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RISK FACTORS FOR PROGRESSION IN HAND OSTEOARTHRITIS: A SYSTEMATIC REVIEW

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ABSTRACT

Objective

To assess the risk factors for progression of hand osteoarthritis (OA).

Methods

In a systematic review of cohort studies, medical literature databases were searched up to May 2012 for articles reporting data on the association between risk factors and hand OA progression. The quality of these studies was assessed by 2 independent reviewers using a criteria scoring system of 16 items, and studies were dichotomized into those with scores of 69% or over. Best evidence synthesis was used to determine the level of evidence per risk factor.

Results

In total, 14 articles that fulfilled the selection criteria were included, of which 8 were of high quality. The most frequently investigated risk factors were age, sex, radiographic features (e.g. erosive OA) and scintigraphy. Progression was mostly defined by radiographic criteria, but also clinical progression as an outcome was described. Most of the investigated factors showed limited or inconclusive evidence for an association with hand OA progression. Limited evidence according to the best evidence synthesis with most available studies was present for the association between a positive scintigraphic scan and radiographic progression (up to 2.8 times more progression than negative joints).

Conclusion

Limited evidence is available for a positive association between an abnormal scintigraphic scans and radiographic hand OA progression. These data suggest that a positive scintigraphy as an inclusion criteria for studies that aim to show structural modification can increase the power of such studies. Future longitudinal studies with a well-defined baseline population are needed to search for risk factors of hand OA progression.

SIGNIFICANCE AND INNOVATION

- This study reports on risk factors contributing to progression of hand OA, since the available evidence was not summarized systematically before.

- Limited evidence according to the best evidence synthesis with most available studies was present for a positive association between an abnormal scintigraphic scans and radiographic hand OA progression. These data suggest that a positive scintigraphy as an inclusion criteria for studies that aim to show structural modification can increase the power of such studies.

- This systematic review is of importance since it gives insight in what risk factors for hand OA progression are already been investigated. Future high-quality studies on risk factors for hand OA progression, especially clinical progression, are needed to determine modifiable factors in symptomatic patients.

INTRODUCTION

Hand osteoarthritis (OA) is a prevalent heterogeneous disorder, which can lead to considerable clinical burden and impact on health-related quality of life[1,2]. Over time the disorder is slowly progressive, although in some patients the progression can be rapid[3,4]. Several risk factors for the development of hand OA have been reported[5]. However, data about risk factors for the disease course in hand OA are scarce and concern mostly radiographic progression. Moreover, the data are controversial, since definitions for progression[6,7], the follow-up time, as well as source populations[8,9] differ. An explanation for the lack of data could be the time and costs investments. Research of the disease course of hand OA is further complicated by the combined assessment of development and progression of hand OA in longitudinal studies, which report on risk factors for progression of hand OA in persons with and without hand OA at baseline and therefore combine progressive and incident hand OA[8-14]. In the latter situation it is not possible to study risk factors for progression of hand OA.

The recognition of potential risk factors for progression of hand OA can be beneficial. When risk factors allow the identification of patients at high-risk for progression, these patients can be included in interventional studies for disease modifying drugs for OA. Given the opinion of the regulatory agencies that delay in structural progression can be a claim for OA modifying drugs[15], it would be especially important when modifiable risk factors could be recognized, since this could have consequences for therapy. Finally, the recognition of risk factors for progression could increase our understanding of the underlying pathophysiology of hand OA.

We performed a systematic review including studies reporting on risk factors contributing to hand OA progression, since the available evidence was not summarized systematically before.

MATERIALS AND METHODS

Identification of studies

Longitudinal studies with baseline determinants that were studied in relation with progression of hand OA were searched with a medical librarian (JP) in medical literature databases (Pubmed, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL)) up to May 2012 (see supplementary file S1 for exact search strings). Thesaurus terms and free text for the concepts 'hand', 'osteoarthritis', and 'progression' were used. Additional articles (lateral references) were searched in the reference lists of identified articles.

Inclusion and exclusion criteria

Selection of titles, abstracts and articles was performed independently by two reviewers (WYK and MK). In case of disagreement a consensus was agreed after discussion. First all retrieved titles were screened, subsequently selected abstracts were retrieved for detailed review and finally full-text articles of the remained references were read.

Studies were included if they fulfilled the following criteria: 1. patients with clinical or radiographic hand OA, 2. baseline determinants were studied in relation to radiographic or clinical progression of hand OA, 3. follow-up duration of at least one year, 4. study design was a cohort study in which determinants were measured at baseline .

Animal studies, studies with patients < 18 years, reviews, abstracts, letters to the editor, case reports, case series, cross-sectional studies and studies reporting on other musculoskeletal diseases than hand OA and studies in other languages besides English and Dutch were excluded. If determinants for progression were investigated in the placebo group of intervention studies, these studies were included. None of the final selected publications were in Dutch.

Data extraction

Standardized forms were used by both reviewers independently to extract information about the following data: 1. study population (population size, patient characteristics, setting and time period of the study, age, gender), 2. follow-up time and participation rate of persons who completed the follow-up time of the study (at least 1 year follow-up and 80% participation rate), type of risk factor as determinant (distribution, mean), 4. outcome (methods of hand OA assessment and progression, blinding, reproducibility) and 5. effect measures and outcomes (relative risk/ratio (RR) or odds ratio (OR)).

Assessment of study quality

The quality of the studies was evaluated by both reviewers independently using 19 criteria based on previous systematic reviews in prognostic factors in the field of musculoskeletal disorders[16-19]. The criteria were adapted to evaluate studies on the association between risk factor and hand OA progression (supplementary file S2). When a criterion was fulfilled in the article, a '1' was given to indicate that the criterion was present; otherwise, a '0' was given to indicate that the criterion was absent. A'0' was also given when no information about the specific criterion was mentioned in the article. Any differences were solved by discussion. A maximum quality score of 16 could be given for cohort studies and 17 for nested case-control studies, and were based on methodological criteria, such as the definition of study population, selection bias, description of the follow-up, assessments of risk factors and the outcome and its analysis. The total quality scores per study were calculated as percentage of the maximum score. The reliability of the criteria list was measured with the Cronbach's α (reflecting the internal consistency of the criteria list, based on the 16 criteria used for the included studies), which was 0.83.

Rating level of evidence

Since the studies in this systematic review were heterogeneous and often reported no effect sizes, a pooled effect estimate could not be calculated. Therefore, evidence was summarized using the best-evidence synthesis based on the guidelines on systematic review of the Cochrane Collaboration Back Review Group[20], which is a method to summarize evidence in observational studies if the study population, assessment

of exposure and outcomes and data analyses are heterogenic. It has five levels of evidence (Table 1) and more weight is given to studies with a cohort design where exposure truly precedes outcomes. The next preferred design is the nested case-control. A study was considered to be of high quality if the total quality score was ≥69% (which is the median of the quality scores).

Table 1: Best-evidence synthesis used in this review[20].

Strong	Consistent findings (≥ 80%) in at least 2 high-quality cohorts
Moderate	One high-quality cohort and consistent findings (≥ 80%) in one or more low-quality cohorts
Limited	Findings of one cohort or consistent findings in one or more low-quality cohorts
Inconclusive	Inconsistent findings irrespective of study quality
No evidence	No study could be found

RESULTS

Selection and inclusion of studies

After removing duplicate references, 2695 unique references were identified for screening (Figure 1). Detailed reviews of abstracts led to 17 relevant full-text articles for selection (all in English)[3,4,21-35]. Of these 17 articles, 3 were excluded, since they were almost similar publications on the same study[25,27,28]. Three publications of Buckland-Wright[25-27] are regarded as one study and 2 publications of Macfarlane and Buckland-Wright[28,32] are regarded as one study from this point forward. In total 14 articles were used for further analyses. No nested-case control studies were retrieved.

Methodological quality of articles

The two reviewers scored 224 items in total and agreed on 207 items (92%, Table 2), with an intraclass correlation coefficient (ICC) for interobserver agreement of 0.92 (95%CI 0.67-0.98). The 18 disagreements were resolved in consensus. The most common reasons for the disagreement were whether the selection of the study subjects were clear and the studied risk factors were presented correctly. Eight of the 14 articles were of high quality (quality score ≥69%).The mean quality score of all articles was 72% (median: 69%, range 31-100%).

The source population in some studies was not clearly described[25-28,30,32]. The participation rates in four articles not available[22,30-32]. Information on withdrawals and completers was seldom given[24]. No or inappropriate report of outcome measures was the case in some studies, leading to lower quality scores of articles[25-30,32].

Study characteristics

The characteristics of the included articles are shown in Table 3. One study included men only[31], all other studies contained more women than men. Most study patients were middle-aged (> 50 years), except for one population-based study[31]. Hand OA was determined

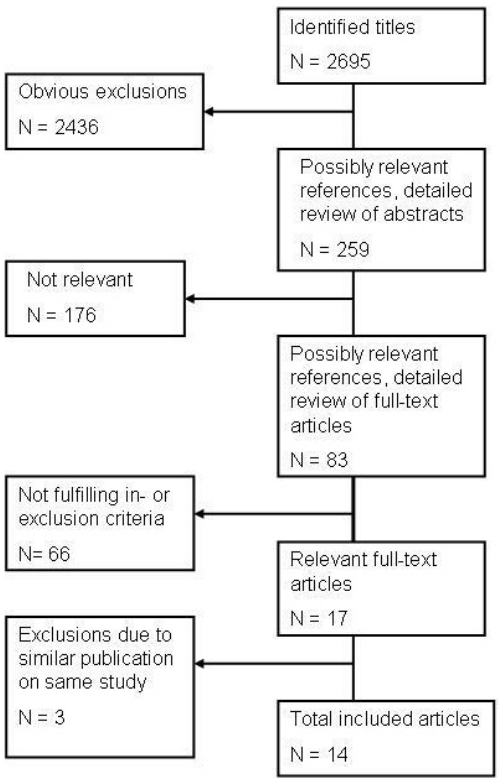

Figure 1: Results of literature search.

by radiographic criteria in 13 studies[3,4,21-23,25-35]. The most frequently used radiographic criteria were the Kellgren-Lawrence (KL) criteria[36]. One study used only clinical criteria of the American College of Rheumatology (ACR) for hand OA[24]. Six articles combined clinical with radiographic criteria for the definition of hand OA[3,4,22,23,30,33]. Five studies used the ACR criteria for hand OA as clinical definition for hand OA at baseline[3,4,22-24].

In almost all studies, progression was defined as radiographic progression (e.g. following the KL or OARSI scoring[37]), whereas in two studies clinical progression was also investigated[3,33]. Radiographic progression of erosive OA (EOA) specifically was investigated in one study[23]. A definition of clinical progression only as outcome was used in one study[21]. The median follow-up time of the included studies was 4 years (range 1-21.8 years).

Association between risk factors and progression

An overview of the investigated determinants and their relationship to radiographic and/or clinical progression of hand OA is shown in Table 3 and summarized below. If negative and positive findings were available in one article, only positive findings were reported in Table 3. Of the 14 included articles, 8 were of good/high quality[3,4,21,23,24,31,34,35]. Table 4 shows the overall level of evidence stratified for determinant and outcome.

Table 2: Results of the study quality assessment scores in chronological order (1: present, 0: absent or no information). Scores solved by discussion are in ***italics***.

Cohort Studies	Criteria																Qual.score
	1	2	3	5	6	7	8	9	10	12	13	14	16	17	18	19	
Hutton[30]	0	0	0	1	1	0	0	0	1	0	0	0	***1***	***1***	0	0	5/16=31%
Kallman[31]	0	0	***1***	1	1	0	0	1	1	1	1	***1***	0	1	1	1	11/16=69%
Buckland-Wright[25-27]	0	***1***	1	1	1	0	0	1	0	1	0	1	***1***	***1***	0	0	9/16=56%
Macfarlane[32], Buckland-Wright[28]	0	***1***	1	1	1	0	0	0	0	***1***	0	***1***	1	1	0	0	8/16=50%
Harris[29]	1	***0***	0	1	1	0	0	1	0	1	0	1	0	1	0	0	7/16=44%
Balblanc[22]	1	1	1	1	1	0	0	0	1	0	1	1	1	1	0	0	10/16= 63%
Olejárová[33]	***1***	1	***1***	1	1	***1***	0	0	0	1	1	0	***1***	1	0	0	10/16=63%
Allen[21]	0	1	1	1	1	0	0	1	1	***1***	***0***	0	1	1	1	1	11/16=69%
Botha-Scheepers[4]	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	15/16=94%
Botha-Scheepers[24]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	16/16=100%
Bijsterbosch[3]	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	15/16 = 94%
Bijsterbosch[23]	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	14/16=88%
Yusuf[35]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	15/16= 94%
Güler-Yüksel[34]	1	1	1	1	1	1	1	1	***0***	1	1	1	1	1	1	1	15/16= 94%

Criteria 4, 11 and 15 were not applicable since no nested-case controls studies were selected for this systematic review. Quality scores in bold are high-quality studies.
The intraclass correlation coefficient (ICC) for interobserver agreement is 0.92 (95%CI 0.67-0.98), based on 224 items.

Scintigraphy

All 4 studies investigating a positive (abnormal) scintigraphic scan (all using 99-Technetium as isotope) as determinant for radiographic progression (table 3)[22,28,30,32,33], reported a positive association. One study also reported a positive association with clinical progression[33]. Limited evidence, based on consistent associations found in four low-quality studies, was present for the positive association of an abnormal scintigraphic scan with radiographic progression (table 4)[22,28,30,32,33]. The reported effect sizes varied from 21%-44% progression in positive joints versus 6.6%-10% progression in negative joints[30,33], to a 2.8 times progression in positive joints compared to negative joints[22].

Age

Age was investigated in four studies as a risk factor for radiographic progression[4,25-27,29,31]. The determinant was analyzed by different methods, from a continuous measurement[25-27,29], to several age categories[31] or dichotomized into two age groups[4]. One study showed a positive association for older age (RR 1.05 (1.03-1.07) with joint space narrowing (JSN) and osteophyte (OST) progression combined)[31], whereas one study showed a negative association for older age (patients aged between 40-59

years versus patients aged ≥60 years for OST progression (adjusted RR 1.9 (1.0-3.2)[4]. In two studies[25-27,29], age showed no association. The level of evidence of age as risk factor for hand OA progression is inconclusive[4,25-27,29,31].

Female sex

One high-quality study showed a positive association for female sex with radiographic progression (adjusted RR 2.9 (1.0-6.4))[4], whereas a low-quality study showed no association[29]. One study suggested that women were more likely than men to report worsening of symptoms over time (clinical progression)[21]. Hence, inconclusive evidence for an association between female sex and radiographic progression[4,29] exists, while limited evidence is available for a positive association with clinical progression[21].

Affected OA group

One high-quality study reported on the association of lower global assessment scores with AUSCAN (Australian/Canadian Osteoarthritis Hand Index)[38] changes in PIP and CMC OA ($p<0.05$). This means that clinical progression of hand OA in PIPJs or 1st CMCJs was associated with an increase of AUSCAN scores[21]. However, this study did not report the association of clinical progression and AUSCAN changes in DIP OA.

One low-quality study reported on an increase of radiographic hand OA (defined as KL-score ≥ 2) in 188/85 DIPJs/PIPJs with OA at baseline to 282/168 DIPJs/PIPJs with OA after 10-year follow-up[29]. The evidence of an affected OA group with radiographic or clinical progression is limited.

Number of OA joints

The number of affected OA joints (KL grade ≥2) at baseline was associated with lower grip and pinch grip strength after 4 years[21] in one high-quality study, demonstrating limited evidence for a positive association between the number of OA joints and clinical progression[21].

Painful joints

One article showed a positive association between the number of painful joints (patient level, in tertiles, by Doyle index[39]) and radiographic and clinical progression (adjusted risk ratios (RRs) (95%CI) 1.63 (1.19-2.00) and 2.39 (1.47-3.37), respectively)[3]. Pain intensity (joint level, in tertiles, by Doyle index) was also positively associated with radiographic progression (adjusted RR 1.7 (1.18-2.19)), whereas it has no effect on clinical progression[3]. Pain on pressure (joint level, yes vs. no) is associated with erosive evolution (adjusted odds ratio (OR) 2.2 (1.4-3.4))[23]. The level of evidence for a positive association of painful joints (presence, intensity and number) with radiographic and clinical progression is limited, since these patients were part of one high-quality study[3,23].

Hand OA subsets

EOA, defined by Verbruggen-Veys scoring method[40], is investigated as risk factor for radiographic and clinical progression over 6 years[3]. EOA was positively associated

Table 3: Study characteristics of the reviewed manuscripts, in chronological order.

First author, year of publication	Source population, no. of patients at FU (% women), mean follow-up (years), mean age (years)	Definition HOA for inclusion	Definition of HOA progression	Determinant	Outcome/ results (95%CI)
Hutton[30], 1986	Unclear, **14** (**86**), *3-5*, 62	'Typical clinical and radiographic features of generalized nodal OA'	Radiographic (method not reported)	Scintigraphic scan	'44% of scan positive joints showed progression compared with 10% of scan negative joints (p<0.001)'
Kallman[31], 1990	General population, (Baltimore Longitudinal Study of Aging, BLSA), **177** (**0**), *21.8*, 49.3	Radiographic (KL grade ≥ 1)	Radiographic (KL or Kallman-score)	Age	Progression per grade increase KL: RR 1.04 (95% CI 1.02-1.07) OST: 1.06 (0.96-1.15) JSN: 1.01 (0.97-1.05) JSN/OST: 1.05 (1.03-1.07)
Buckland-Wright[25-27], 1990, 1991	Unclear, **32** (**91**), *1.5*, 62	Radiographic (≥2 features: OST, JSN, subchondral sclerosis)	Radiographic (change in JSN or subchondral cortical thickness) on quantitative microfocal radiography	Age, subchondral cortical thickness	No difference
Macfarlane[32], 1991, Buckland-Wright[28], 1995	Unclear, **32** (**91**), *1*, 62	Radiographic (≥2 features: OST, JSN, subchondral sclerosis)	Radiographic (change in OST length or area (mm^2), or OST no.) on quantitative microfocal radiography	Change in scintigraphic scan over 12 months	Increased or positive bone scan: mean change in area 0.51 (SD 2.91), versus decreased or negative bone scan: mean change 0.08 (1.32) (p:< 0.005)
Harris[29], 1994	Secondary care, **59** (**76**), *10*, 69	Radiographic (unclear)	Radiographic (KL or Kallman score)	Age, sex, BMI, knee OA, knee OA progression, affected OA joints in PIP/DIP sites	No difference, except 'weak' correlation (p= 0.059) for affected OA joints in PIP/DIP sites
Balblanc[22], 1995	Unclear, **15** (**93**), *4*, 59	Clinical, radiographic (ACR criteria)	Radiographic	Scintigraphic scan	'The mean increase in the radiographic progression was 2.81 times greater in positive than in negative joints (p<0.002).'

Table 3: *Continued*

First author, year of publication	Source population, no. of patients at FU (% women), mean follow-up (years), mean age (years)	Definition HOA for inclusion	Definition of HOA progression	Determinant	Outcome/ results (95%CI)
Olejárová[33], 2000	Secondary care, **45** (**88**), *2*, 67.0	Radiographic and clinical (KL ≥ 2, symptoms on most days during last month)	Radiographic (Kallman score), Clinical (sum of joint tenderness scores)	Scintigraphic scan	Radiographic/clinical progression in positive joints: 21.0%/21.2% vs. in negative joints: 6.6%/13.7% (both p: <0.001)
Allen[21], 2006	Familial hand OA, (GOGO study), **426** (**80**), *4.1*, 67.7	Structural and radiographic (bony enlargements, KL ≥ 2)	Clinical (change in AUSCAN, (pinch) grip strength)	Global assessment of change	Adj. β* (p-value) AUSCAN, right/left hand: 0.29 (<0.001)/ 0.24 (<0.001) Adjusted β**(p-value): Grip strength (right/left hand): -0.16 (0.003)/-0.13 (0.015) Pinch grip (right/left hand):-0.13 (0.022)/-0.11 (0.060)
Botha-Scheepers et al.[4], 2008	Familial OA, recruited from primary and secondary care (GARP Study), **172** (**79**), *2*, 59.7	Clinical, structural and radiographic (ACR criteria, bony swellings, KL ≥ 2)	Radiographic (OARSI)	Post-menopausal stage, age, sex, self-rep. pain and function	Adj. RR† (95%CI) - JSN progression: Early post-menopausal stage: 3.2 (1.1-6.6) - OST progression: Younger age: 1.9 (1.0-3.2) Female sex: 2.9 (1.0-6.4) Early post-menopausal stage: 2.6 (1.0-4.6) Self-reported pain/function not associated

Table 3: *Continued*

First author, year of publication	Source population, no. of patients at FU (% women), mean follow-up (years), mean age (years)	Definition HOA for inclusion	Definition of HOA progression	Determinant	Outcome/ results (95%CI)
Botha-Scheepers et al.[24], 2007	GARP, **154** (**80**), *2*, 60.4	Clinical (ACR criteria)	Radiographic (OARSI)	Concordance between siblings	Adj. OR†† (95%CI) JSN progression: 1.3 (0.4-4.0) OST progression: 1.2 (0.4-3.8)
Bijsterbosch, et al[3], 2010	GARP, **289** (**83**), *6.1*, 59.5	Clinical, radiographic (KL ≥ 2, ACR criteria)	Radiographic and clinical (OARSI, AUSCAN pain and function)	Self-rep. pain and function, no. of painful joints, pain intensity, no. of nodes, OST, JSN, erosive OA, nodal OA, thumb base OA	Adj. RRs # (95%CI) for clinical progression in pain/function in highest tertile Self-rep. pain: 5.74 (4.38-6.65)/3.56 (1.63-5.83) Self-rep. function: 2.57 (1.26-4.13)/6.88 (5.30-7.90) No. of painful joints: 2.11 (1.25-3.08)/2.39 (1.47-3.37) Adj. RRs ## for radiographic progression in highest tertile: Self-rep. pain:1.62 (1.14-2.02) Pain intensity: 1.70 (1.18-2.19) No. of nodes: 1.84 (1.19-2.48) Osteophytes: 1.86 (1.38-2.21) JSN: 1.24 (0.82-1.63) Erosive OA: 1.55 (1.04-1.8) Nodal OA: 1.94 (1.37-2.48) Thumb base OA: 1.16 (0.91-1.36)

Table 3: *Continued*

First author, year of publication	Source population, no. of patients at FU (% women), mean follow-up (years), mean age (years)	Definition HOA for inclusion	Definition of HOA progression	Determinant	Outcome/ results (95%CI)
Bijsterbosch et al[23], 2010	GARP, **236 (83)**, *6.1*, 58.9	Clinical, radiographic (KL ≥ 2, ACR criteria)	Radiographic (Verbruggen-Veys)	Concordance between sibling, erosive joints, self-rep. pain/ stiffness, pain on pressure, nodes, limited motion, JSN, OST, AUSCAN	Adj. †† OR (95%CI) for erosive evolution: Concordance between sibling: 6.2 (1.4-27.5) Adj. OR§ for erosive evolution: Self-rep. pain: 2.8 (1.7-4.7) Self-rep. stiffness: 2.3 (1.3-4.0) Pain on pressure: 2.2 (1.4-3.4) Nodes: 2.7 (1.7-4.5) Limited motion: 2.6 (1.2-5.4) JSN 9.8: (5.7-16.6) Osteophytes: 0.7 (0.3-2.0) AUSCAN: 1.07 (1.02-1.12)
Yusuf et al[35], 2011	GARP, **164 (81)**, *6*, 60	Radiographic (KL ≥ 2)	Radiographic (OARSI)	Adiponectin, leptin, resistin	Adjusted RR†† for hand OA progression: Adiponectin level 16.6-28.4 μg/ml: 0.3 (0.2-0.7) Adiponectin level > 28.4 μg/ml: 0.3 (0.2-0.7)
Güler-Yüksel[34], 2011	GARP, **181 (80)**, *2*, 60	Radiographic (KL ≥ 2)	Radiographic (OARSI)	Accelerated metacarpal bone mineral density (BMD)	Adjusted RR§§ for progressive hand OA: Accelerated BMD loss (> 3 mg/cm^2/year): 2.1 (1.1-4.3)

*= adjusted for age, number of joints with OA and time between assessments; **= adjusted for age, sex, time between assessments; †= adjusted for age, sex and familial effects; ††= adjusted for age, sex, BMI; #= adjusted for age, sex, clinical outcome measure, follow-up time and family effects; ## = adjusted for age, sex, baseline OST and JSN scores, follow-up time and family effects; § = adjusted for family effects, anatomical phase at baseline; §§ = adjusted for ages, sex, post-menopausal status, BMI, family effect, smoking status, use of hormone replacement therapy, bisphosphonates, calcium and vitamin D supplements, BMD scores at baseline.

Table 4: Overall levels of evidence, stratified for determinant and outcome.

Determinant	No. of studies (total)	Outcome (no. of studies)	No. of all positive studies/no. of high-quality positive studies	Overall evidence radiographic OA	Overall evidence clinical OA
Scintigraphy[22,25-28,30,32,33]	4	Rad. (4)/ Clin. (1)	4/0, 1/0	Limited pos.	Limited pos.
Age[4,25-27,29,31]	4	Rad. (4)	1/1	Inconclusive	-
Sex[4,21,29]	3	Rad. (2)/ Clin. (1)	1/1, 1/1	Inconclusive	Limited pos.
Affected OA group[21,29]	2	Rad.(1)/ Clin. (1)	1/0, 1/1	Limited pos	Limited pos.
No. of OA joints[21]	1	Clin. (1)	1/1	-	Limited pos.
Painful joints (intensity, no.)[3,23]	1	Rad. (1)/ Rad EOA (1)/ Clin. (1)	1/1, 1/1, 1/1	Limited pos./Limited pos.	Limited pos.
Self-reported pain[3,4,23]	1	Rad. (1)/Clin. (1)	1/1, 1/1	Limited pos.	Limited pos.
Self-reported function[3,4,23]	1	Rad. (1)/Clin. (1)	0/0, 1/1	Limited no	Limited pos.
Self-reported stiffness[23]	1	Rad. (1)	0/0	Limited no	-
Limited motion of joint[23]	1	Rad. (1)	0/0	Limited pos.	-
Erosive OA[3,23]	1	Rad. (1)/ Clin. (1)	1/1, 0/0	Limited pos.	Limited no
Nodal OA[3]	1	Rad. (1)/ Clin. (1)	1/1, 0/0	Limited pos.	Limited no
Nodes (no. and presence)[3,23]	1	Rad. (1)/ Rad. EOA (1)/ Clin. (1)	1/1, 1/1, 0/0	Limited pos/Limited no	Limited no
Thumb OA[3]	1	Rad. (1)/ Clin. (1)	0/0, 0/0	Limited no	Limited no
Osteophytes[3,23]	1	Rad. (1)/ Rad. EOA (1)/ Clin. (1)	1/1, 0/0, 0/0	Limited pos./Limited no	Limited no
JSN[3,23]	1	Rad. (1)/ Rad. EOA (1)/ Clin. (1)	0/0, 1/1, 0/0	Limited no/Limited pos.	Limited no
Subchondral cortical thickness[25-27]	1	Rad. (1)	0/0	Limited no	-
Knee OA presence/ progression[29]	1	Rad. (1)/ Rad. (1)	0/0, 0/0	Limited no/ Limited no	-
Family effect[23,24]	1	Rad. (1)/ Rad. EOA (1)	0/0, 1/1	Limited no/ Limited pos.	-
Early menopause[4]	1	Rad. (1)	1/1	Limited pos.	-
BMI[29]	1	Rad. (1)	0/0	Limited no	-
Adiponectin[35]	1	Rad. (1)	1/1	Limited pos.	-
Accelerated BMD loss[34]	1	Rad. (1)	1/1	Limited pos.	-

Reference 3, 4, 23 and 24 were regarded as one study in this table, since the patients originated from the same study population.
BMD = bone mineral density; OA = osteoarthritis; EOA = erosive OA; Rad. = radiographic; Clin. = clinical; JSN = joint space narrowing; BMI = Body Mass Index; Limited no = limited evidence for no association with hand OA progression; Limited pos. = limited evidence for a positive association with hand OA progression; Inconclusive = inconclusive evidence for an association with hand OA progression.

with radiographic progression (adjusted RR 1.55 (1.04-1.88)) and not with clinical progression[3]. If a proband had ≥3 erosive joints, the sibling had higher risk to have radiographic erosive progression (adjusted OR 6.2 (1.4-27.5))[23]. The evidence for the positive association between presence of EOA and radiographic progression is limited.

The presence of nodal OA (presence of Heberden/Bouchard nodes affecting ≥ two rays of either hand) was associated with radiographic progression (adjusted RR 1.94 (1.37-2.48))[3]. A positive association was found between the number of nodes and radiographic progression (adjusted RR 1.84 (1.19-2.48))[3]. A positive association between the presence of nodes and erosive evolution of hand OA was reported (adjusted OR 2.7 (1.7-4.5))[23]. Limited evidence is available that symptomatic thumb base OA (pain/stiffness in 1st CMCJ on most days) is not associated with radiographic or clinical progression[23].

Self-reported pain, function and stiffness, limited motion of the joint

Three high-quality articles (with patients originating from the same study) investigated self-reported pain. Self-reported pain was positively associated with radiographic progression after 6 years in one study[3,23]; one article reported no association for radiographic progression after two years[4]. Also a positive association was found for clinical progression in one article (adjusted RR 3.56 (1.63-5.83))[3]. Limited evidence is available for the association between self-reported pain and radiographic/clinical progression.

In the same three high-quality articles self-reported function was investigated. Limited evidence for a positive effect is available for clinical progression after 6 years (adjusted RR 6.88 (5.30-7.90)[3] and limited evidence for no association is available for radiographic progression after 2 and 6 years[3,4,23].

Self-reported stiffness was not associated with radiographic progression[23]. Limited evidence is available for a positive association between limited motion of the joint with erosive evolution[23].

Radiographic OA features and scores

The presence of osteophytes (highest tertile, by OARSI) was positively associated with radiographic progression (adjusted RR 1.86 (1.38-2.21)), but not with clinical progression after 6 years[3]. No association was seen between an OARSI grade 2-3 osteophyte with erosive evolution on joint level[23]. For an OARSI grade 2-3 JSN, a positive association is found with erosive evolution (adjusted OR 9.8 (5.7-16.6))[23]. Limited evidence is available for the inverse association between the highest tertile of JSN with radiographic and clinical progression[3].

Knee OA at baseline, knee OA progression and subchondral cortical thickness of hand joints are not associated with radiographic hand OA progression[25-27,29].

Family effect

Two articles (with patients originating from the same study) investigated the familial effect as determinant, of which one showed no association between the familial effect and radiographic progression after 2 years (adjusted OR 1.3 (0.4-4.0))[24]. A positive

association was reported for the concordance between probands and siblings for erosive evolution in interphalangeal joints after 6 years (adjusted OR 4.7 (1.4-15.8))[23]. There is limited evidence that familial effect does not contribute to radiographic hand OA progression[24] and limited evidence for a positive association with erosive evolution[23].

Hormonal factors (menopause, adiponectin, leptin, resistin) and Body Mass Index (BMI)

Menopause was investigated in one study, showing a positive association for women in an early post-menopausal stage (≤ 10 years) with radiographic progression (adjusted RR 3.2 (1.1-6.6) for JSN progression)[4].

One high-quality study showed that higher levels of adiponectin in serum was associated with a lower risk of hand OA progression after 6 years[35], whereas no association was found for leptin and resistin in the same study[35]. BMI (as continuous measurement) showed no association with radiographic progression[29]. The evidence is limited for these factors since these findings were reported in one single study [4,29,35].

Bone mineral density (BMD) loss

One high-quality article reported that accelerated metacarpal BMD loss, defined as > 3mg/cm^2/year, was positively associated with radiographic hand OA progression after 2 years (adjusted RR 2.1 (1.1-4.3))[34].

DISCUSSION

To our knowledge, this is the first systematic review that summarizes determinants for radiographic and clinical progression in hand OA. Limited evidence in four studies is available for scintigraphy as risk factor for radiographic progression in hand OA. Other baseline factors (e.g. number of painful joints, EOA) show limited evidence for positive association. Factors as age and sex show conflicting evidence in their association with hand OA progression. This study suggests that a positive scintigraphic test could be used to study the progression of pain and function as well as study structural progression in hand OA.

The strength of this systematic review is that pre-defined qualitative levels of evidence were used to summarize the data, by using a set of criteria as proposed in prognostic studies[16,18]. Another strength is that the set of criteria was scored by two independent readers. However, only statistical significances were included in the judgment for a positive or negative association and the sample size of the study was not taken into account. If a small study showed a positive, but statistically not significant association, this information was not incorporated. Most risk factors were only investigated in one or two single studies. Since the studies were heterogeneous and often no effect sizes were given a formal pooling and subsequent meta-analysis was not possible. This could be one of the explanations why some factors (e.g. age, sex) showed inconclusive evidence. Another reason why limited associations with hand OA progression were found is that very few studies investigated the same determinants of interest.

By the strict a priori selection of papers, a relatively large proportion of articles were not considered in the systematic review, although they reported on risk factors for the disease course in hand OA. The most common reason for exclusion was that incident development and progression of hand OA were investigated at the same time during follow up[8-14,41,42], resulting in a heterogenenous case-mix of the study population of interest. The risk factors that are investigated in these types of studies cannot be exclusively associated with progression of hand OA. A 10-year follow-up study showed that radiographic changes over time in incident hand OA (patients who started without OA at baseline and progress to 'new OA') and progressive hand OA (patients with established OA at baseline and progress in their OA over time) occurred most frequently in the DIPJs[8]. The paper was excluded for this review since subjects were selected on prior meniscetomy and not on having hand OA at baseline. Another study showed that the rate of degeneration in PIPJs is much lower than in DIPJs; unfortunately this paper included also normal non-OA subjects at baseline[9]. If these papers would have reported analyses separately for incident and progressive hand OA, additional evidence could be possibly provided for the risk factor 'affected hand OA group'. Other risk factors as running, blood pressure and carotid intima media thickness were also investigated in relation to hand OA progression, but these study populations also contained mixed non-OA and established hand OA cases at baseline[11,13,41].

The limited evidence for a positive association of an abnormal scintigram with radiographic progression is based on four low-quality studies from the 1980s-1990s[22,30,32,33]. In a technetium-scintigram labeling with diphosphonates is used. Uptake of diphosphonates in bone can indicate an increased blood flow representing inflammation, with high sensitivity but low specificity. Higher bone uptake can also indicate new bone formation[43]. In clinical practice for hand OA patients, performance of a scintigram is not an easy method since radiation is used. More recently, imaging modalities such as Magnetic Imaging Resonance (MRI) in hand OA are introduced. MRI is able to visualize features such as bone marrow lesions and synovitis. Comparative studies of scintigraphy and MRI in rheumatoid arthritis showed good correlation between these methods with respect to visualization of inflammatory signs in subchondral bone[44,45]. Studies in sacroilitis showed that MRI could even be more sensitive for subcortical bone marrow edema than scintigraphy[46]. Studies in the future should investigate whether the meaning of MRI is similar to the meaning of scintigraphy in hand OA and could be of value as biomarker for hand OA progression.

Whether age is a risk factor for OA progression is unsure[4,25-27,29,31]. Discrepancies in results between studies can be explained by differences in parameters for age that have been used and in duration of follow-up between studies. Further studies have to be done to elucidate a possible age effect. A female predominance in the development of clinical and radiographic hand OA was previously reported[47].Female sex was not a conclusive risk factor for radiographic hand OA progression[4,29]. The difference in study results could be explained by the difference in follow-up duration and mean age of the study participants; in relatively young women an association with progression was found when compared to men[4], but in relatively older women such an association was not seen. This suggests an interaction between sex and age, which

have to be investigated further. For clinical progression a positive association was found with female sex, which could be explained by the notion that that women may report more often than men about their worsening of symptoms over time[21].

For all other risk factors that were summarized in this review, the conclusion was based on one single study. It gives insight in what is been investigated already, but further research is needed to confirm these associations.

Most studies in this review focused on radiographic progression and not clinical progression, although at the moment no consensus is available how clinical or radiographic hand OA progression should be defined. The results suggest that structural determinants such as nodes, nodal OA, osteophytes and erosions are especially risk factors for radiographic progression, whereas clinical symptoms such as self-reported function is a risk factor for clinical progression. Another remarkable finding is the difference in risk factors for radiographic progression and erosive evolution. These results could reflect difference in underlying processes that play a role in different types of progression. However since the number of studies that investigated these determinants is small, more studies are warranted.

Several limitations can be addressed to this systematic review. Unfortunately, it was not possible to pool the data into a meta-analysis to provide a more precise estimate of the association with the outcome due to heterogeneity of the studied populations and progression. However, the heterogeneity of studies and lack of appropriate effect sizes in this review is a strong argument against a meta-analysis[48]. The results cannot be generalized for the general population, since most studies were hospital-based. Furthermore, studies used different kind of definitions for hand OA progression, since no consensus is available how hand OA progression should be defined. Publication bias could not be assessed for example with a funnel plot[49], since only a few studies reported ORs or RRs. No judgment can be made whether only positive findings are published.

In conclusion, this systematic review revealed that limited evidence is present for scintigraphy at baseline as risk factor for hand OA progression, based on four studies. All other factors showed also limited (mostly based on one paper) or conflicting evidence. Future high-quality studies on risk factors for hand OA progression, especially clinical progression, are needed to replicate these findings and determine modifiable factors in symptomatic patients.

SUPPLEMENTARY MATERIAL

Supplementary file S1: exact search strings used in this systematic review

Exact search string used in Pubmed

(osteoarthritis OR arthritis OR arthrosis OR osteoarthrosis OR osteoarthrit* OR arthriti* OR arthros* OR osteoarthros* OR osteoartrit* OR artriti* OR artros* OR osteoartros*) AND (hand OR hands OR Fingers OR finger OR Thumb OR thumbs OR Metacarpus OR metacarp* OR Wrist OR wrists OR Hand Deformities OR hand joints OR hand bones OR hand injuries) AND ("disease progression"[MeSH Terms] OR progression OR progressive OR prediction OR predictiv* OR prognostic OR prognos* OR precipitate) AND (cohort OR follow up OR followup OR prospective OR retrospective OR case control OR longitudinal)

Exact search string used in EMBASE (OVID)

(Osteoarthritis/ OR exp Arthritis/ OR osteoarthrit* OR osteoartrit* OR arthriti* OR artriti* OR arthros* OR artros* OR osteoarthros* OR osteoartros*) AND (exp hand/ OR finger/ OR finger joint/ OR hand joint/ OR index finger/ OR metacarpophalangeal joint/ OR thumb/ OR wrist/ OR hand*.ti. OR finger* OR thumb OR thumbs OR metacarp* OR wrist*) AND (progression OR progress* OR predictor variable/ OR predict* OR prognosis/ OR prognos* OR precipitation/ OR precipitat*)

Exact search string used in CINAHL

(MH "Osteoarthritis, Wrist" OR MH "osteoarthritis+" OR MH "Arthritis+" OR "osteoarthrosis" OR osteoarthrit* OR arthriti* OR arthros* OR osteoarthros* OR osteoartrit* OR artriti* OR artros* OR osteoartros*) AND (MH "Hand+" OR "hand" OR "hands" OR MH "Fingers+" OR "finger*" OR MH "Thumb" OR "thumb*" OR MH "Carpometacarpal Joints" OR MH "Metacarpophalangeal Joint" OR "metacarp*" OR MH "Wrist" OR "wrist*" OR MH "Wrist Joint" OR MH "Hand Joints+" OR MH "Hand Deformities, Acquired+") AND (MH "Disease Progression" OR "progression" OR "progressive" OR MH "Predictive Research" OR MH "Predictive Validity" OR "prediction" OR "predictiv*" OR MH "Prognosis+" OR "prognos*")

Supplementary file S2: Criteria used for the assessment of methodological quality of included studies

Item	Criteria	Applicable for:
	Definition of study population	
1	Sufficient description of characteristics of study groups *A '1' is given when a paper describes at least setting and time of period of the study, ages of patients (and its range) and man:woman ratio*	C/NCC
2	Presence of hand OA was according to valid definition and the classification was standardized. *ACR criteria did not request radiographic findings in making a diagnosis of hand OA, whereas EULAR recommendation proposed that multiple features on hand radiographs is adequate to make a diagnosis hand OA. A '1' will than given for a study which used ACR criteria or standardized radiological criteria for hand OA, like those from Kellgren and Lawrence, Kallman and OARSI.*	C/NCC
	Selection bias	
3	Clear desription of selection of study subjects. *When a paper described how the study subjects were selected (description of in- and exclusion criteria) from the population level to the study level, a '1' will be given.*	C/NCC
4	Cases and controls were drawn from the same source population. *This is to exclude the possibility of selection bias.*	NCC
	Follow-up	
5	Data collection *A '1' is given when a study measured the exposure before the outcome hand OA progression.*	C/NCC
6	Follow up time ≥ 1 years *One year was an arbitrary margin to say about the acceptable duration of follow-up to measure progression.*	C
7	Participation rate ≥ 80% for study groups *80% was an arbitrary margin chosen to determine the quality of the selection of study subjects.*	C/NCC
8	No difference in withdrawal in both groups, including information on completers and withdrawals	C
	Assessment of prognostic factors	
9	Exposure was measured with standardized or valid instruments	C/NCC
10	Exposure assessment was blinded	C/NCC
11	Exposure was measured identically for cases and controls	NCC
	Assessment of the outcome: Hand Osteoarthritis (hand OA) progression	
12	Hand OA progression was measures were valid, e.g. radiographic measures	C/NCC
13	Hand OA progression assessment was blinded *A '1'is given if the observers when making the diagnosis ' hand OA progression' (by reading patient's chart or reading the radiographs) did not aware of patients' exposure.*	C/NCC
14	Presence of hand OA progression was assessed reproducibly *A '1' is given if hand OA progression was assessed repeatedly at least in a subgroup, whether by the same observer or different observers.*	C/NCC
15	Hand OA progression was assessed identical in cases and controls *A '1' is given if assessment of hand OA progression was the same in controls as in cases.*	NCC
	Analysis and Data Presentation	
16	Frequencies of the most important prognostic factors were given	C/NCC
17	Frequencies of most important outcomes were given	C/NCC
18	Appropriate analysis techniques with estimates were used	C/NCC
19	Adjusted for at least age and gender	C/NCC

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