VIII.

High serum Insulin-like Growth Factor-1 (IGF-1) levels are associated with the presence of primary osteoarthritis, but not with radiographic progression: the GARP Study

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ABSTRACT

BACKGROUND: Several studies point towards a role of the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis in the pathophysiology of primary osteoarthritis (OA). Few epidemiological studies investigated the relationship between serum IGF-1 levels and radiographic OA, reporting inconsistent results.

OBJECTIVE: To investigate the relationship between serum IGF-1 and the presence and progression of radiographic OA in patients with a severe familial form of OA.

METHODS: We studied 340 subjects from the GARP (Genetics, osteoARthritis and Progression) Study with symptomatic OA at multiple joint sites on a familial base. Serum IGF-1 concentrations were measured and expressed as standard deviation scores (SDS), adjusted for age and sex. Radiographs of hands, knees and hips were obtained. Joint space narrowing (JSN) and osteophytes were scored semi-quantitatively using the Osteoarthritis Research Society (OARSI) atlas. Radiographic OA progression was defined as change ≥1 in osteophyte and/or JSN score. Generalized Estimated Equations (GEE) analysis was performed to adjust for intra-patient and intra-family relationships, with additional adjustments for age, sex, and BMI.

RESULTS: Mean (±SD) IGF-1 SDS was +0.79±1.39, which was significantly increased when compared to reference control values ($p<0.01$). Baseline IGF-1 SDS was not associated with the presence of radiographic OA, at none of the investigated joints. In addition, no association was found between IGF-1 SDS and radiographic OA progression or worsening of individual radiographic features after 2 years of follow-up.

CONCLUSIONS: Mean IGF-1 SDS was increased in patients with familial and symptomatic OA at multiple sites when compared to reference values. In this cohort, consisting exclusively of systemically affected patients, no relationship was found between IGF-1 SDS and either the presence or progression of radiographic OA. Further study has to clarify the complex role of the GH/IGF-1 axis in OA pathophysiology.

INTRODUCTION

Primary osteoarthritis (OA) is a debilitating disease, characterized by progressive degradation of articular cartilage and bone remodeling. Etiology is known to be multifactorial, in which age, body mass index (BMI), genetic, hormonal and local biomechanical factors play a role (1-3). With respect to the hormonal system, the interesting role of growth factors in this process is not elucidated. Insulin-like Growth Factor-1 (IGF-1) is the main factor involved in longitudinal skeletal growth (4). Growth Hormone (GH) secreted by the pituitary stimulates IGF-1 secretion mainly at the liver, but also by other tissues. IGF-1 mediates the effects of GH at the tissue level. Serum IGF-1 concentrations are age-dependent, being highest during puberty and adolescence, and declining thereafter with aging. In addition, they are influenced by many other factors, such as estrogens and BMI (5;6).

Several lines of research suggest a role of the GH/IGF-1 axis in the pathogenesis of primary OA. First, IGF-1 enhances chondrocyte proliferation and proteoglycan and collagen synthesis (7;8). Second, genetic functional variations of GH/IGF-1 genes, such as the exon 3 deletion of the GHR (d3-GHR), are associated with primary OA (9-12). The d3-GHR polymorphism is associated with an increased signal transduction, resulting in an enhanced GH responsiveness of the GHR and, thereby, increasing GH/IGF-1 activity. Third, in pathologically high GH/IGF-1 conditions, which is the case in acromegaly, a rare endocrine disease caused by a GH-producing pituitary adenoma, there is a strongly increased risk to develop secondary OA (13). In acromegaly, GH/IGF-1 activity (at diagnosis) has been associated with radiographic severity and progression of arthropathy (14-16), further supporting the hypothesis of GH/IGF-1 axis involvement in OA pathophysiology. Fourth, recent GWAS data show genetic evidence for significant association between height, being largely dependent on IGF-1 concentrations during the process of longitudinal skeletal growth, and OA, being suggestive of a common genetic etiology (17).

Recently, in a systematic review summarizing the evidence for association between serum IGF-1 and primary OA, results among studies were inconsistent (18). However, sample sizes were small and sex and BMI, both important factors for the interpretation of IGF-1 levels, were not taken into account in most studies. Moreover, only two studies had a longitudinal design enabling to study OA progression (19;20).

Based on the evidence in literature, we hypothesize that an increased GH/IGF-1 activity, as reflected by increased serum IGF-1 levels, increases the risk of primary OA. We, therefore, investigated the relationship between serum IGF-1 and the presence and progression of radiographic OA in a well-characterized OA population with a severe OA phenotype.

MATERIALS AND METHODS

PATIENTS: The GARP (Genetics, osteoARthritis and Progression) Study is a prospective cohort study, aimed at identifying determinants of OA susceptibility and progression. The GARP Study consists of 192 sib pairs (N=384) between 40 and 70 years of age of Dutch ancestry, all having symptomatic OA at multiple sites in the hands or in ≥2 of the following joint sites: hand, spine (cervical or lumbar), knee, or hip. Patients with other (secondary) forms of OA were excluded. Details of recruitment and patient selection have been reported elsewhere (21). Sib pairs with at least one subject with symptomatic knee or hip OA (but not in a radiographic end-stage OA) were eligible for the 2-year follow-up visit, resulting in the inclusion of 105 eligible sib pairs (N=210)(22). The GARP Study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

IGF-1 MEASUREMENT: Baseline blood samples were drawn and stored. Serum IGF-1 concentrations (nmol/l) were measured using an immunometric technique on an Immulite 1000 (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA), since February 2006. The lower limit of detection was 25ng/ml and the inter-assay variation was 6.4%–3.8% in the range of 60–400ng/ml. In order to adjust IGF-1 levels for age and sex, which is common practice in the evaluation of endocrine diseases, IGF-1 levels were expressed as standard deviation scores (SDS), using lambda-mu-sigma smoothed (LMS) reference curves based on the widely accepted method of Rikken and Cole (23;24), with a normal IGF-1 SDS reference range between -2 and +2 SDS. Serum IGF-1 measurement was successfully performed in 340 patients.

RADIOGRAPHIC ASSESSMENT: Conventional radiographs of the hands, knees, hips, and spine were obtained according to a standardized protocol, as previously described in detail (21). Radiographic OA was scored according to the Kellgren-Lawrence (KL) scale by a single experienced musculoskeletal radiologist (H.K.), as described in detail elsewhere. ICCs were good (21;25). Radiographic OA was defined according to the ROA score, which is described in detail elsewhere (26). Radiographic knee and hip OA were defined as KL≥2

in, respectively, at least one knee or hip. Radiographic OA in the hand was defined as KL≥2 in at least 3 of the following joints: distal interphalangeal joint (DIP) 2–5, proximal interphalangeal joint (PIP) 2–5, interphalangeal joints 1, and carpometacarpal (CMC) joint 1. Spinal disc degeneration was defined as KL≥2 at at least 3 levels.

Individual OA features, being joint space narrowing (JSN) and osteophytes were assessed semi-quantitatively (Grade 0-3), using the Osteoarthritis Research Society (OARSI) atlas, in consensus opinion of two experienced readers (26). OARSI≥1 reflects presence of JSN or osteophytes. The reproducibility for JSN and osteophyte grading was based on the repeat reading of 20 radiographs (randomly selected throughout the study period) and was depicted by the intra-class correlation coefficient (ICC). ICCs for, respectively, JSN and osteophytes were 0.92 and 0.98 in the hands, 0.88 and 0.87 in the knees and 1.00 and 1.00 in the hips.

To assess radiographic OA progression, baseline and 2-year radiographs of the knee, hip, hands, and spine were scored in consensus paired without knowledge of chronological order, blinded for patient characteristics, for osteophytes and JSN by two experienced readers, using the OARSI atlas. Progression was defined as the change in JSN or osteophyte scores above the smallest detectable change (SDC), reflecting the change above measurement error (27;28). Since the SDCs for osteophytes and JSN were respectively 0.22 and 0.71 in the knee, 0.00 and 0.00 in the hip, and 0.35 and 0.62 in the hand, a change ≥1 in osteophyte/JSN score was defined as progression at all sites. Also joints (without end-stage (Grade 3) OA at baseline) replaced by a knee or hip prosthesis during follow-up, were considered to have radiographic progression.

STATISTICAL ANALYSIS: SPSS version 20.0 (SPSS inc., Chicago, IL, USA) was used for data analysis. Mean IGF-1 levels were compared between males and females using an Independent Samples T test. To compare mean IGF-1 SDS between GARP patients and 906 healthy literature controls from Rikken *et al.*(24), we performed a pooled variance *T* test, since sample sizes differ substantially between both groups. Mean baseline IGF-1 SDS was studied in relation to presence of radiographic OA at different sites, using a One-way ANOVA test. To assess the risk of radiographic OA at a given IGF-1 SDS, a Generalized Estimated Equations (GEE) analysis was carried out, thereby adjusting for intra-patient and intra-familial effects in GARP. A binary logistic model was used, stratified for sex, with presence of radiographic OA as dependent variable and age, BMI, and IGF-1 SDS divided into tertiles (based on the distribution in the patients) as covariates.

In a subset of patients with available follow-up radiographs, baseline IGF-1 SDS (tertiles) was studied in relation to progression of osteophytes and JSN over 2 years. We performed a GEE-analysis with a binary logistic model to take into account intra-patient and intra-family relationships, with additional adjustments for age, sex, BMI, and radiographic score at baseline.

RESULTS

PATIENT DESCRIPTION: Complete set of radiographs and successful serum IGF-1 measurements were available of 340 patients with symptomatic OA at multiple joint sites (82% female, of which 9.6% premenopausal). Baseline characteristics are shown in *Table 1*. Radiographic knee, hip, hand, and spine OA were, respectively, present in 37%, 26%, 74%, and 89% of the females, and in 38%, 28%, 70%, and 83% of the males. Eight patients from separate families had a unilateral knee replacement; one patient had bilateral knee replacements. In the hip, 22 patients had a unilateral prosthesis and fifteen patients had bilateral prostheses. Mean serum IGF-1 level was 18.2±6.3 nmol/l, being significantly higher in males than in females (p=0.013). As expected, IGF-1 levels were negatively correlated with age (Pearson correlation coefficient r=-0.119, p=0.030) and BMI (r=-0.162, p=0.003).

RELATIONSHIP BETWEEN SERUM IGF-1 SDS AND RADIOGRAPHIC OA: Mean IGF-1 SDS among GARP patients was +0.79±1.39 (95%CI +0.64;+0.93), with 67 patients (20%) above +2 SDS. When compared to 906 literature controls, mean IGF-1 SDS was significantly increased in GARP patients (p<0.01). Mean IGF-1 SDS did not differ between specific joint sites with radiographic OA. In addition, no dose-response relationship between baseline IGF-1 SDS and the presence of radiographic OA was observed, at none of the investigated joint sites, although in females a trend towards associations between higher baseline IGF-1 SDS and both knee and discus OA was observed (*Table 2*). No significant differences were seen between males and females or between patients <65 years and ≥65 years.

RELATIONSHIP BETWEEN SERUM IGF-1 SDS AND PROGRESSION OF RADIOGRAPHIC OA OVER 2 YEARS OF FOLLOW-UP: IGF-1 SDS and complete baseline and 2-yr follow-up radiographs were available in 174 patients (80% female). Radiographic progression of respectively knee, hip, and hand OA was seen in 37 (21.3%), 17 (9.8%) and 60 (34.5%) patients, being comparable between males and females. Baseline IGF-1 SDS was not related to radiographic progression of hip, knee or hand OA (*Table 3*), or worsening of individual radiographic features (*i.e.* osteophyte growth or joint space loss) (*data not shown*).

Table 1. Baseline characteristics of GARP subjects (N = 340)

Clinical characteristics	**Females* (N= 280)**	**Males (N= 60)**
Age, years	59.6 ± 7.5	60.1 ± 6.8
BMI, kg/m^2	27.0 ± 4.9	27.2 ± 3.4
Radiographic OA		
Knee (N (%))	103 (37%)	23 (38%)
Hip (N (%))	72 (26%)	17 (28%)
Hand (N (%))	206 (74%)	42 (70%)
Spine (N (%))	248 (89%)	50 (83%)
IGF-1 (nmol/l)	17.8±6.3	20.1±6.3
IGF-1 SDS	0.69±1.40	1.23±1.26

Data are shown as mean±SD, unless mentioned otherwise, and were stratified for sex. Radiographic OA was defined as ROA≥1, based on KL≥2(26). Spine OA is defined as radiographic disc degeneration of the spine.
**, 27 of the 280 studied females (9.6%) were premenopausal.*

GARP, Genetics, osteoARthritis and Progression Study; N, number of patients; OA, osteoarthritis; BMI, body mass index; IGF-1, Insulin-like Growth Factor-1; SDS, standard deviation score; KL, Kellgren-Lawrence score.

Table 2. Risk of having radiographic OA according to tertiles of IGF-1 SDS for, respectively, 60 male and 280 female patients with familial OA at multiple joint sites

Males

	Radiographic OA risk: adjusted OR (95%CI)*			
IGF-1 SDS (tertiles)	**Knee (N=23)**	**Hip (N=17)**	**Hand (N=42)**	**Discus (N=50)**
1	1.0	1.0	1.0	1.0
2	0.7 (0.2-2.4)	0.8 (0.2-3.8)	0.3 (0.1-1.6)	0.2 (0.0-2.7)
3	0.6 (0.2-2.3)	0.9 (0.2-3.8)	0.3 (0.1-1.5)	0.2 (0.0-2.5)

Females

	Radiographic OA risk: adjusted OR (95%CI)*			
IGF-1 SDS (tertiles)	**Knee (N=103)**	**Hip (N=72)**	**Hand (N=206)**	**Discus (N=248)**
1	1.0	1.0	1.0	1.0
2	1.6 (0.9-3.0)	0.4 (0.2-0.9)	0.8 (0.4-1.6)	1.4 (0.5-3.8)
3	1.7 (0.9-3.2)	0.8 (0.4-1.6)	0.7 (0.3-1.4)	2.8 (1.0-8.3)

** IGF-1 SDS at the time of the baseline study visit was divided into tertiles (based on the distribution among patients). A Generalized Estimating Equations (GEE) analysis was performed to adjust for intra-patient and intra-familial effects, stratified for sex. A binary logistic model was used with radiographic OA as outcome parameter and IGF-1 SDS tertiles, age, and BMI as covariates. The lowest IGF-1 SDS tertile was used as reference level.*

N, number of patients with radiographic OA according to Kellgren-Lawrence ≥2; OR, odds ratio; CI, confidence interval; OA, osteoarthritis; IGF-1, Insulin-like Growth-Factor 1; BMI, body mass index; Disc, disc degeneration.

Table 3. IGF-1 SDS at baseline were not related to radiographic progression of knee, hip or hand OA over 2 years of follow-up in patients with familial OA at multiple joint sites (N = 174)

	Number of patients (N=174)		
Knee OA**			
IGF-1 SDS (tertiles)	**With progression (N=37)**	**Without progression (N=137)**	**Adjusted OR (95%CI)***
1	11	44	1.0
2	14	47	1.3 (0.5-3.3)
3	12	46	1.1 (0.4-2.7)
Hip OA**			
IGF-1 SDS (tertiles)	**With progression (N=17)**	**Without progression (N=157)**	**Adjusted OR (95%CI)***
1	5	50	1.0
2	10	51	0.7 (0.2-2.4)
3	2	56	0.4 (0.1-1.6)
Hand OA**			
IGF-1 SDS (tertiles)	**With progression (N=60)**	**Without progression (N=114)**	**Adjusted OR (95%CI)***
1	20	35	1.0
2	21	40	0.6 (0.2-1.3)
3	19	39	0.7 (0.3-1.7)

** IGF-1 SDS at the time of the baseline visit was divided into tertiles (based on the distribution among patients). A Generalized Estimating Equations (GEE) analysis was performed to adjust for intra-patient and intra-familial effects. A binary logistic model was used with radiographic OA progression as dependent variable and IGF-1 SDS tertiles, age, sex, BMI, and radiographic score at baseline as covariates. The lowest IGF-1SDS tertile was used as reference level.*

*** Radiographic OA progression was defined as an increase of ≥ 1 in OARSI score for JSN and/or osteophytes.*

N, number of patients; OR, odds ratio; CI, confidence interval; IGF-1, insulin-like growth-factor 1; SDS, standard deviation score; BMI, body mass index.

DISCUSSION

In the present longitudinal study, we investigated the association between serum IGF-1 and, respectively, the presence and progression of radiographic OA in patients with familial OA at multiple joint sites from the GARP Study. Mean IGF-1 SDS in OA patients was significantly higher than in reference values from controls, indicating that, overall, serum IGF-1 concentrations are high. When looking at specific joint sites, however, we did not observe a relationship between IGF-1 SDS and the presence of radiographic OA. In addition, baseline IGF-1 SDS was not related to radiographic OA progression over 2 years or worsening of individual OA features.

IGF-1 is an important growth promoting polypeptide belonging to the same family of growth factors as insulin (4). IGF-1 is mainly produced by the liver and mediates the effects of GH in many organs, primarily by the IGF-1 receptor type 1. Serum IGF-1 concentrations reflect the GH concentrations over 24 hours and IGF-1 bioavailability is regulated by IGF-1 binding proteins. Serum IGF-1 concentrations in adulthood decrease progressively with age and are influenced by many other factors, such as estrogen and BMI (5;6). In clinical practice, serum IGF-1 levels are converted into IGF-1 SDS in order to standardize IGF-1 levels for age and sex.

Several functional genetic variants involved in the process of endochondral ossification, being the main process in longitudinal growth, are identified to be associated with primary OA (9;10;12). GH and IGF-1 play important roles in this process (29). Recently, we found evidence for an association between the common d3-GHR polymorphism, associated with an enhanced GH responsiveness, and primary OA in females, indicating that increased activity of the GH/IGF-1 axis might play a role in OA pathophysiology (9). *In vitro* studies also indicate that IGF-1 has stimulatory effects in chondrocyte proliferation and proteoglycan and collagen synthesis (7;8;29), supporting involvement of the GH/IGF-1 axis in OA development. Moreover, in acromegaly disease, GH/IGF-1 activity has been associated with radiographic severity and progression of arthropathy (14-16). With respect to the association between serum IGF-1 levels and primary OA, only few epidemiological studies have been previously performed. A recent systematic review summarizing literature on this association showed moderate evidence for no relationship between serum IGF-1 and radiographic OA (18). However, this review included mainly cross-sectional data and study sizes were relatively small. In addition, most studies did not adjust for age, sex, and BMI, which all independently influence IGF-1 concentrations. In this respect, it

should also be noted that comparisons between studies are difficult, since differences exist in IGF-1 assays, OA scoring methods, reading order of baseline and follow-up radiographs, mean age of participants and statistical analyses used.

In the present study, we found that mean IGF-1 SDS was significantly increased in GARP patients when compared to control/reference values, suggesting that high serum IGF-1 levels are associated with the presence of a severe familial form of OA. Although mean IGF-1 SDS was high in the GARP Study, no clear dose-response relationship was found between IGF-1 SDS and either the presence or progression of OA. This might probably be explained by the fact that per inclusion all GARP patients had severe radiographic and clinical OA at multiple joint sites on a familial base. Furthermore, serum IGF-1 levels of most GARP subjects were within the normal reference range, probably resulting in too less variation in IGF-1 levels to detect a dose-response relationship with radiographic occurrence or progression of OA. In addition, an important question which requires further investigation is whether circulating total IGF-1 levels truly reflect peripheral IGF-1 activity. There is increasing evidence that measuring free unbound IGF-1 levels and IGF-1 bioactivity better reflect the GH/IGF-1 status than total IGF-1 (30;31). However, because of methodological difficulties in measurement, total serum IGF-1 is often used to assess GH/IGF-1 activity (30). Presence of negative endocrine feedback systems further complicates the interpretation of IGF-1 levels.

Strengths of the present study are, first, the relatively large number of patients with a severe, familial form of primary OA. This specific OA phenotype increases the a priori chance to detect an association between IGF-1 levels and OA. Second, we had the availability of a cohort that was longitudinally followed and we were, therefore, able to study IGF-1 in relation to OA progression. Since a population with OA at multiple joint sites, such as the GARP Study, is associated with rapid progression, our study population is suitable to investigate OA progression within a relatively short period. In this respect, we chose the 2-year time point to study progression, since we expect more differentiation in (and faster) OA progression, increasing the sensitivity to detect risk factors. Third, we adjusted for age, sex, and BMI in our analyses, since all these factors are important confounders when studying IGF-1 in relation to primary OA.

This study has a number of limitations. First, since all GARP subjects have a severe OA phenotype of familial OA at multiple joint sites, joint-specific analyses are difficult to perform. In addition, since the GARP Study is a very homogeneous cohort with less variation in OA phenotype (*i.e.* all patients have severe familial symptomatic OA at multiple joint sites), the detection of a clear relationship with OA at different joint sites is very difficult. In this respect, also the generalizability of our results in other population settings has to be investigated (32). Second, it should be noted that the GARP Study consists mainly of females, a phenomenon that is well-known from OA literature (33). To adjust for the female overrepresentation in our cohort, analyses were stratified for sex. Third, IGF-1 measurement by serum samples is very complex, because individual IGF-1 levels are liable to temporal variations and are inversely correlated to age, estrogen levels, and BMI. Fourth, we compared mean IGF-1 SDS of the GARP cohort with literature-based reference values. Ideally, it would be preferred to use a control population of subjects without signs of OA for comparison. Furthermore, radio-immuno assays (RIA) for measuring serum IGF-1 are subject to analytical difficulty. Finally, in general, it should be noted that due to a complex pathophysiology, the extent to which hormones are involved in common diseases is difficult to assess. Therefore, to investigate the individual roles of GH and IGF-1 in joint disease, acromegaly is a unique human model of which findings might possibly be extrapolated to primary OA (14;34;35).

In conclusion, mean IGF-1 SDS was increased in patients with familial OA at multiple joint sites when compared to control values from literature, suggesting that high serum IGF-1 is associated with OA. This is similar to several lines of previous evidence suggesting a role for increased GH/IGF-1 activity in the pathophysiology of OA. However, no clear relationship between IGF-1 SDS and either the presence or progression of radiographic OA at different joint sites was found. Taking into account imperfections in IGF-1 measurement and the homogeneous OA phenotype in the GARP Study thereby prohibiting the detection of a clear dose-response association, further research has to clarify the complex role of the GH/IGF-1 axis in OA pathophysiology.

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