Pathophysiology of the GH/IGF-1 axis : long-term consequences on joints and bone

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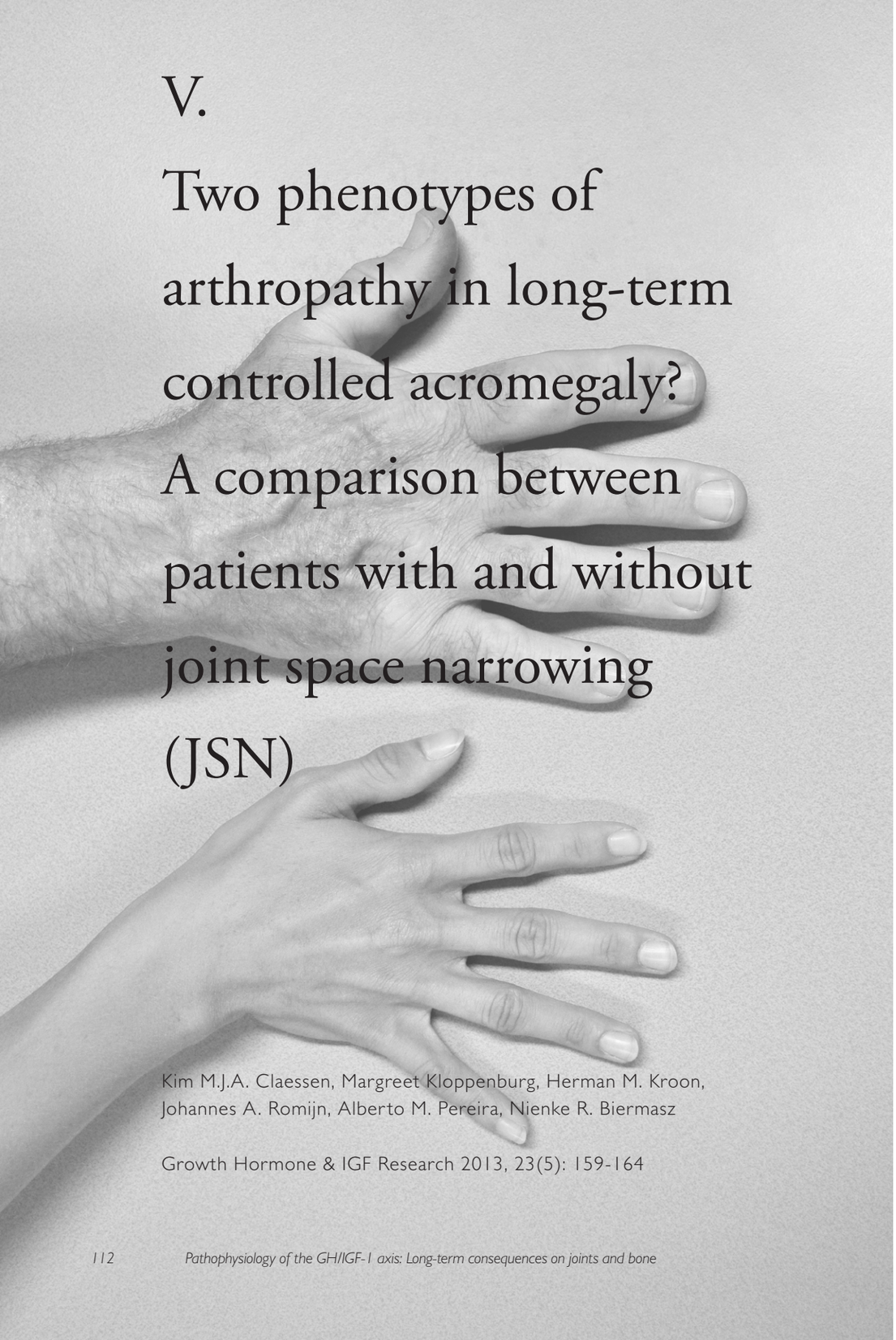

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Two phenotypes of arthropathy in long-term controlled acromegaly? A comparison between patients with and without joint space narrowing (JSN)

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Growth Hormone & IGF Research 2013, 23(5): 159-164

ABSTRACT

BACKGROUND: Arthropathy is an invalidating complication of acromegaly, also in long-term controlled patients, and is radiographically characterized by osteophytes and preserved joint spaces. However, joint space narrowing (JSN) is observed in the minority of patients. It is unknown whether JSN is the end-stage of acromegalic arthropathy or whether this feature develops independently of acromegaly.

OBJECTIVE: To gain insight into the pathophysiology of acromegalic arthropathy, and, more specifically, in the process of JSN, risk factors for radiographic JSN were studied in a cross-sectional study.

METHODS: We studied hips and knees of 89 well-controlled acromegaly patients (mean age 58.3 years, 51% female). Joints were divided into two groups based on the presence of JSN, defined as an Osteoarthritis Research Society (OARSI) score ≥1. Potential risk factors for JSN were assessed, and its relationship to joint complaints. Individual knees and hips were analyzed in a Generalized Estimating Equations model, adjusted for age, sex, BMI and intra-patient effect.

RESULTS: In controlled acromegaly, JSN was found in, respectively, 10.3% and 15.4% of the hips and knees. Increasing age and female sex were associated with more JSN; acromegaly-specific risk factors for JSN were joint-site specific. In the hip, JSN was related to more active disease: higher pre-treatment GH/IGF-1, longer and more severe GH exposure and immediate postoperative cure was less frequently achieved. In the knee, especially previous knee surgery, not acromegaly-specific characteristics, was associated with JSN. The presence of JSN was associated with more joint complaints.

CONCLUSIONS: JSN is an infrequent finding in patients with acromegalic arthropathy, but is associated with more symptoms. This study indicates that, at least in the hip, early and ongoing GH/IGF-1 activity play a role in JSN development.

INTRODUCTION

Acromegaly is a chronic endocrine disease with high prevalence of arthropathy in active and cured disease, resulting in considerable functional disability (1). It is suggested that increased exposure to Insulin-like Growth Factor-1 (IGF-1), the main mediator of Growth Hormone (GH) action, is the driving mechanism in secondary osteoarthritis (OA) in acromegaly (2). In a hypothetical model, acromegalic arthropathy has a bi-phasic pattern with initially reversible endocrine changes, followed by mechanical changes. First, elevated GH and/or IGF-1 levels promote the growth of articular cartilage and peri-articular ligaments, leading to cartilage hypertrophy with a limited range of movements. This early stage is thought to be, at least partially, reversible with adequate biochemical disease control. Subsequently, when GH excess persists, changes become irreversible. At this late stage, acromegalic joints acquire the characteristics of degenerative joint disease (3). However, little clinical studies are available to support this hypothesis.

Previously, we have demonstrated that the prevalence of arthropathy is high, also in patients with long-term biochemical disease control (4). These patients have a 4- to 12-fold increased risk to develop OA, even at very young ages, in comparison to the general population (5). GH/IGF-1 activity at diagnosis is related to the prevalence of radiographic OA (ROA) (6). Interestingly, despite long-term cure, the distribution of radiological abnormalities remained different from regular degenerative joint disease, *i.e.* primary OA. The radiographic phenotype in acromegaly is predominantly characterized by severe osteophytosis, frequently in combination with preserved normal or even widened joint spaces. Therefore, it is suggested that GH hypersecretion is especially involved in bone formation, but may protect against cartilage loss (7). This observation conflicts with the previous hypothesis that there is a final common pathway with primary OA, at least in the majority of patients.

Nonetheless, a minority of acromegaly patients shows radiographic joint space narrowing (JSN), mimicking primary OA, instead of the characteristic joint space widening of acromegaly. This suggests that in acromegaly, there are two types of arthropathy: first, osteophytosis in combination with preserved/widened joint spaces, and second, in a small group, JSN with or without osteophytes. At present, the process of JSN is not fully understood, and it is unknown whether radiographic JSN is the end-stage of acromegalic arthropathy when the GH/IGF-1 excess has exceeded a critical threshold or whether it is a radiographic feature which develops independently of acromegaly, caused by, for example, high biomechanical forces or previous joint surgery.

In order to gain insight in the pathophysiology of acromegalic arthropathy and, more specifically, in the process of JSN, we compared patients with and without radiographic JSN in the knee and hip with respect to patient and treatment characteristics and physical stress. Both patients with and without JSN were derived from the same long-term controlled acromegaly cohort.

METHODS

Patients

All consecutive patients with acromegaly, who were referred for treatment from 1977 onwards to the Leiden University Medical Center, were collected in a database. For the present study, 126 consecutive patients with long-term controlled acromegaly (defined as ≥2 years) were invited for participation. Thirty-seven patients preferred not to participate for various reasons such as illness, travel distance, lack of time or psychological reasons. Consequently, 89 patients were included in the present analysis. The 37 non-included patients did not differ from the participating patients with respect to age, sex, BMI, active disease duration, pre-treatment GH/IGF-1 levels, type of treatment, follow-up duration and self-reported joint complaints (6).

Detailed yearly follow-up was performed from the onset of acromegaly treatment. The first treatment option in the majority of patients was transsphenoidal surgery (TPS) performed by a single specialized neurosurgeon. If necessary, adjuvant treatment consisted of radiotherapy (RT) (prior to 1985) or SMS analogs (from 1985 onwards). From 1998, some patients received depot formulations of long-acting SMS analogs as primary treatment. Since 2003, Pegvisomant was available for treatment-resistant acromegaly.

Disease activity was assessed yearly by oral glucose tolerance tests (except in medically treated patients), fasting serum GH and IGF-1 levels. Remission of acromegaly was defined as a normal glucose-suppressed serum GH <1.25 (RIA assay until 1992) or 0.38μg/l (immunofluorometric assay (IFMA) from 1992 onwards), serum GH levels of <1.9μg/l (all years), and normal IGF-1 levels for age (from 1986 onwards) (4;8;9). Patients not meeting these criteria were offered additional treatment.

Hypopituitarism was supplemented with thyroxine, hydrocortisone,

testosterone/estrogens according to the following definitions (10). Estrogen deficiency in women was present in case of LH/FSH deficiency in premenopausal women with prolonged amenorrea >1 year without adequate replacement therapy or by a low serum oestradiol concentration of <70 nmol/l and 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 free thyroxine level below the reference range (<10 pmol/l). Adrenocorticotrophic hormone (ACTH) deficiency was defined as an insufficient increase of cortisol (peak <0.55 μmol/l) after corticotrophin releasing hormone test or insulin tolerance test. GH deficiency was not routinely assessed.

Patients were seen at the outpatient clinic for a single visit. The study protocol was approved by the Medical Ethics Committee, and all subjects gave written consent.

Study parameters

QUESTIONNAIRES: A standardized questionnaire was completed concerning demographic data, medical history, OA symptoms and signs and information on type of occupation and type of sport. Other relevant details of treatment and patient characteristics were derived from patient records.

PHYSICAL EXAMINATION: Physical examination was performed by a single physician (M.W.) trained in structured joint assessment. Internal rotation and flexion of the hip and extension of the knees was assessed, in combination with both pain and crepitation.

RADIOGRAPHIC PROTOCOL: Radiographs were obtained from all patients between September and December 2007. Conventional radiographs of the knee (posterior-anterior (PA), weight-bearing, fixed-flexion (11;12) and hips (PA, supine) were obtained from all patients, according to a standardized protocol with a fixed film-focus distance and fixed joint position. All radiographs were performed by a single experienced radiology technician.

ASSESSMENT OF RADIOGRAPHIC OA: For a semi-quantitative assessment of the radiographic cartilage damage, JSN was graded in the knee (both medial and lateral femorotibial compartments) and hip on a scale from 0 to 3, using the Osteoarthritis Research Society (OARSI) atlas (13). Radiographs were scored by consensus opinion of two experienced readers (M.W. & K.M.J.A.C.), blinded for patient characteristics. In cases of disagreement, the lower, more conservative score was adopted. The reproducibility for JSN in the hip and knee, reflected by the intra-class correlation coefficient (ICC), was good (0.89 and 0.82, respectively, for the hip and knee). The reproducibility was based on the repeat reading of 15 randomly selected radiographs. JSN was defined as an OARSI score of ≥1 at a particular joint site. Based on the presence of JSN, patients were divided into two groups (i.e. OARSI ≥1 vs OARSI 0), independently for the knee and hip joint. Joint prostheses could not be scored with OARSI, and therefore, these joints (i.e. 3 knees, 2 hips) were excluded from the analyses.

Radiographic knee and hip OA were also scored according to the Kellgren-Lawrence (KL) scale, including other OA features, by a single experienced musculoskeletal radiologist (H.M.K.) (14). ICCs were 0.89 and 1.00 for the knee and hip, respectively. Radiographic OA was defined as KL ≥2 or presence of a knee or hip prosthesis.

DEFINITION OF CLINICAL OA: We used the clinical American College of Rheumatology (ACR) criteria for the assessment of clinical hip and knee OA. Criteria for clinical hip OA were pain in combination with internal rotation of ≥15° and morning stiffness for ≤60 min (15). Clinical criteria for knee OA were pain, crepitation on physical examination and morning stiffness ≤30 min in combination with bony enlargements (16).

PARAMETERS OF ACROMEGALIC DISEASE: Active 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-1 levels after surgery or additional therapy. Remission duration was calculated from the date of normalization of serum IGF-1 concentrations until start of the present study, supported by the findings during the oral glucose tolerance test (oGTT). Both surgically and/or irradiation cured patients and patients with controlled disease by treatment with SMS analogs were collectively referred to as 'in remission'.

ASSAYS: Blood samples were taken in the post-absorptive state to assess the actual GH and IGF1 concentrations. Serum GH was measured with a sensitive 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: 0.01ug/l, interassay coefficient of variation (CV): 1.6-8.4% of 0.01-15.38ug/l) from 1992 onwards. For the conversion of ug/l to mU/l, the values have to be multiplied by 2.6. Prior to 1992, GH was measured by RIA (Biolab, Serona, Coissins, Switzerland), calibrated against WHO IRP 66/21 (detection limit: 0.5mU/l, with an interassay CV less than 5%; for the conversion of ug/l to mU/l, multiply by 2).

Serum IGF-1 concentration (nmol/l) was measured using an immunometric technique on an Immulite 2500 system (Diagnostic Products Corporation, Los Angeles, CA, USA). The intra-assay variations at mean plasma levels of 8 and 75nmol/l were 5.0 and 7.5%. IGF-1 levels were expressed as SDS, using lambda-mu-sigma smoothed reference curves based on the measurement in 906 healthy individuals (17;18).

Statistical analysis

SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA), was used for data analysis. Data are presented as a mean±SD, unless specified otherwise. P<0.05 was considered to reflect statistical significance. Because hip and knee OA may be associated with different risk factors, these joints were analyzed independently (19), and, therefore, results are presented separately. For both hip and knee, joints were divided into two groups based on the radiographic presence of JSN in order to assess risk factors for JSN. Left and right hips, and left and right knees, respectively, were analyzed independently in a Generalized Estimating Equations (GEE) analysis, taking into account intra-patient effect. A binary logistic model was performed with adjustments for age, sex and BMI.

RESULTS

PATIENT CHARACTERISTICS: We studies 89 acromegaly patients (mean age 58.3 ± 11.5 years, 51% female), who were all in remission for a mean of 14.1 ± 6.2 years (*Table 1*). Fifty patients were cured by surgery alone, 11 patients were cured by surgery and postoperative radiotherapy, and 28 patients were medically controlled by long-acting SMS analogs, either as primary or secondary treatment. Three patients were co-treated with Pegvisomant. Mean estimated duration of active disease was 8.9 ± 7.4 years. Mean actual IGF-1 SDS was 0.6 ± 1.5.

Hip joint: We studied hips of 87 acromegaly patients (n=174), of which 56 hips (32.2%) had radiographic OA (*i.e.* KL ≥2). With respect to cartilage damage, 18 hips (10.3%) had JSN and 156 hips (89.7%) had preserved joint spaces. JSN in the hip was associated with age (p<0.001). There were no significant relationships between JSN and sex, BMI or menopausal status.

DURATION AND SEVERITY OF GH OVERPRODUCTION: Patients with JSN in the hip did not differ in age of diagnosis, active disease duration or remission duration from patients without JSN. As shown in *Table 1*, pre-treatment GH levels were higher in patients with JSN (153.6±170.2 ug/l *vs* 83.3±108.1 ug/l, p=0.025). In addition, patients with JSN had higher pre-treatment IGF-1 SDS than patients with normal joint spaces (9.7±5.6 *vs* 7.0±4.5, p=0.038). As a measure for GH exposure, we studied the interaction term of pre-treatment GH levels and active disease duration. Patients with JSN had higher GH exposures compared to patients without JSN, indicating that JSN was related to longer GH excess and higher GH levels (p=0.04).

TREATMENT OF ACROMEGALY (*TABLE 2*): Patients with and without JSN in the hip differed significantly with respect to the type of acromegaly treatment. Patients with JSN received SMS analogs more frequently than patients without JSN (50% *vs* 22.2%, OR=8.16 (1.1-61.8), p=0.042), and immediate postoperative cure was less frequently achieved (OR=0.18 (0.03-0.98), p=0.047). There was a trend of higher SMS exposure, calculated by the interaction term between duration of SMS treatment and SMS dose, in patients with JSN than patients without JSN in the hip, although not-significant after adjustments for age, sex and BMI (p=0.091).

Table 1. Clinical characteristics of 89 patients with acromegaly

Clinical characteristics	**Patients (N = 89)**
Age (years)	58.3 (11.5)
Sex, female (n (%))	45 (51)
BMI (kg/m^2)	28.5 (4.7)
Treatment (n (%))*	
Surgery only	50 (56)
Surgery + RT	11 (13)
SMS analogues	
Primary	5 (6)
Following surgery	19 (21)
Following RT	1 (1)
Following surgery + RT	3 (3)
Disease duration (years)	8.9 (7.4)
Duration of remission (years)	14.1 (6.2)
Pre-treatment GH (µg/L)	36.8 (48.0)
IGF-1 SD scores	
Pre-treatment	7.4 (4.7)
Actual	0.6 (1.5)
Hypopituitarism (n (%))	
Corticotrope failure	22 (25)
Thyreotrope failure	18 (20)
Gonadotrope failure**	49 (55)

Values are means (SD) unless stated otherwise.

GH, growth hormone; IGF-1, insulin-like growth factor 1; BMI, body mass index; RT, radiotherapy; SMS, somatostatin (analogs).

* *Three patients (3%) were co-treated with Pegvisomant.*

** *Including natural menopause (N = 40 (45%)) and hypogonadotropic hypogonadism*

Table 2. Acromegaly-specific risk factors for JSN in the hip, studying 87 well-controlled acromegaly patients

	No JSN (OARSI 0) n = 156	**JSN (OARSI ≥1) n = 18**	**Adjusted OR (95%CI)**	**Adjusted P value**
Age at diagnosis (yr)	40.2 ± 12.6	44.2 ± 9.1	1.0 (0.9-1.0)	0.259 #
Active disease duration (yr)	8.6 ± 7.6	10.1 ± 4.6	1.0 (0.9-1.1)	0.949
Duration of remission (yr)	13.7 ± 5.9	16.6 ± 7.5	1.1 (0.9-1.2)	0.318
Pre-treatment GH (µg/L)	83.3 ± 108.1	153.6 ± 170.2	1.01 (1.01-1.01)	0.025
Pre-treatment IGF-1 SDS	7.0 ± 4.5	9.7 ± 5.6	1.1 (1.01-1.3)	0.038
Treatment				
Surgery and/or Radiotherapy (%)	77.6	50.0	8.2 (1.1-61.8)	0.042 *
SMS analogs (%)	22.4	50.0		
Immediate postoperative cure (%)	57.3	21.1	0.2 (0.03-0.98)	0.047

n represents total number of hip joints included. Data are shown as mean, unless mentioned otherwise. Immediate cure was defined as immediate postoperative cure, without requiring additional radiotherapy and/or postoperative medical treatment for persisting disease activity. Data were analyzed by Generalized Estimating Equations (GEE) analysis taking into account intra-patient effect, with additional adjustments for age, sex and BMI (except for #).

CI, confidence interval; BMI, body mass index; SMS, somatostatin analogs.

* *SMS analogs vs other therapies for acromegaly disease.*

LOCAL BIOMECHANICAL FACTORS: Three patients had previous hip fractures or hip surgery for another reason. There was no association between physical intensive jobs or sports and JSN.

RELATIONSHIP BETWEEN JSN IN THE HIP AND JOINT COMPLAINTS: Seventy-three % of the patients with JSN of the hip met the ACR criteria for clinical hip OA, indicating a much higher prevalence of clinical OA than in patients with preserved joint spaces, of which only 17.6% met the clinical ACR criteria (OR=14.0 (2.5-79.3), p<0.001). Pain/stiffness at physical examination did not differ between patients with and without JSN.

Knee joint: We studied knees of 88 patients (n=175), of which 48 knees (27.4%) had radiographic OA (i.e. KL ≥2). With regard to cartilage damage, twenty-seven knees had JSN (15.4%) and 148 knees (84.6%) had preserved joint spaces. JSN in the knee was associated with age (65.2±8.0 years vs 57.1±11.6 years, p<0.001) and female sex (70.0% vs 56.3%, p=0.018). There were no differences in BMI or menopausal status, but waist circumference was higher in patients with JSN (p=0.032).

DURATION AND SEVERITY OF GH OVERPRODUCTION: JSN in the knee was not related to age at diagnosis, active disease duration, duration of remission, pre-treatment GH levels or pre-treatment IGF-1 SDS (*Table 3*). However, GH exposure (product of pre-treatment GH levels and active disease duration) was higher in patients with JSN (p=0.029).

TREATMENT OF ACROMEGALY: Acromegaly treatment was not different between patients with and without JSN in the knee. However, immediate postoperative cure was less frequently obtained in patients with JSN (p=0.019), but this did not remain significant after adjustments for age, sex and BMI.

LOCAL BIOMECHANICAL RISK FACTORS: JSN in the knee was associated with a history of knee surgery (p=0.019): especially, the prevalence of meniscectomy was high in patients with JSN (14.8% *vs* 6.1%, p=0.006) (*Table 2*). With respect to physical work load, type of occupation or type of sport were not related to JSN in the knee.

After consideration of age, sex, BMI, pre-treatment IGF-1 levels, surgical cure *vs* medical control and meniscectomy in a multivariate GEE-model, only age and meniscectomy were significantly associated with JSN in the knee (ORs were 1.1 (1.0-1.1) and 16.9 (3.1-92.1), p=0.012 and p=0.001, respectively), but no acromegaly-specific characteristics.

RELATIONSHIP BETWEEN JSN IN THE KNEE AND JOINT COMPLAINTS: Patients with JSN reported more knee pain than patients without JSN (56.5% *vs* 33.6%) (p=0.035). Clinical knee OA, as assessed by the ACR criteria, was more prevalent in patients with JSN than in patients with preserved joint spaces (63.3% *vs* 18.1%; OR=8.2 (2.9-23.1), p<0.001). There were no significant differences found in pain and/or stiffness at physical examination.

Table 3. Acromegalic-specific and general risk factors for JSN in the knee in 88 well-controlled acromegaly patients

	No JSN (OARSI 0) n = 148	**JSN (OARSI ≥1) n = 27**	**Adjusted OR (95%CI)**	**Adjusted P value**
Age at diagnosis (yr)	40.2	43.2	1.0 (0.9-1.0)	0.133 #
Active disease duration (yr)	8.0 ± 4.7	13.1 ± 4.6	1.1 (1.0-1.2)	0.111
Duration of remission (yr)	14.0 ± 6.4	14.6 ± 5.1	1.0 (0.9-1.1)	0.845
Pre-treatment GH (µg/L)	96.5 ± 119.4	93.2 ± 151.1	1.0 (1.0-1.01)	0.559
Pre-treatment IGF-1 SDS	7.2 ± 96.5	8.8 ± 93.2	1.1 (1.0-1.2)	0.146
Treatment				
Surgery and/or Radiotherapy (%)	75.7	70.3	1.4 (0.4-5.0)	0.576 *
SMS analogs (%)	24.3	29.6		
Immediate postoperative cure (%)	56.4	32.1	0.6 (0.2-1.6)	0.295
Knee Surgery (%)	15.2	40.7	3.5 (1.2-9.8)	0.019
History of meniscectomy (%)	6.1	14.8	7.8 (1.8-34.3)	0.006

n represents total number of knee joints included. Data are shown as mean, unless mentioned otherwise. Immediate cure was defined as immediate postoperative cure, without requiring additional radiotherapy and/or postoperative medical treatment for persisting disease activity. Data were analyzed by Generalized Estimating Equations (GEE) analysis taking into account intra-patient effect, with additional adjustments for age, sex and BMI (except for #).

CI, confidence interval; BMI, body mass index; SMS, somatostatin analogs.
** SMS analogs vs other therapies for acromegaly disease.*

DISCUSSION

This is the first study focusing on the process of JSN in acromegaly patients. JSN appears to be an infrequent finding in patients after long-term follow-up of acromegaly, with a prevalence ranging between only 10 and 15 % in our cohort. This low prevalence is in contrast to previous notions on the pathophysiology of this secondary form of OA. We found a clear association with well-known risk factors of OA, such as age, whereas other disease-specific risk factors for JSN were joint-site specific. At the hip site, disease characteristics reflecting more active disease were related to JSN: higher GH/IGF-1 levels at diagnosis, longer and more severe GH exposure, and immediate postoperative cure was less frequently achieved. This suggests that the GH/IGF-1 axis not only plays a role in the early stage of acromegalic arthropathy, but also in the late stage, as reflected by JSN. At the knee site, we did not find acromegaly-specific characteristics to be associated with JSN. Previous knee surgery was a risk factor for JSN in the knee, suggesting that JSN at the knee site is unrelated to GH excess.

In acromegaly, the late effects of arthropathy are striking, even after long-term control of GH overproduction. The assumption is that persistent exposure to pathologically elevated GH and/or IGF-1 levels results in progressive changes in joint geometry. The phenotype of acromegalic arthropathy is characterized by osteophytosis, but most patients have preserved or even widened joint spaces (7). However, in a small subgroup of adequately treated patients radiographic JSN is present, suggesting that in acromegaly probably two types of arthropathy exist. In the present study, JSN was related to both well-known risk factors and acromegaly-specific risk factors. The high prevalence of JSN in older and female patients is in line with previous observations in primary OA (20). In the knee, JSN was strongly associated to previous knee surgery, especially meniscectomy. It is well-known from primary OA that joint dysplasias, fractures of articular surfaces, and tears of menisci and ligaments, which all increase joint instability, frequently precede the development of OA (20). This suggests that the JSN phenotype in the knee is probably unrelated to the previous GH excess.

Remarkably, higher pre-treatment GH and IGF-1 levels were associated with JSN in the hip. These findings suggest that JSN in acromegalic joints can be predicted by a more severe biochemical presentation at diagnosis. An interesting observation is the difference in acromegaly treatment between patients with and without JSN of the hip. JSN was highly prevalent in patients controlled by SMS analogs, in contrast to a relatively low prevalence in patients cured postoperatively. This was not observed in the knee, which is most probably explained by the fact that the hip is the joint site that is most frequently systemically involved. The high prevalence of JSN in SMS-treated patients could be explained by the higher disease activity in patients with SMS analogs, since, during SMS treatment, subtle abnormalities in the GH secretion pattern persist (21). In accordance, previous studies report worse outcome in SMS-treated patients with respect to QoL and diastolic heart function (22;23). Alternatively, SMS analogs possibly could have a direct, IGF-1 independent, effect on joint structure. There is evidence for direct inhibitive local effects of SMS on cartilage (24;25), and, in addition, SMS receptors were demonstrated in bone cells (26). The finding that JSN occurs more frequently in patients with higher SMS-exposure (interaction term of SMS duration and dose) supports this hypothesis. Further studies have to establish the physiological significance of long-term SMS therapy on joint architecture. Another explanation is a generally less favorable previous course of acromegaly in SMS-treated patients, in which other acromegalic-specific factors within the group of SMS-treated patients could probably result in more severe cartilage damage (*i.e.* bias by indication). However, most previous studies failed to demonstrate a relationship between duration of active disease and arthropathy (4;27;28).

JSN appeared to be related to a higher presence of joint complaints (both knee and hip), when applying clinical ACR criteria. Furthermore, JSN was related to more self-reported pain in the knee. Previously, acromegalic patients were reported to have better joint functions and, therefore, have less joint-replacement surgery than patients with primary OA, despite a higher prevalence of osteophytes. It was hypothesized that the preserved joint spaces in acromegaly may protect against pain caused by osteophytes, and, therefore, prevent acromegalic patients from a decrease in functional capability (7).

Some limitations of this study have to be addressed. First, the used scoring methods, such as the OARSI score and clinical ACR criteria are subject to debate, since, at present, there are no acromegaly-specific classification systems for arthropathy available. Therefore, we were limited to the use of primary OA scales for the definition of arthropathy, although these methods are developed and validated for the use in primary OA. With respect to radiographic OA, these primary OA scales can not evaluate a main feature of acromegalic arthropathy, *i.e.* joint space widening. Therefore, we were unable to differentiate between preserved or widened joint spaces, reflecting cartilage hypertrophy. Second, the present study is a cross-sectional study, and therefore, the causality of the association between GH/IGF-1 activity and JSN is difficult to assess.

In conclusion, JSN is an infrequent finding in patients with acromegalic arthropathy. Patients with JSN have more joint complaints. Well-known risk factors, such as age and female sex, are associated with JSN. In addition, especially at the hip site, acromegalic-specific risk factors reflecting more active disease are related to JSN. Remarkable is the high prevalence of JSN in patients who were controlled by SMS analogs when compared to patients immediately cured postoperatively. The findings of the present study suggest that, at least in the hip, there is a role for excessive GH/IGF-1 activity, not only in the early stage of acromegalic arthropathy, but also in the late phase of the disease, as reflected by JSN.

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