD scores significantly correlated with the degree of radiographic osteoarthritis in all investigated joint sites.

Other potential factors of influence

Age at diagnosis showed a positive correlation with osteoarthritis. Patients with a relatively young age at diagnosis showed less osteoarthritis than patients with an older age at diagnosis. The adjusted regression coefficient for total body osteoarthritis was 0.37 (95% CI 0.24 to 0.52). The duration of active disease was not significantly correlated with osteoarthritis. However, after adjustment for pre-treatment IGF-I SD scores there was a significant, negative correlation between osteoarthritis and duration of active disease (adjusted regression coefficient -0.03, 95% CI -0.06, -0.01). There was no significant association between osteoarthritis and pre-treatment GH levels. In addition, the presence or the severity of radiographic osteoarthritis

was not influenced by the type of treatment (*Table 4*), pre-treatment GH levels, duration of follow-up, actual GH and IGF-I concentrations, hypopituitarism, hypogonadism, gender or BMI (P=NS).

Table 3. Regression analysis for IGF-I influencing osteoarthritis, with variable adjustments

	Osteoarthritis in >1 joint (n (%))	**IGF-I SD unadjusted (CI)**	**IGF-I SD adjusted* (CI)**	**IGF-I SD Adjusted** (CI)**
Radiographic osteoarthritis				
Cervical spine disc (0-6)	55 (86 %)	NS	NS	0.10 (0.02-0.18)
Lumbar spine disc (0-5)	53 (83 %)	NS	NS	0.11 (0.02-0.21)
Hip (0-2)	24 (38 %)	0.07 (0.02-0.11)	0.07 (0.03-0.11)	0.07 (0.02-0.12)
Knee (0-2)	27 (42 %)	NS	NS	0.05 (0.00-0.10)
DIP (0-8)	35 (55 %)	NS	0.13 (0.01-0.24)	0.14 (0.01-0.27)
PIP (0-8)	28 (44 %)	NS	NS	0.13 (0.01-0.25)
CMC (0-2)	15 (23 %)	NS	0.04 (0.01-0.08)	0.06 (0.02-0.09)
IP (0-2)	30 (47 %)	NS	NS	NS
Total body † (0-35)	63 (98 %)	NS	0.43 (0.19-0.67)	0.48 (0.21-0.75)

N= 67. Data are presented as regression coefficient with 95% confidence interval if significant. Radiographic osteoarthritis was scored for each joint at the separate joint sites. Correlations between IGF-I SD scores and radiographic osteoarthritis were performed by analysis of covariance. The distribution of the residuals were checked. There were no gross violations of normality.

* Regression coefficient adjusted for age, gender, and BMI.

** Regression coefficient adjusted for age, gender, BMI, and disease duration.

† total body: sum of all radiographic examined joints of the cervical and lumbar spine, hips, knees and hands.

IGF-I: insulin-like growth factor I, SD: standard deviation, n: number, NS: not significant, DIP: distal interphalangeal (joints), PIP: proximal interphalangeal (joints), IP: interphalangeal (joints), CMC: carpometacarpal (joints), CI: confidence interval.

Table 4. The distribution of osteoarthritis according to treatment type, separated for individual joints.

	Surgery	Radiotherapy	SMS	p-value
	N=43	N=8	N=16	
Cervical spine disc	35 (81 %)	7 (88 %)	13 (81 %)	0.78
Lumbar spine disc	36 (83 %)	6 (75 %)	11 (69 %)	0.97
Hip	14 (34 %)	3 (38 %)	7 (44 %)	0.93
Knee	18 (41 %)	3 (38 %)	6 (38 %)	0.82
DIP	23 (53 %)	4 (50 %)	8 (50 %)	0.91
PIP	18 (42 %)	3 (38 %)	7 (44 %)	0.89
CMC	9 (21 %)	2 (25 %)	4 (25 %)	0.76
IP	10 (47 %)	3 (38 %)	7 (44 %)	0.88
Total body †	41 (95 %)	7 (88 %)	15 (94 %)	0.85

Data are expressed as n(%). Osteoarthritis at the different joint sites was dichotomized, according to the presence or absence of osteoarthritis. Data were analyzed with binary logistic regression analyses adjusted for age.
Definitions: Surgery: primary surgical treatment. Radiotherapy: as adjuvant therapy to surgery (no patients underwent primary RT) combined with or without SMS analog treatment. SMS analog treatment: current treatment (primary or additional to prior surgery). † total body: sum of all radiographic examined joints of the cervical and lumbar spine, hips, knees and hands, SMS: somatostatin (analogs).

DISCUSSION

Acromegalic patients with long-term cure or control of disease activity have a high prevalence of osteoarthritis in multiple joints. This study documents that the risk to develop osteoarthritis in these patients is predicted by IGF-I concentrations at the time of initial diagnosis. A four-fold and almost five-fold increase in risk for radiological osteoarthritis of the hip and hand, respectively, was found in patients in the highest tertile of pre-treatment IGF-I SD scores compared with patients in the lowest tertile of pre-treatment IGF-I scores. These associations were not caused by differences in age, gender, or BMI. In addition, the extensiveness of osteoarthritis in all joints, except for the IP joints, was associated with pre-treatment IGF-I SD scores when adjusted for age, gender, BMI, and disease duration.

Osteoarthritis is caused by degeneration of hypertrophied cartilage, which was hypertrophied due to the anabolic effect of elevated GH and IGF-I levels during the active phase of the disease. Osteoarthritis is a multi-factorial disease, with different predictive factors per joint site, like age, gender, and BMI. In general, radiological osteoarthritis of the hip has a specific genetic and geographically prevalence pattern, which suggests the involvement of systemic fac-

tors[13;23]. Moreover, the hip is the joint, which is the least affected by occupational and physical causes of osteoarthritis[13]. Since an effect of BMI and gender could not be identified in our patient group, we assumed that disease specific factors were predictors of secondary osteoarthritis of acromegaly.

IGF-I stimulates chondrocytes to synthesize extracellular matrix components in cartilage. Its action is mediated through the type I IGF receptor[24;25]. The function of IGF-I and its receptor in cartilage formation, both during developmental stages and remodeling of adult cartilage, may be relevant to the etiology of osteoarthritis. IGF-I may also influence osteoarthritis by osteophyte formation[24;25]. In this context, it is interesting to note that Meulenbelt *et al.* observed that the IGF-I allele 3 is associated with radiological osteoarthritis in the general population at any joint site (knee, hip, hand, and spine), and that carriers of the IGF-I 3 allele were predisposed for radiological osteoarthritis at any possible joint[23]. This association was strongest in subjects with radiological osteoarthritis of the hip. In the present study, we extend this observation to patients with acromegaly: the strongest correlation with pre-treatment IGF-I SD scores was demonstrated for the hips. Therefore, in long-term cured patients with acromegaly, the hip is also most prone to secondary osteoarthritis caused by systemic increase of levels of IGF-I during the active phase of the disease and, apparently, this mechanism influences the prevalence of osteoarthritis even after long-term cure.

In the present study we also studied pain and stiffness, but since pain is a subjective finding, we focussed on objective radiological endpoints. Pre-treatment GH or IGF-I SD scores were not associated with pain. Not everyone with an established diagnosis of radiological osteoarthritis report pain and *vice versa* [26]. Pain can be influenced by other factors for example age and gender and can be caused by other musculoskeletal problems.

Two IGF-I assays were used in the follow-up period. However, all pre-treatment IGF-I concentrations were measured with the same RIA assay, and we calculated all pre-treatment IGF-I SD values using own reference data[19]. The GH assay was changed in 1992. For the glucose tolerance tests performed before 1993 we have defined normal suppression of GH < 2.5 mU/L (1.25 mcg/L). However, it is of note that that in follow-up all patients were also controlled according to the GH criteria of the currently used assay and suppressed to below 0.38 mcg/L (on GTT).

Age at diagnosis was positively associated with osteoarthritis after long-term cure. Interestingly, other factors indicating severity of the disease, including pre-treatment GH levels,

disease duration *per sé*, type of treatment, and duration of follow-up, did not predict osteoarthritis. In our study mean serum GH concentrations at diagnosis did not predict osteoarthritis. This may be due to the limitation to accurately measure the actual mean GH concentrations or to the change in assay. However, we repeated the statistical analyses for each GH assay, which did not change our conclusion. It is likely that the serum GH concentration is a main determinant of locally produced IGF-I concentration. In tissue studies locally produced IGF-I was found to be important in the development of osteoarthritis[27].

Our findings are in contrast to the data of previous studies, which studied several potential predictive factors for acromegalic arthropathy, including disease duration, disease severity, pre-treatment GH levels, age of disease onset, disease duration, IGF-I levels, age, and gender[4;9;28-30] (*Table 5*). Only a few studies were able to establish predictive factors. Dons *et al*. identified a predictive effect of baseline GH levels on arthropathy over a 5-year follow-up period of acromegalic patients treated by pituitary irradiation[11]. Layton *et al*. demonstrated a positive predictive effect for disease duration on the severity of arthropathy[9]. The relation between IGF-I and arthropathy was studied in few previous studies, which failed to show a relationship between pretreatment IGF-I levels and arthropathy[28-29]. Potential explanations for the discrepant findings between those studies and the present study are probably related to differences in study design including the inaccuracy of the estimation of disease duration, small sample sizes and differences in disease activity and follow-up duration.

Previously, we documented that disease duration was related significantly to other co-morbidities of acromegaly, including valvular heart disease and survival[28;30]. Interestingly, the negative influences of pre-operative disease activity on survival were strongest in the first 5 years of postoperative follow-up and diminished afterwards[28]. In contrast, arthropathy appears to be irreversible and the effects of previous disease activity remain present even after long-term cure.

Transsphenoidal surgery was the initial treatment for all our patients with acromegaly diagnosed from 1977 onwards and, in case of persistent GH excess, followed by adjuvant therapy in the form of radiotherapy and treatment with SMS analogs. An increasing number of acromegalic patients received initial medical treatment since the introduction of SMS analog depot preparations. However, an effect of initial treatment on osteoarthritis could not be detected.

Table 5. Overview of literature on factors of influence on arthropathy in acromegaly.

				Factors of influence on arthropathy	
Authors	**Date of publication**	**Patient number, Disease status**	**Methods**	**Investigated**	**Identified**
Bluestone *et al.*	1971	42 de novo acromegaly	CR, RG	Duration of active disease Severity of disease	-
Dons *et al.*	1988	43 active acromegaly 47 follow-up 5 yrs after RT	CR, RG	Baseline GH levels	Baseline GH levels
Layton *et al.*	1988	19 active acromegaly	CE, RG	Age of disease onset Pre-treatment GH levels Duration of active disease	Duration of active disease
Ezzat *et al.*	1994	114 de novo acromegaly 386 not well controlled	Scoring of complaints	Not assessed	-
Colao *et al.*	1998	18 active acromegaly 12 cured (2 yrs)	USG	Duration of active disease	-
Colao *et al.*	1999	12 de novo acromegaly	CE, USG	Duration of active disease	-
Colao *et al.*	2003	30 de novo acromegaly 30 cured (3.6 yrs) acromegaly	USG	Duration of active disease	-
Scarpa *et al.*	2004	54 active acromegaly	CR, RG	Age at acromegaly onset Duration of active disease Serum GH levels Serum IGF-I levels Serum Insulin levels	-
Biermasz *et al.*	2005	118 long time cured acromegaly	Self-reported complaints	Age Gender Duration of active disease Serum GH levels Serum IGF-I levels	Female gender
Miller *et al.*	2008	47 cured (duration not mentioned) 11 active acromegaly	CE, QOL questionnaires	Serum GH levels Duration of active disease	-

Current study	-	89 long-term cured acromegaly	CR. CE, RG	Duration of active disease Duration of follow-up Duration since diagnosis Pre-treatment GH levels Pre-treatment IGF-I SD scores Current GH levels Current IGF-I SD scores	Pre-treatment IGF-I SD scores

Pt: patients; co: controls; CR: clinical records; CE: clinical examination; RG: radiographs; USG: Ultra-sonography; QOL: quality of life.

We studied a relatively large acromegalic population with long-term cured disease and a high prevalence of secondary osteoarthritis. Our data demonstrate a predictive role for pre-treatment IGF-I SD scores on radiologic osteoarthritis in patients systemically exposed to high levels of GH and IGF-I for a mean of more than 8 years. This effect was seen at all joint sites. Other disease-specific predictive factors could not be identified. Many subjects cured from acromegaly suffer from subjective complaints due to arthropathy. For instance in a previous study we observed that pain and stiffness at minimal 1 joint-site was reported by 72% of patients. However, radiological manifestations of osteoarthritis at minimal 1 joint-site were present in 99% of patients[31]. This observation indicates that objective radiological manifestations of acromegalic arthropathy are not always reflected in clinical signs of arthropathy. In conclusion, our data demonstrate a predictive role for pre-treatment IGF-I SD scores on osteoarthritis in acromegaly patients with long-term disease control.

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