Acromegaly : irreversible clinical consequences

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Chapter 4.

OSTEOARTHRITIS IS EQUALLY PREVALENT IN MEN AND WOMEN WITH LONG-TERM CONTROLLED ACROMEGALY.

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ABSTRACT

Objective: Primary osteoarthritis (OA) preferentially affects women. We evaluated whether female gender is also a risk factor for OA development in acromegaly, a disease caused by a growth hormone producing pituitary adenoma.

Design: We conducted a case-control study

Methods: We compared 46 male and 43 female patients (mean: 58 years) with controlled acromegaly for a mean of 14 years. Study parameters were clinical assessment and radiographs of knee, hand and hip. Radiological OA was defined as a Kellgren and Lawrence (KL) score of ≥2. Symptomatic and clinical OA was defined according to the American College of Rheumatology (ACR) criteria combining symptoms with radiological abnormalities or abnormalities at physical examination, respectively. The prevalence of clinical OA was compared with age- and environment-matched controls and the prevalence of radiological OA with a Dutch historical population sample.

Results: Radiological knee, distal interphalangeal joint, and hip OA was seen in 35, 56, and 44% of patients, respectively, and was equally prevalent in women and men. Taking in account symptoms (symptomatic OA) lowered the prevalence but did not change the distribution over the genders. Clinical OA was similarly prevalent in both genders except for hand OA, which was encountered more in women. In comparison with controls and the historical population sample, OA prevalence was increased in women, but even more so in men.

Conclusion: In acromegaly, the prevalence of OA at all joint sites is similar in male and female patients, suggesting that the overproduction of GH and IGF-I overrules the potential role of risk factors, including hormonal factors, in primary OA.

INTRODUCTION

The exact pathogenesis of osteoarthritis (OA) is unknown, but ample evidence suggests that OA is a multifactorial disease[1]. Gender is one of the most important risk factors for primary OA. Women, especially women after 55 years of age, are more frequently affected than men in their knees, hands, and hips, representing the most prevalent subtypes of OA[2-4]. This gender difference in the prevalence of primary OA is not clearly understood, although systemic, hormonal, and genetic factors may play a role[5;6]. Since this gender difference, especially in knee and hand OA, becomes more prominent after the age of 55 years (around the menopause), hormones like estrogens may be of importance in the development of OA[2;3;5-7].

Acromegaly is caused by a growth hormone (GH)-secreting pituitary adenoma. Increased GH concentrations lead to increased insulin-like growth factor-I (IGF-I) secretion by peripheral tissues, especially the liver. Arthropathy is present in 50 to 75% of the patients with active and treated acromegaly[7-12]. In long-standing acromegaly, this arthropathy is mostly characterized as secondary OA and may be the result of cartilage hypertrophy and laxity of ligaments induced by GH and IGF-I excess with secondary damage to the joint[8-13].

In acromegaly, there are no gender differences in disease characteristics, incidence and prevalence[14-16]. It has never been examined whether the risk factors for primary OA, female gender and menopause, are also present in patients with OA due to acromegaly. Since estrogens negatively influence GH-dependent IGF-I production in the liver, it is likely that gender and estrogen status are important in the pathogenesis of GH and IGF-I induced arthropathy.

The aim of this study was to analyze joint site specific gender differences in clinical and radiological characteristics of OA in patients with long-term controlled acromegaly, in order to get more insight both in pathophysiological processes that play a role in OA in acromegaly and in OA in general.

PATIENTS AND METHODS

Patients

All consecutive patients with acromegaly who were referred to our center were collected in a

database. From 1977 onwards, the first treatment option in the majority of patients was transsphenoidal surgery. If necessary, adjuvant treatment was given by radiotherapy (prior to 1985) or predominantly somatostatin analogs (from 1985 onwards). From 1998, some patients received primary somatostatin analog treatment. Disease activity was assessed yearly, and biochemical control was defined as a normal glucose suppressed serum GH <0.38 μg/liter, serum GH levels <1.9 μg/liter and normal IGF-I levels for age[17]. These strict biochemical criteria for control were used from the beginning of the study. This patient cohort is well-characterized and treatment results and biochemical and clinical follow-up results have been described in detail previously[17]. Patients cured or controlled' during somatostatin analog treatment were collectively referred to as 'in remission'.

Hypopituitarism was treated promptly with thyroxine, hydrocortisone, or estradiol/testosterone when deficiencies were documented using appropriate basal hormone and dynamic tests[18]. In men, hypogonadism was defined as a testosterone level below the reference range (8.0 nmol/l) and low or normal luteinizing hormone/follicle-stimulating hormone (LH/FSH) concentrations. Pre-menopausal women were hypogonadal if secondary amenorrhea was present more than 1 year, and post-menopausal women in case of LH/FSH levels below the normal postmenopausal range (LH<10 U/l and FSH <30 U/l).

Study design

For the present study, 126 consecutive patients in long-term biochemical remission were invited for participation. Thirty-seven patients (29%) preferred not to participate in the study for various reasons, including co-morbidities, travel distance, lack of time and psychological reasons. They were not different from the study population in disease characteristics or self-reported joint complaints. Each patient was asked to provide a control person of comparable age (non-relative) to compose a control population with a comparable socioeconomic status, derived from the same geographical area. The study protocol was approved by the Medical Ethics Committee, and all subjects gave written consent for their participation.

Eighty-nine patients (participation rate 71%) and 67 controls participated. They completed questionnaires, underwent a physical examination, hormonal evaluation for actual fasting morning GH/IGF-I concentrations, and conventional radiographs. Radiographs were taken from the patients only to avoid unnecessary radiation exposure to the controls and in the presence of available radiological control data from a large Dutch (n= 4842) historical

population sample, reporting normative values for radiological OA for gender specific 5-year age groups (mean age 56.1 ± 8.7 year, 53% females)[1]. Treatment and patients characteristics were derived from the patient records. The prevalence and radiological characteristics of joint disease were described previously[11]. In this analysis, we focus on the gender difference of OA in acromegaly and controls.

Study parameters

Clinical parameters

A structured standardized questionnaire was completed concerning medical history, and symptoms and signs of OA, i.e. joint-site specific complaints of pain and/or stiffness.

Acromegaly disease duration was defined as the duration between the onset of symptoms and remission (the date that serum IGF-I normalized after treatment[18]. Hypopituitarism was present in case of clinically relevant hormonal deficiencies in ≥1 axis. For this study, we considered estrogen deficiency present in case of LH/FSH deficiency in premenopausal women with prolonged amenorrhea >1 year without adequate replacement therapy and all postmenopausal women.

Physical examination and clinical scoring

Distal interphalangeal joints (DIPJs), proximal interphalangeal joints (PIPJs), first interphalangeal joints (1st IPJs), metacarpophalangeal joints (MCPJs) and first carpometacarpal joints (1st CMCJs) joints were examined for bony and soft-tissue swelling and deformities by a single physician (MW) trained in structured physical examination of the musculoskeletal system and recorded in a standardized manner. The knees were examined for crepitation, bony enlargement and pain on palpation of joint margins. The hips were examined for in- and external rotation.

In order to perform a Doyle index, 20 joint groups were examined for tenderness by pressure on the joint margin or by passive movement of the joint (48 joints; maximal score 144)[19].

Radiological investigation and radiological scoring

Radiographs of the knees (posterior-anterior, weight-bearing, fixed-flexion[20] and lateral), hands (dorso-volar) and hips (posterior-anterior) were acquired by a single experienced radiographer following a standardized manner with a fixed film-focus distance. Radiographs were scored by a

single experienced musculoskeletal radiologist (HK) blinded for patient characteristics, according to the Kellgren-Lawrence atlas (KL)[21]. In the hands the DIPj's, PIPj's, IPj's, and the 1st C-MCj's were scored. The intra-class correlation coefficient (ICC) based on the repeated scoring of 10 randomly selected patients was 0.81 (hands), 0.89 (tibiofemoral joints) and 1.00 (hips).

Definition of OA

We used different definitions for OA:

1. Radiological OA was defined as a KL score of ≥2.
2. Symptomatic OA was defined as pain and stiffness on most days of the preceding month in combination with a KL score of ≥2. For symptomatic hand OA at least 2 hand joints had to be affected [22;23].
3. Clinical OA was scored according to the American College of Rheumatology (ACR) criteria to enable comparison with controls[22-24].

For all definitions a joint prosthesis in the knees and/or hips as a result of end stage OA was included as OA in that particular joint.

Assays

Actual GH and IGF-I concentrations were assessed at the study visit in the fasting state. 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 0.3 μg/l; intra-assay coefficient of variation (CV) 1.6-8.4% of 0.0.1-15.4μg/l). 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 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[25;26].

Statistical analysis

SPSS for Windows version 16.0 (SPSS inc., Chicago, IL, USA) was used for data analysis. Data are presented as mean (SD), unless specified otherwise. Comparisons between male and female patients on clinical characteristics were made by analysis of variance and adjusted for age and

BMI. Results were displayed as difference with 95% confidence interval (95% CI) and corresponding p-values.

Symptoms of pain and/or stiffness and OA were dichotomized according to the presence or absence of it. The difference between male and female patients on prevalence of OA and self-reported joint symptoms was analyzed by a binary logistic regression analysis with males as reference category and adjusted for age and BMI. As reference for radiological OA we utilized historical data from the Dutch population from a study reporting normative values for radiological OA[1]. Binary logistic regression analysis with adjustment for 5-year age categories was used to compare our patients with the historical reference group. As reference for clinical OA we utilized the age- and environment-matched controls collected for the present study. Binary logistic regression with adjustment for age and BMI was used for comparison.

When applicable, all analyses were adjusted for age, BMI, estrogen state, disease duration, somatostatin analog treatment, irradiation, hypopituitarism, physical trauma, smoking, and occupational and physical activities.

RESULTS

Clinical characteristics

We studied 46 male and 43 female acromegaly patients. Men were slightly younger than women (55.9±10.7 vs. 60.8±11.9, p=0.04). BMI was comparable between both genders and not different from BMI at times of diagnosis of acromegaly (28.5±4.7 (females) *vs.* 28.9±4.5 (males), p=0.48). The mean duration of active disease was 8.9±7.3 years. All patients were in remission for a mean of 14 years (range 2-28). As treatment for acromegaly 55% of patients received surgery alone, 16% surgery in combination with somatostatin analogs, 7% of patients were treated primarily with somatostatin analogs and 22% received additional radiotherapy. Treatment modalities were not different between the genders. Twenty (23%) patients were currently using somatostatin analogs.

There was no gender difference in duration of active disease, serum GH levels, IGF-I SD-scores at diagnosis and during the evaluation. Because of natural menopause females had a higher prevalence of hypogonadism, i.e. estrogen deficiency, than males (*Table 1*).

Table 1. Clinical characteristics of male and female acromegalic patients with long-term disease control

	Acromegaly patients			Controls from environment	
	Males N=46	Females N=43	Difference (95% CI)	Males (n=28)	Females (n=39)
Age (yrs)	55.9 (10.7)	60.8 (11.9)	-4.9 (-9.75,-0.02)	57.9 (10.1)	58.5 (10.4)
BMI (kg/m²)	28.7 (4.5)	28.3 (4.9)	0.3 (-1.75,-2.35)	26.4 (4.1)	26.0 (4.6)
Menopause					
Pre-menopausal		5 (11 %)			4 (10%)
Post-menopausal		38 (89 %)			35 (90%)
Disease duration	8.1 (5.1)	9.7 (9.1)	0.4 (-3.9, 3.0)	NA	NA
Duration of remission	14.5 (6.5)	13.7 (6.0)	1.3 (-1.8, 4.4)	NA	NA
GH (µg/l)				NA	NA
Pre-treatment	40.2 (49.6)	32.6 (45.8)	3.4 (-17.9, 24.7)		
Current	0.87 (1.77)	0.95 (0.96)	-0.1 (-0.7, 0.5)		
IGF-I SD scores				NA	NA
Pre-treatment	7.9 (4.7)	6.7 (4.7)	1.3 (-1.1, 3.8)		
Current	0.6 (1.6)	0.5 (1.9)	-0.1 (-1.0, 1.4)		
Hypopituitarism	13 (28 %)	16 (37 %)	-0.1 (-0.29, 0.12)	NA	NA

Data are shown as mean (SD), unless mentioned otherwise. Clinical characteristics were compared between males and females by analysis of variance and adjusted for age and BMI, results were displayed as difference (95% CI) en by P-value. NA: not available. There were no differences in BMI and age in controls from the environment. Yr: years, kg/m²: kilograms per square meter, µg/l: micrograms per liter, SD: standard deviation, BMI: body mass index, GH: growth hormone, IGF-I:insuline like growth factor, CI: confidence interval.

From the environment of the patients 67 controls (50 spouses and 17 friends) participated with comparable mean age and gender distribution as the patients (mean age 58.2 years; 58% women). The mean BMI was 26.2 kg/m², which was significantly lower than in the patients (p=0.01). Women and men did not differ on age and BMI in the control population (*Table 1*).

Five-year normative radiographic data from a large Dutch reference population (n= 4842) were utilized.

Radiological OA

Comparison of male and female acromegalic patients

The prevalence (based on KL≥2) and the severity (frequencies of KL 2, 3 and 4) of radiological OA was not different between men and women with long-term cured acromegaly at all

joint sites, even after adjustment, except for the1st CMCJs (*Table 2*). Due to end-stage OA two patients had undergone hip replacement and 2 patients had undergone knee replacement.

Table 2. Gender differences of radiological osteoarthritis in acromegalic patients with long-term disease control.

	Male n=46	Female n=43	Adjusted OR (95% CI)	P-value
Knee	18 (39 %)	13 (30 %)	0.8 (0.32 – 2.10)	0.67
Hand				
DIP	21 (46 %)	29 (67 %)	2.1 (0.67 – 6.81)	0.25
PIP	15 (33 %)	23 (51 %)	1.6 (0.56 – 4.39)	0.39
CMC1	7 (15 %)	17 (38 %)	3.0 (1.04 – 8.81)	0.04
IP	14 (30 %)	24 (53 %)	2.3 (0.82 – 6.38)	0.11
Hip	20 (44 %)	19 (44 %)	0.5 (0.18 – 1.31)	0.19

Data are presented as n (%). Radiological osteoarthritis at each joint site was dichotomized and compared between males and females by binary logistic regression analysis. Odds ratios (OR) were adjusted for age, BMI, physical trauma, smoking and occupational- and physical activities. Males were reference category. DIP: Distal interphalangeal, PIP: proximal interphalangeal, MCP: metacarpophalangeal, CMC1: first carpometacarpal, CI: confidence interval.

Comparison with the Dutch reference population

Radiological OA in acromegaly patients was determined by the same scoring method used in the reference population. Acromegalic patients had a higher chance to have radiological OA at

Table 3. Radiological osteoarthritis in acromegalic patients with long-term disease control compared with a Dutch reference population.

	Males		Females		All	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Knee right	3.6	1.9-7.1	1.7	0.8-3.3	2.3	1.5-3.8
Knee left	3.6	1.7-6.5	1.4	0.7-2.8	2.1	1.3-3.3
DIP hands	1.7	0.9-3.3	2.0	1.0-4.2	1.7	1.1-2.8
PIP hands	4.5	2.3-8.9	4.7	2.4-9.4	4.2	2.6-6.8
CMC1 hands	7.6	4.0-14.4	8.2	3.9-17.6	7.0	4.3-11.4
Hip right	9.2	4.6-18.6	5.1	2.4-10.8	6.9	4.1-11.5
Hip left	8.7	4.4-18.5	4.9	2.2-10.8	6.7	4.0-11.4

Data represent odds ratios (OR) with 95% confidence intervals (95%CI) derived from binary logistic regression analysis. ORs were adjusted for 5-year age categories. The Dutch reference group was the reference category. DIP: Distal interphalangeal, PIP: proximal interphalangeal, MCP: metacarpophalangeal, CMC1: first carpometacarpal, CI: confidence interval. OR's between male and female acromegalic patients were not significantly different.

all joints (*Table 3*). The odds ratios reflecting the comparison between patients and the reference population were higher for males than for females for the knee and hip, but these gender differences were not significantly.

Symptomatic OA

Comparison of male and female acromegalic patients

Binary logistic regression analysis with adjustments for age, BMI, and factors indicating activity of acromegaly demonstrated no difference in symptomatic knee (17% *vs.* 35%, adjusted OR (95%CI) 0.4 (0.12-1.14)), hip (28% *vs.* 19%, 0.4 (0.12-1.14)), and hand (57% *vs.* 64%, 1.2 (0.45-3.23)) OA between men and women.

Self-reported symptoms

Comparison of pain and stiffness between male and female acromegalic patients

The prevalence of self-reported pain and stiffness was not different between male and female acromegalic patients at the knees (46% *vs.* 58% 1.1 (0.40-2.98)) and hands (76% *vs.* 81% 1.2 (0.47-3.01)), irrespective of adjustment. Only at the hip site, female patients reported more pain and stiffness than male patients (72% *vs.* 46% 2.3 (1.1-4.5)). The Doyle index for male and female patients, 7.0 (12.7) (range 0 to 28) and 7.6 (13.1) (range 0 to 37) respectively, did not differ significantly.

Compared with controls

Fifty-seven percent of female controls reported complaints of pain and stiffness, compared with 31% in male controls (OR: 3.2 (2.1-4.5). Female controls of >55 years, suffered significantly more complaints of pain and stiffness of the hip (56% *vs.* 27% 3.3 (1.7-4.6)) and hand (67% *vs.* 43% OR: 2.9 (1.8-4.0)) than male controls of >55 years. Both male and female acromegalic patients had a significantly higher chance to suffer symptoms of pain and stiffness in the knees, hands and hips when compared with male and female controls after adjustment, with ORs between 2.7 (male hip symptoms and female hand symptoms) up to 13.2 for female hand symptoms (data not shown).

Clinical osteoarthritis

Comparison between male and female acromegalic patients

Clinical knee OA was equally prevalent in male and female patients (15% *vs.* 21%, 1.1 (0.4-1.9). Clinical hand OA was significantly more prevalent in female than in male acromegalic patients (56% *vs*. 26%, 2.9 (1.6-4.1)). In addition, hand OA was more prevalent in both younger and older women compared with males (<55 yrs, p = 0.02 and >55 yrs p = 0.04, respectively). Clinical hip OA was equally prevalent in male and female patients (16% *vs.* 23%, OR 1.3 (0.6-2.1)).

Compared with controls

The prevalence of hip, knee and hand OA in controls was 0%, 5%, and 16%, respectively. Within the controls females >55 years suffered significantly more clinical hand OA (28% *vs.* 12%, p=0.04), than males >55 years. No gender difference could be demonstrated for hip and knee OA.

Table 4. Clinical osteoarthritis in acromegalic patients compared with an age-matched control group derived from the environment from the patient.

	Males			Females			All		
	OA	No OA	Adjusted OR (95% CI)	OA	No OA	Adjusted OR (95% CI)	OA	No OA	Adjusted OR (95% CI)
Knee OA									
patients	6	40		9	34		15	74	
controls	1	27		2	37		3	64	
			4.4 (1.9-22.5)			3.6 (1.3-16.9)			3.7 (1.1-13.6)
Hand OA									
patients	12	34		24	19		36	53	
controls	4	24		7	32		11	56	
			4.8 (1.7-13.5)			3.8 (1.4-16.4)			3.5 (1.6-7.9)
Hip OA									
patients	7	39		10	33		17	72	
controls	0	28		0	39		0	67	
			∞			∞			∞

OA and no OA are represented in numbers. Data represent odds ratios with 95% CI derived from binary logistic regression analysis, with covariates: age, BMI, physical trauma, smoking and occupational- and physical activities. Controls from the patient's environment were the reference category. DIP: Distal interphalangeal, PIP: proximal interphalangeal, MCP: metacarpophalangeal, CMC1: first carpometacarpal, CI: confidence interval.

Both male and female acromegalic patients had a higher chance to have clinical knee or hand OA when compared with the controls at all sites, also after adjustment (*Table 4*). None of the controls had clinical hip OA. The ORs reflecting the comparison between patients and controls were lower for female acromegalic patients than for male acromegalic patients for the knee and hand, however, not significant.

DISCUSSION

Osteoarthritis of the knees, hands and hips is very prevalent in acromegalic patients with long-term disease control. In this study we document that osteoarthritis equally affects male and female patients with acromegaly. The only exception was clinical hand OA and radiological 1stCMC OA, being more prevalent in female patients. The near equal gender distribution of clinical and radiological OA in acromegaly contrasts with the gender difference that is observed in primary OA in which (postmenopausal) women are more frequently affected than men[1].

Patients previously treated for acromegaly have a high prevalence of radiological, symptomatic, and clinical OA despite long term control of GH excess[11]. Elevated GH/IGF-I levels cause cartilage hypertrophy, and laxity of ligaments[8;10;13]. Thereafter, secondary changes result in irreversible damage to the joints, and OA. This second stage may be modulated by factors that also play a role in the development of primary OA[13]. However, our data indicates that, in acromegaly, female gender, which is a risk factor for primary OA[27], is not a risk factor for radiological and clinical OA in most joints, except in the hand.

We hypothesize that the lack of gender difference in acromegaly may be explained by the large effect of GH and IGF-I oversecretion in OA development, overruling other risk factors. However, since estrogens negatively interact with GH induced IGF-I secretion, an alternative explanation is that female patients with acromegaly are relatively protected for pathological changes induced by GH overproduction.

In primary OA, with increasing age women are affected more frequently and with much more severe OA than males[1;2;27;29]. It is suggested that a higher prevalence of OA in older women can, at least partially, be related to post-menopausal estrogen loss[30], and this is supported by epidemiological studies reporting that post-menopausal women taking estrogens have a decreased prevalence and incidence of radiological OA[4;5;31]. Although there is evidence for

estrogen receptors in cartilage and in synovium, a biological role of estrogens in the articular joint has not been established[32-35].

Estrogens have well-known effects on the somatotrope system, affecting both GH[36;37] and IGF-I secretion[38]. In the liver estrogens inhibit GH-dependent IGF-I production. Interestingly, in 1951, estrogens were proposed as the first medical treatment in women with acromegaly[39]. Thus, in acromegaly, both the protective effect of estrogens in itself, as the inhibitory action of estrogens on IGF-I production resulting in less severe IGF-I exposure, may relatively protect women with GH excess during their premenopausal years from OA. However, the ultimate effects of acromegaly on joint pathophysiology appear to be so strong that the prevalence of OA is highly increased in both male and female patients with acromegaly.

Several limitations of this study have to be addressed. First, female acromegalic patients were somewhat older than male patients. The fact that we did not find a gender difference in OA, except for the hand, despite the older age in females further underscores our observation that in acromegaly females are not more affected by OA than men[1]. Acromegalic patients did have a higher BMI than the controls, which is characteristic for the disease; to eliminate a possible effect of the higher BMI we adjusted all analyses for BMI. Unfortunately, normative radiographic data for 5-years age groups were not normalized for BMI, hence we were unable to adjust comparisons for BMI. Third, in the definition of clinical OA self-reported pain is utilized. Since women in general report more pain than men[40], it is unclear whether the more reported pain in the hips and more clinical hand OA in women is the result of more pain *per sé* or of more OA. The hip, more than the hand, is prone to systemic factors influencing the development of OA. The hand is more susceptible for physical and occupational activities. Hip OA is might be the best joint-site to demonstrate a specific effect due to acromegaly, since hip OA is equally common in males and females.

In conclusion, our data demonstrate that secondary OA is equally common in male and female acromegalic patients after long-term cure of disease, with the exception of a higher prevalence of clinical OA of the hands in female patients. These findings are remarkable since primary OA is more common in postmenopausal women than in men.

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