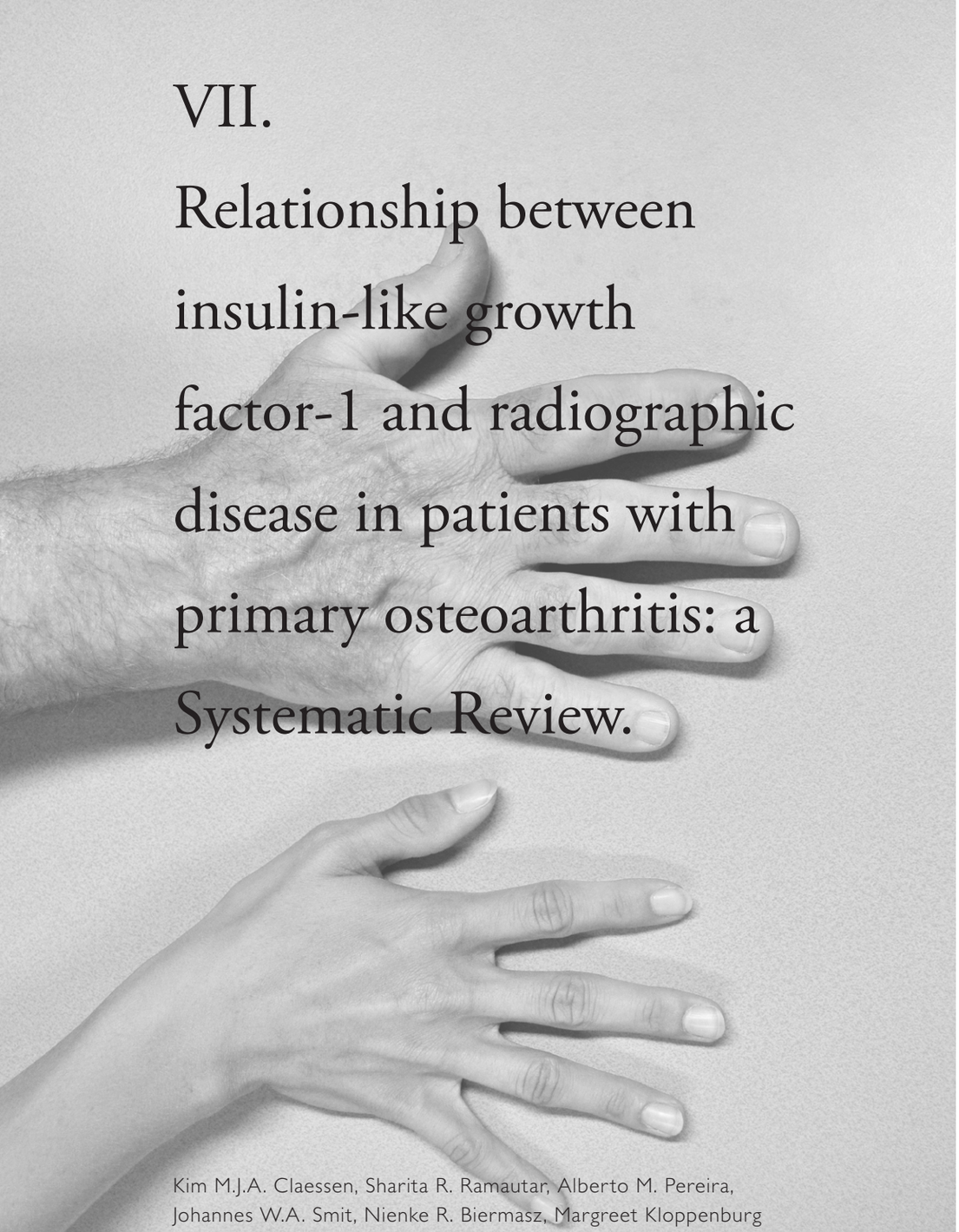
Part B

The role of the GH / IGF-1 axis in primary OA

VII.

Relationship between insulin-like growth factor-1 and radiographic disease in patients with primary osteoarthritis: a Systematic Review.



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ABSTRACT

OBJECTIVE: To evaluate the association between radiographic osteoarthritis (OA) and either serum insulin-like growth factor-1 (IGF-1) levels or IGF-1 gene polymorphisms in patients with primary OA.

METHODS: We conducted a systematic review of reported associations between circulating IGF-1 and/or IGF-1 gene polymorphisms and radiographic OA. Studies were eligible when: 1) investigating serum IGF-1 and/or IGF-1 gene polymorphisms in relation to prevalent or incident radiographic OA; 2) written in English; 3) full-text article or abstract; 4) patients had primary OA in knee, hip, hand or spine; 5) longitudinal, case-control or cross-sectional design. Quality assessment was done using a standardized criteria set. Best-evidence synthesis was performed based on guidelines on systematic review from the Cochrane Collaboration Back Review Group, using five evidence levels: strong, moderate, limited, conflicting and no evidence.

RESULTS: We included 11 studies with more than 3000 primary OA cases. Data on the relationship between serum IGF-1 and radiographic OA were inconsistent. Adjustment for body mass index (BMI) was often omitted. Of four high-quality studies, three studies reported no association, one study found significantly higher IGF-1 levels in OA patients compared to controls. Patients with IGF-1 gene promoter polymorphisms and a genetic variation at the IGF-1R locus had an increased OA prevalence compared to controls.

CONCLUSIONS: Observational data showed no association between serum IGF-1 and occurrence of radiographic OA (moderate level of evidence), and a positive relationship between IGF-1 gene polymorphisms and radiographic OA (moderate level of evidence); however the confounding effect of BMI was insufficiently addressed. Future well-designed prospective studies should further elaborate the role of the complex GH/IGF-1 system in primary OA.

INTRODUCTION

Osteoarthritis (OA) is a common disease, characterized by progressive degradation of articular cartilage and bone remodeling, resulting in pain and disability. Despite the increase in molecular knowledge accrued during the last years, the exact pathogenesis of the destructive process remains unknown. OA is considered to be a multifactorial disease in which age, body mass index (BMI), hormonal and local biomechanical factors together with genetic predisposition play a role (1-5). In OA, the stable equilibrium between synthesis and breakdown of cartilage components is disrupted and the rate of loss of proteoglycans and other matrix components eventually exceeds their formation rate (6). Factors responsible for preservation or loss of the articular cartilage matrix are of considerable interest to clinicians and scientists. Among chondrotrophic growth factors, insulin-like growth factor-1 (IGF-1) and its response on mature adult cartilage has been studied extensively.

IGF-1 is an important growth promoting peptide with structural and functional homology to pro-insulin. IGF-1 is mainly produced by the liver and mediates the effects of growth hormone (GH) at tissue level. In addition, IGF-1 is a key factor for longitudinal skeletal growth (7). Serum IGF-1 concentrations in adulthood decrease progressively with age and are influenced by many other factors, such as BMI (8,9). Three lines of research suggest IGF-1 involvement in OA pathogenesis.

Firstly, IGF-1 has been shown to enhance chondrocyte proliferation and proteoglycan and collagen synthesis by chondrocytes in normal cartilage, both *in vivo* and *in vitro* (10-20), also during cytokine exposure, which drives most predominating catabolic processes in cartilage. Furthermore, IGF-1 inhibits cytokine-stimulated degradation of proteoglycans directly in normal cartilage *in vitro* (21,22). These anabolic and protecting properties make IGF-1 an obvious candidate for a major role in cartilage repair.

Secondly, serum IGF-1 is elevated in acromegaly, a rare endocrine disease caused by GH overproduction from a pituitary adenoma. The GH excess results in high serum GH and IGF-1 levels and is associated with an increased risk of secondary OA (23,24). Prevalence and severity of arthropathy worsen with the duration of uncontrolled acromegaly. Furthermore, pre-treatment IGF-1 levels predict radiographic OA in a dose-dependent manner (25).

Finally, earlier studies showed that genes regulating formation, degradation and repair of articular cartilage and subchondral bone remodelling may be involved in OA pathogenesis (26-29). Probably, genetic variations of GH/IGF-1 genes with functional properties may affect the pathogenesis of primary OA.

Several epidemiological studies have explored the role of serum IGF-1 in primary OA, showing various results (30-33). We aimed to systematically review observational studies on the relationship between radiographic OA and either serum IGF-1 and IGF-1 gene polymorphisms in patients with primary OA, taking in account the variable quality of studies.

MATERIALS AND METHODS

IDENTIFICATION AND SELECTION OF THE LITERATURE: To identify studies investigating the relationship between IGF-1 and radiographic primary OA, we searched the following databases, up to May 2011: Medline, EMBASE, Web of Science, the Cochrane Library, ScienceDirect, CINAHL, LWW Journals, Wiley, Academic Search Premier and WHO International Clinical Trials Registration Platform. The following combined key words were used: ("Insulin-Like Growth Factor I" OR "IGF-1" OR "Insulin-Like Somatomedin Peptide I" OR "Somatomedin C" OR "IGF-I-SmC" OR "Receptor, IGF Type 1" OR "IGF-1 Receptor" OR "IGF 1 Receptor" OR "IGF-I Receptor" OR "IGF I Receptor" OR "IGF-1 Receptors" OR "IGF Type 1 Receptor" OR "Insulin-Like-Growth Factor I Receptor") AND ("Osteoarthritis" OR "Osteoarthritides" OR "Osteoarthrosis" OR "Osteoarthroses" OR "Degenerative Arthritides" OR "Degenerative Arthritis"). References of relevant articles were checked for additional articles.

A study was eligible for inclusion with the following criteria: (1) the association between serum IGF-1 levels and/or IGF-1 gene polymorphisms and prevalent or incident radiographic OA was investigated; (2) written in English; (3) full-text article or abstract; (4) patients had primary OA in knee, hip, hand or spine; (5) longitudinal, case-control or cross-sectional design. Incident OA was defined as the development of OA in joints that were previously unaffected during the specified time period in a longitudinal study. Prevalent OA was defined as the presence of OA at the moment of the study visit in a cross-sectional or case-control study.

A study was excluded if the studied population had a specific underlying pathology, such as trauma (fractures), infection, rheumatoid arthritis, or ankylosing spondylitis. Only human studies were evaluated.

DATA EXTRACTION AND ANALYSIS: Data extraction and eligibility were assessed by two independent investigators (K.M.J.A.C. and S.R.R.). Inconsistencies in data extraction were resolved by consensus. We used data comparing serum IGF-1 and/or presence of IGF-1 gene polymorphisms between patients with radiographic OA and controls without radiographic OA.

The following data were extracted: (1) study population (patient characteristics, population size, gender, age, BMI); (2) exposure (serum IGF-1 or IGF-1 gene polymorphisms), (3) outcome (methods of assessment of radiographic OA, reproducibility, blinding); (4) potential confounders (age, sex, BMI, height, race).

METHODOLOGICAL QUALITY ASSESSMENT : The quality of each included paper was assessed by two independent reviewers (K.M.J.A.C. and S.R.R.) using a standardized set of criteria (*Table 1*), which have been used previously in reviews on musculoskeletal disorders (34) and were modified to cover the topic of our review.

When the criterion was met in the article, '1' was given, otherwise '0'. A '0'was also given when no information was given about the specific criterion mentioned in the article. Several items are not applicable to certain types of study design and therefore do not contribute to the total score of that particular study. The maximum score (100%) for each study was based only on the items applicable to that particular study design (cohort and case-control 14, cross-sectional 11). Total scores per study were calculated as the percentage of maximum obtainable scores. For example, a quality score of 57% (8 / 14 x 100%) was assigned to a case-control study with 8 positive items. A study was considered high-quality (HQ) if the methodological quality score was ≥64%, chosen as the median of all quality scores.

Level of evidence synthesis: Because the observational studies were heterogeneous with regard to study population, methodological quality and determinants and measures of radiological OA assessment, we followed standard practice and refrained from statistically pooling the data and performed a 'best evidence' synthesis. A prospective cohort study was judged as the preferred design, followed by a case-control study, and then by a cross-sectional study. Subsequently, the studies were ranked according to their methodological quality score. The following ranking of the levels of evidence was formulated based on the guidelines on systematic review of the Cochrane Collaboration Back Review Group, a method to summarize evidence in observation studies with heterogeneous methodological study characteristics (*Table 2*) (35,36).

Table 1. List of criteria used for methodological quality assessment.

Item	Criterion	CH/CC/CS/GA*
Study population		
1.	Clear description of selection of study subjects.	CH/CC/CS/GA
2.	Sufficient description of characteristics of study groups.	CH/CC/CS/GA
3.	Cases and controls were drawn from the same source	CC
5.	population.	
	Participation rate ≥ 80% for cases/cohort.	CH/CC/CS/GA
	Participation rate ≥ 80% for controls.	CC
Assessment of risk factor: serum IGF-1 levels/IGF-1 gene polymorphism		
6.	Serum IGF-1/IGF-1 gene polymorphism was assessed with standardized or valid instruments.	CH/CC/CS/GA
7.	IGF-1 measurement/IGF-1 gene polymorphism assessment was identical in the studied population.	CH/CC/CS/GA
Radiographic OA assessment		
8.	Radiographic OA measures were valid.	CH/CC/CS/GA
9.	Presence of radiographic OA was assessed reproducibly.	CH/CC/CS/GA
10.	Radiographic OA was assessed identically in all patients.	CH/CC/CS/GA
Analysis and data presentation		
11.	Mean levels of IGF-1 (e.g. serum and/or synovial) were given.	CH/CC/CS
12.	Frequencies of radiographic OA were given.	CH/CCCS/GA
13.	Appropriate analysis techniques were used.	CH/CC/CS/GA
14.	Adjusted for at least age, sex and BMI.	CH/CC/CS/GA

OA=osteoarthritis. IGF-1=insulin-like growth factor 1.
** Applicable to CH=cohort study. CC=case-control study. CS=cross sectional study. GA=genetic association study.*

Table 2. Levels of evidence used in best-evidence synthesis.

Strong	Generally consistent findings were presented in multiple high-quality cohort studies.
Moderate	One high-quality cohort study and two or more high quality case-control studies, or when at least three high-quality case-control studies show generally consistent results.
Limited	Generally consistent findings were found in a single cohort study, or in one or two case- control studies or in multiple cross-sectional studies.
Conflicting	Less than 75% of the studies reported consistent findings.
No evidence	No study could be found.

Sensitivity analyses by defining other cut-offs (mean score of all studies instead of median) of HQ studies were performed. Furthermore, a sensitivity analysis was performed based on all positive studies, regardless of methodological quality. A study was regarded as positive if it showed a significant association between serum IGF-1 and radiographic OA.

RESULTS

IDENTIFICATION AND SELECTION OF THE LITERATURE: From initial 668 potentially relevant studies identified, 634 were excluded on the basis of title and abstract. 34 papers were retrieved for detailed assessment: 7 were excluded because no primary OA patients were included, 10 because OA was not assessed radiographically, and 3 were not original articles. One abstract appeared to be a duplicate of a full text article and was excluded. Another 2 studies were excluded because they studied OA progression and severity, respectively, and not prevalent or incident OA. Consequently, a total of 11 studies were included (*Figure 1*).

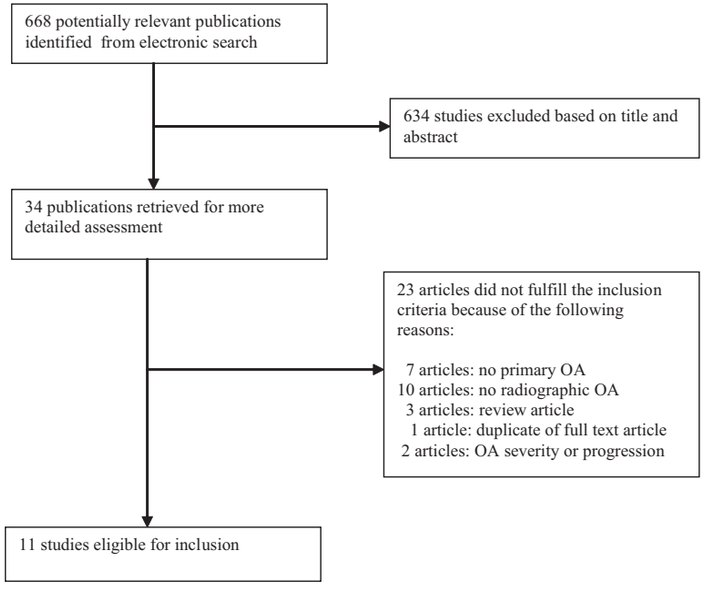

Figure 1. Flow diagram of study selection and exclusion stages.

STUDY DESCRIPTION: A detailed study description is given in *Tables 3a&3b*. These studies provided data on the relationship between serum IGF-1 and radiographic OA of knee (n=5) (30,33,37,38,40), hand (n=1) (32), OA in general (n=3) (31,39), and IGF-1 gene polymorphisms (n=3) (26-28). The studies were published from 1992 onwards. One had a nested case-control design; the other 10 were case-control/cross-sectional studies. All studies used a radio-immuno assay (RIA) for IGF-1 measurement in serum. Assays were generally done blinded to case status.

Most studies investigated a middle-aged population and three exclusively included women (31,32,40). The majority of studies adjusted for age and sex, two studies were matched (30,39). Three studies adjusted for at least three variables (26,28,38).

Six studies assessed radiographic OA according to the Kellgren&Lawrence (KL) score, and two studies used personal scoring systems for individual radiographic OA features (individual score by Scott *et al.* **(33)**, individual score by the principles of KL (30)). Two studies used both KL and a scoring method for individual OA characteristics. Two studies also assessed clinical OA; one by the American College of Rheumatology criteria (ACR) criteria for knee OA (37), the other used a question about knee pain from the Health and Nutrition Examination Survey (30).

METHODOLOGICAL QUALITY ASSESSMENT: The quality of studies was assessed according to the criteria stated in *Table 1* and methodological quality scores are shown in *Table 4*. The scores ranged from 14 to 82% of the maximum obtainable score for each study design, with a median score of 64%. Only four of the eight studies on serum IGF-1 and radiographic OA (one cohort study, three case-control/cross-sectional studies) and all three studies on IGF-1 gene polymorphisms were HQ studies.

Overall, selection of study subjects was not clearly described. In addition, none of studies described participation rates for cases and controls in detail. Reproducibility of radiological OA scoring was described in only three studies with kappa or intracorrelation coefficient. Three studies adjusted for age, sex and BMI; the other studies did not correct for BMI-related IGF-1 changes.

ASSOCIATION BETWEEN SERUM IGF-1 AND RADIOGRAPHIC OA IN PRIMARY OA PATIENTS: The largest study (Lloyd *et al.*, N=761) showed a positive association between high serum IGF-1 and radiographic knee OA (31). In this HQ case-control study, a clear dose-response relationship was shown with the strongest association in patients with bilateral and more

severe knee OA (p<0.0001). High IGF-1 levels were also associated with hand OA, especially in the distal interphalangeal (DIP) joint (p=0.006). Results were adjusted for age, weight and height. Fraenkel *et al.* reported a trend towards significance for higher serum IGF-1 in men with bilateral knee OA, in a HQ longitudinal study with a nested case-control design. Adjustments for age, sex, BMI, height and race were made (30).

In contrast, Denko *et al.* reported lower serum IGF-1 concentration in patients with general radiographic OA (39). In this low-quality (LQ) case-control study (N=111; *Tables 3a&3b*), patients and controls were matched on age, sex, race, height and weight.

Five studies (two HQ (33,38), three LQ (32,37,40)), all case-control studies, reported no association between serum IGF-1 and radiographic OA. Three studies (37,38,40) found no relation between serum IGF-1 and knee OA. In two cross-sectional studies (32,33), Hochberg *et al.* reported significantly lower IGF-1 levels in patients with radiographic hand and knee OA from the Baltimore Longitudinal Study of Aging cohort. However, after adjustments for age-related IGF-1 decline, results were no longer significant. None of these studies corrected for BMI.

By taking the mean of all methodological quality scores as cut-off point, a study was considered high-quality with a score ≥59%. Using this alternative cut-off point didn't change the results. The sensitivity analysis based on all positive studies without quality assessment, showed similar results with moderate evidence for no association between serum IGF-1 and radiographic OA, and a positive association between IGF-1 gene polymorphisms and radiographic OA.

GENETIC ASSOCIATION BETWEEN IGF-1 GENE POLYMORPHISMS AND RADIOGRAPHIC OA: Three studies, all HQ studies, provided data on the outcomes of genetic association studies, in which Single Nucleotide Polymorphisms (SNPs) in the IGF-1 and IGF-1 receptor genes were investigated in relation to radiographic OA. All studies were cross-sectional; one study contained only women from a Japanese population (27).

Meulenbelt *et al.* investigated polymorphisms in the promoter region of the IGF-1 gene in relation to radiographic OA. Nine different alleles were identified, of which allele 3 and 4 (A3, A4) were associated with a higher prevalence of radiographic OA at any joint site, mostly in the hip. Especially A3, which is less prevalent than A4, is from a population genetic point the most likely allele associated with radiographic OA. Subjects heterozygous for A3 had a 1.9 times increased risk of radiographic OA compared to wildtypes (adjustments for age, sex, BMI and BMD). A 3.6 times increased risk of radiographic OA was found in patients homozygous for A3, however non-significant (26).

Zhai *et al.* studied the 192bp allele of the IGF-1 promotor polymorphism in relation to radiographic OA in the knee, hip, hand and spine. Cases had at least one of the four joint sites affected. Previously, absence of 192bp (wildtype) allele was found to be associated with lower serum IGF-1 levels and lower height (41), indicating functional properties. In the overall study population, the polymorphism increased radiographic OA risk, although not statistically significant. In a subgroup aged ≤65years radiographic OA risk was significantly higher in SNP carriers (p=0.03 for trend), with highest prevalence in homozygotes (OR=1.9), suggesting an allele-dose effect. These findings were independent of age, sex, BMI and BMD (28).

Urano *et al.* studied a SNP at intron1 in the IGF-1 receptor gene (IVS1+ 14488C>G, rs11247361) in relation to radiographic features of spinal disc degeneration in healthy postmenopausal Japanese women, assessed semi-quantitatively by the Genant method. In this population-based study, the genetic variation was correlated with spinal disc narrowing (OR=2.0, p=0.0033), especially in homozygotes, suggesting a possible contribution of IGF-1R to human cartilage metabolism. Occurrence of endplate sclerosis and osteophytosis was comparable between SNP genotypes (27).

Table 3a. Study characteristics of studies on serum IGF-1 and radiographic OA.

Author, year (ref.)	N	Study design	Population	Sex	Age (years, mean±SD)	Assessment ROA Hand	Knee	Spine	Total	Adjustments Age	Sex	BMI	Height	Race	Results on IGF-1 & ROA	Quality Score
Hochberg, 1993 (32)	115	Case-control	Baltimore Longitudinal Study of Aging 60 hand OA 55 healthy controls	♀ 100%	53.6 ± 18.2	KL	-	-	-	Yes	NA	No	No	No	NS (P≥0.50)	57%
McAlindon, 1993 (30)	156	Case-control	Bristol Community Survey 78 knee OA 78 healthy controls	♀ 60% ♂ 40%	71.8 ± 7.6	-	TFJ& PFJ OP &JSN &SCL	-	-	Yes	Yes	No	No	No	NS (P 0.48)	64%
Denko, 1994 (39)	111	Case-control	57 generalized OA 54 healthy controls	♀ 68% ♂ 32%	♀ 66 ± 12 ♂ 68 ± 11	-	-	-	JSN& OP	Yes	Yes	No	Yes	Yes	Low IGF-1 P<0.001	43%
Hochberg, 1994 (33)	187	Case-control	Baltimore Longitudinal Study of Aging 59 knee OA 128 healthy controls	♀ 38% ♂ 62%	♀ 54 ± 18 ♂ 56 ± 17	-	KL	-	-	Yes	NA	No	No	No	NS	64%
Fernihough, 1996 (37)	27	Case-control	16 knee OA 11 healthy controls	♀ 44% ♂ 56%	µ69	-	ACR criteria	-	-	No	No	No	No	No	NS	29%
Lloyd, 1996 (31)	761	Case-control	Chingford study, 606 patients with OA at different locations 155 healthy controls	♀ 100%	54.2 ± 6	KL	KL	KL	-	Yes	NA	No	Yes	No	High IGF-1 & DIP P=0.006, knee P<0.001	79%
Fraenkel, 1998 (38)	423	Nested case-control	Framingham OA Study 202 knee OA 221 healthy controls	♀ 66% ♂ 34%	µ69.9	-	KL	-	-	Yes	Yes	Yes	Yes	Yes	NS ♀ OR 0.9 (0.6-1.7) ♂ OR 1.2 (0.6-2.6)	71%
Jubb, 1998 (40)	162	Case-control	74 polyarticular OA 37 knee OA 61 healthy controls	♀ 100%	NA	-	Not specified	-	Not specified	Yes	NA	No	No	No	NS	14%

OA=osteoarthritis. IGF1=insulin-like growth factor1. ROA=radiological osteoarthritis. ACR criteria=American College of Rheumatology criteria. KL=Kellgren&Lawrence. OP=osteophytosis. JSN=joint space narrowing. SCL=sclerosis. DIP=distal interphalangeal. PIP=proximal interphalangeal. CMC=carpometacarpal. NA=not applicable, NS=not significant. µ=mean. TFJ=tibiofemoral joints. PFJ=patellofemoral joint. N=number of studied patients. – =not assessed.

Table 3b. Study characteristics of genetic association studies.

Author, year (ref.)	N	Study design	Population	Sex	Age (years, mean±SD)	BMI (kg/m2, mean ±SD)
Meulenbelt, 1998 (26)	785	Cross-sectional	Rotterdam Study 651 OA cases 135 healthy controls	♀ 60% ♂ 40%	55-65	ROA+ 26.6±3.7 ROA- 25.1±3.1
Zhai, 2004 (28)	1575	Cross-sectional	Rotterdam Study 1355 OA cases 191 healthy controls	♀ 59% ♂ 41%	55-70	ROA+ 26.5±3.7 ROA- 25.0±3.3
Urano, 2008 (27)	434	Cross-sectional	Japanese population-based study 342 cases with disc narrowing	♀ 100%	66.5 ± 8.4	CC 22.3±2.8 GC 21.8±3.0 GG 22.6±3.2

Genetic test	Assessment ROA				Adjustments			Results on IGF-1 & ROA	Quality score
	Hand	Knee	Spine	Hip	Age	Sex	BMI		
IGF-1 gene promoter polymorphisms Allele 1-9 (A1-A9)	KL	KL	KL	KL	Yes	Yes	Yes	A3 at IGF-1 locus associated with ROA at any joint site. OR 1.9 (1.2-3.1)	82%
IGF-1 gene promoter polymorphism: absence of 192bp allele	KL	KL	KL	KL	Yes	Yes	Yes	Positive association, only in a subgroup≤65yr (p=0.03), allele-dose effect. OR 1.9 (1.1-3.3) for homozygotes	82%
C>G SNP (rs11247361) IGF-1R gene at intron1	NA	NA	OP, SCL, DN	NA	Yes	NA	No	Positive association (p=0.0033), mostly with disc narrowing. (OR 2.0, 1.3-3.3)	64%

Table 4. Methodological quality scores of the studies, according to study type.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Individual score	Total obtainable	Total score
Longitudinal (nested case-control)																	
Fraenkel, 1998	0	1	1	0	0	1	1	1	1	1	1	0	1	1	10	14	71%
Case-control																	
Lloyd, 1996	1	1	1	0	0	1	1	1	1	1	1	1	1	0	11	14	79%
McAlindon, 1993	0	1	1	0	0	1	1	0	1	1	1	1	1	0	9	14	64%
Hochberg, 1994	0	1	1	0	0	1	1	1	0	1	1	1	1	0	9	14	64%
Hochberg, 1993	0	1	1	0	0	0	1	1	0	1	1	1	1	0	8	14	57%
Denko, 1994	1	1	0	0	0	1	1	0	0	0	1	0	1	0	6	14	43%
Fernihough, 1996	0	0	0	0	0	1	1	0	0	0	1	0	1	0	4	14	29%
Jubb, 1998	0	0	0	0	0	1	1	0	0	0	0	0	0	0	2	14	14%
Cross-sectional																	
Meulenbelt, 1998	1	1	NA	0	NA	1	1	1	0	1	NA	1	1	1	9	11	82%
Zhai, 2004	1	1	NA	0	NA	1	1	1	0	1	NA	1	1	1	9	11	82%
Urano, 2008	0	1	NA	0	NA	1	1	1	0	1	NA	1	1	0	7	11	64%

Table 4: Each item was scored 1 if it met the methodological criteria listed in Table 1, if not or otherwise not described, a score of 0 was assigned. Positive scores were summed to give an overall internal validity score. NA=not applicable.

OA=osteoarthritis. SNP=single nucleotide polymorphism. IGF-1=insulin-like growth factor ERGO=Erasmus Rotterdam Gezondheid Ouderen. ROA=radiological osteoarthritis. PSM=postmenopausal. μ=mean. KL=Kellgren&Lawrence. PMS=postmenopausal. OP=osteophytosis. SCL, sclerosis. DN, disc narrowing. NS=not significant. NA=not applicable. N=number of studied patients. CC=wildtypes. GC=heterozygotes. GG=homozygotes.

DISCUSSION

A relationship between IGF-1 and radiographic primary OA is suggested from *in vitro* and anecdotal evidence, but is infrequently studied in observational studies. This is the first systematic review that summarizes current data on the relation between radiographic OA and either serum IGF-1 levels or IGF-1 gene polymorphisms, taking into account important factors influencing IGF-1 concentration, such as age, sex and BMI. Using strictly defined criteria, a total of only eight studies were included that studied serum IGF-1 in relation to radiographic OA. Based on these studies, we can conclude that there is moderate evidence for no association between serum IGF-1 and radiographic OA, although there is moderate evidence for a positive relationship between IGF-1 gene polymorphisms and radiographic OA.

Only the HQ study of Lloyd *et al.* showed high serum IGF-1 to be related with radiographic knee and hand OA, especially in bilateral and more severe knee OA (31). Fraenkel *et al.* reported a trend for higher serum IGF-1 levels in men with bilateral knee OA, although non-significant. In contrast, Denko *et al.* found low IGF-1 levels to be associated with general radiographic OA (39)**;** however, this study was ranked as low methodological quality. The remaining six studies (three HQ, three LQ) showed no significant relationship.

We were able to include three HQ studies (26-28) on genetic polymorphisms in the GH/IGF-1 pathway in relation to radiographic OA. All three showed associations between IGF-1 gene polymorphisms and OA, in accordance with the hypothesis that genetic variations in the GH/IGF-1 system may be involved in OA pathogenesis. The SNP in the IGF-1 gene promotor region studied in Zhai *et al.*, was earlier found to be associated with lower IGF-1 levels and lower body height, suggesting that chronic low IGF-1 levels play a role in the pathophysiology of primary OA (41). However, the exact role of the IGF-1 polymorphism in the GH/IGF-1 pathway has not yet been elucidated. The other SNPs (26,27) were not studied in relation to circulating IGF-1 levels. Furthermore, we have to take into account interactions between polymorphisms. Zhai *et al.* studied the interaction with a collagen type II A1 (COL2A1) polymorphism, which is associated with an extreme OA phenotype (29). Highest OA prevalence was found in individuals with both IGF-1 and COL2A1 risk phenotype, suggesting that the IGF-1 effect occurs in interaction with the COL2A1 gene (28).

Our review may suffer from several limitations. Firstly, the review is based mainly on cross-sectional data and therefore the strength of evidence is limited by the quality of the available studies. Unfortunately, only one longitudinal study (nested case-control study) (38), investigated OA incidence in relation to serum IGF-1. There was an additional longitudinal study (44) on IGF-1 and radiographic OA, though this study focuses on OA progression and was therefore excluded. In this 12-year follow-up study, Schouten *et al.* found high serum IGF-1 levels to be a risk factor for knee OA progression, especially of osteophytosis, independently of age, sex and BMI. Because the progression data could underline findings on prevalent and incident OA, more research is needed on the relationship between serum IGF-1 and primary OA progression. Secondly, we cannot rule out publication bias, especially in the genetic field, which can be explained by a selection of positive studies for publication. Thirdly, small study sizes may influence the findings, especially since the IGF-1 concentration is affected by many factors that also influence OA risk. Finally, there is a possibility of misclassification of OA by inclusion of conventional radiographs only, which may contribute to not finding a consistent association between IGF-1 and radiographic OA. Magnetic resonance imaging (MRI) may give additional information to plain films**,** however at this moment no MRI studies have investigated the relationship between IGF-1 and OA.

Several sources of between-study heterogeneity can be identified. First of all, the study design can lead to heterogeneity. Secondly, assessing the role of IGF-1 in OA by serum samples is very complex, because individual IGF-1 levels are liable to temporal variations. Furthermore, IGF-1 levels are inversely correlated to age, estrogen levels and BMI (9,42,43), so adjustments for these factors are essential for interpretation of IGF-1 levels. Most studies corrected for age and sex, however, only three adjusted for BMI. In addition, RIAs for measuring serum IGF-1 are subject to analytical difficulty. This means that large sample sizes are required for demonstrating an IGF-1 effect on radiographic OA at population level; unfortunately, only the study of Lloyd *et al.* (31) reported a large sample size (N=761). Another remaining problem is OA case definition. For epidemiological studies, there is general consensus that radiological features are the preferred method. However, the included studies used different scoring methods (KL, Ahlback, ACR criteria) at different joint sites.

Because of heterogeneity of several study aspects, no meta-analysis could be performed. We provided an alternative by performing a best-evidence synthesis and methodological quality assessment, although no

generally accepted criteria set exists for methodological quality assessment in observational studies and for performing a best-evidence synthesis. Lievense *et al.* presented a reproducible criteria list for methodological quality assessment, which we modified to cover our review topic (36). The use of quality scores could be a technical limitation of our review at the same time, because using different criteria sets could result possibly in different interpretation of our results. According to our criteria set (*Tables 3a&3b*), four of the eight studies on serum IGF-1 and all three genetic association studies were considered as HQ studies.

Knowledge of the association between serum IGF-1 levels and radiographic OA is very important, because this could increase our understanding of the pathogenesis of OA, which subsequently could lead to development of new treatment options.

An important question that needs further research is whether circulating total IGF-1 levels truly reflect tissue concentrations. Preliminary data indicate that measuring free unbound IGF-1 levels and IGF-1 bioactivity better reflect GH/IGF-1 status than serum total IGF-1 (45-47). Free IGF-1 is the major biologically active form of IGF-1; however, because of methodological difficulties in measurement, total serum IGF-1 is often used to assess GH/IGF-1 axis activity (45). This could possibly explain not finding a consistent effect of total IGF-1 on radiographic OA.

In conclusion, *in vitro* studies, genetic association studies and the high secondary risk in pathological IGF-1 states suggest all an effect of the GH/IGF-1 system in OA development. Although the largest cross-sectional study (31) and the longitudinal study on OA progression (44) found a positive association with high serum IGF-1, inconsistent results were shown in studies on serum IGF-1 and radiographic OA. This systematic review concludes that there is moderate evidence that IGF-1 is no risk factor for primary radiographic OA. Since we cannot exclude that methodology, publication bias and small sample size of the available studies have influenced the results, we suggest that future well-designed large prospective studies are needed to strengthen the evidence for the role of IGF-1 in primary OA.

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