Clinical aspects of hand osteoarthritis : are erosions of importance?

Kwok, W.Y.

13 SUMMARY AND DISCUSSION

SUMMARY

This thesis focuses on epidemiological studies of hand OA in secondary care, erosive OA as a subset of hand OA and the added value of imaging in hand OA to understand better the pathophysiology of hand OA and seek for opportunities to define progression in an earlier stage.

Chapter 2 gives an overview about the current knowledge on hand OA and it is clear that hand OA is a prevalent, heterogeneous disorder (including several hand OA subsets) that can cause considerable pain and disability. Much less is known about the risk factors of progression in hand OA. Moderate evidence for an abnormal scintigram at baseline was found as a risk factor for radiographic progression in a systematic review as described in chapter 3. In rheumatology practice, the most prevalent phenotype of OA is hand OA as depicted in chapter 4. This symptomatic population experience a substantial lower health-related quality of life compared to the general population.

The collaborations with the Rotterdam Study and NorStOP Study (chapter 5, 6, 7) revealed that 2.8% of the general population rising to 10.2% in the symptomatic population is affected by erosive disease in the interphalangeal joints (IPJs). Furthermore, erosions are not present in IPJs only and prevalence of erosive disease in 1st carpometacarpal joints (CMCJs) is also given. Persons with erosive OA in the interphalangeal joints report more pain and functional limitations, however to a lesser extent than persons with other rheumatic inflammatory diseases.

Inflammation does play a role in OA joints with erosions, as assessed with Power Doppler Signal, greyscale synovitis and effusion on ultrasound (chapter 8). Also in OA joints without erosions, inflammatory signs are visible on ultrasound (chapter 9).

Regarding other imaging modalities used in hand OA research, quantitative joint space width (JSW) measurements in hand OA joints have been shown to be associated with self-reported pain, functional ability and structural abnormalities (chapter 10), whereas features on Magnetic Resonance Imaging (MRI, such as abnormal collateral ligaments and bone marrow lesions) are also associated with pain upon palpation in individual joints (chapter 11).

Finally, the health-related quality of life in hand OA patients in rheumatology practice can be improved with a protocol-led consultation about increasing the use of helping aids and acetaminophen given by a clinical nurse specialist (chapter 12).

DISCUSSION

Risk factors in progression of hand OA

Current knowledge about risk factors in hand OA progression was assessed with a systematic review in **chapter 3** and showed that moderate evidence is available for scintigraphy as risk factor for radiographic progression in hand OA. Other baseline factors (e.g. number of painful or OA joints, affected OA group, erosive OA) show limited evidence for positive association. Factors such as age and sex show conflicting evidence in their association with hand OA progression. By the strict a priori selection of papers, a relatively large proportion of articles were not considered in the systematic review. The most common reason for exclusion was that incident development and progression of hand OA were investigated at the same time during follow up[1-7]. The risk factors that are investigated in these types of studies cannot be exclusively associated with progression of hand OA. If these papers would have reported analyses separately for incident and progressive hand OA and the results would be valid in both patient groups, additional evidence could be possibly provided for the investigated risk factors. Not much factors with strong or moderate evidence for any association with progression could be found in this systematic review. This could be explained by the fact that determinants of interest were mostly investigated only in few studies, which were heterogeneous and reported different outcomes.

The limited evidence for a positive association of an abnormal scintigram with radiographic progression is based on two high and two low-quality studies from the 1980s-1990s[8-11]. In a technetium-scintigram labeling with diphosphonates is used. Uptake of diphosphates 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[12]. In clinical practice for hand OA patients, performance of a scintigram is not an easy method since radiation is used. However, it is interesting to discover that years ago scintigraphy was considered to be a possible biomarker for hand OA progression. 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[13,14]. Studies in sacroiilitis showed that MRI could even be more sensitive for subcortical bone marrow edema than scintigraphy[15]. Studies in the future should investigate whether the MRI could be a biomarker for hand OA progression.

Hand OA in rheumatology practice

In **chapter 4**, an observational study of OA patients referred to secondary care was conducted between 2005-2009. This study included 487 consecutive OA patients with complaints who seeked medical care for their condition and showed that the most prevalent phenotype of OA in rheumatology practice is hand OA, with or without involvement of other joint sites. The majority of these patients who visit the rheumatologist are women, more often overweight, married and having employment than controls from the general population. Of all hand OA patients (n=439), 7.7%

reported pain in 1st CMCJs only, 41.2% in DIPJs and PIPJs only and 42.8% in 1st CMCJs with DIPJs/ PIPJs. Health-related quality of life (HRQoL) is lowered in hand OA patients and is associated with disability, but not with pain. Clear focus on improvements of hand function seems relevant in treatment of these patients.

The predominance of hand OA in rheumatology practice reflects the referral policy in the Netherlands. Hand OA patients visit rheumatologists especially when there is doubt about the inflammatory or degenerative origin of disease. Hip and knee OA patients will be referred to orthopedic surgeons. The physical HRQoL was lowered in all OA patients, which was in line with an earlier study reporting a lower HRQoL in 190 female hand OA patients than in healthy controls[16,17]. Limitations in daily activities and pain are major problems in hand OA. Recently, the clinical burden in different hand OA subgroups was reported; however, this study was performed in patients who were selected with familial OA[18,19]. In **chapter 4;** we were able to investigate HRQoL, pain and function in a less selected population and confirm the previous findings that limitations in daily activities and pain are major problems in hand OA. Interestingly, a higher score on the Australian/Canadian Hand Osteoarthritis Index[20] (AUSCAN) function subscale in our study was associated with a lower HRQoL, but AUSCAN pain subscale was not associated. It could be that pain is not the major problem why patients visit rheumatologists.

Studies on erosive OA as a subset of hand OA

The investigation of the occurrence of erosive OA and its relation to patient symptoms was possible due to fruitful collaborations with researchers from two large population-based cohorts. The Rotterdam Study is ongoing since 1990 to study determinants of chronic disabling disease. All inhabitants living in the Ommoord district (Rotterdam, the Netherlands, n=10,275), aged ≥55 years, were invited to participate. The present study involves 7,983 persons, who were examined from 1990-1993 (response 78%)[21]. Extensive home interviews were conducted by trained interviewers. The study population was a selection of 3,906 individuals, who were available for follow-up 6 years later, for whom standardized posterior-anterior radiographs were available. For 451 persons, no information about the osteophyte scores and for 25 persons, no complete clinical data were available. Eventually, 3430 persons were included in the analyses in **chapter 5**.

The North Staffordshire Osteoarthritis Project (NorStOP) Study is a prospective study of epidemiology and management of clinical osteoarthritis in a general population of older adults in the United Kingdom[22-24]. In short, all adults aged ≥ 50 years registered with two general practices were invited to participate in a two-stage postal survey. If they indicated that they had experienced hand symptoms within ≤ 12 months of the first postal questionnaire, they were invited to the research clinic. Those who attended the research clinic were included in the Clinical Assessment Study of the Hand (CAS-HA, n=623)[22]. Participants of the Clinical Assessment Study of the Knee (CAS-K, n=819) were recruited from a further three general practices using recruitment methods identical to CAS-HA, except that participants were invited for a clinical assessment in the CAS-K study if they reported knee pain (rather than hand symptoms) within last year[23]. Only CAS-HA or CAS-K participants who indicated that

they experienced hand symptoms (pain, aching, stiffness) ≥ 1 day during last month are included in the analyses of **chapter 6**.

In **chapter 5** the prevalence for erosive OA in the interphalangeal joints in the middle-aged general population is estimated for the first time, at 2.8%. For radiographic and symptomatic radiographic hand OA a prevalence of 5.0% and 10.2% was seen, respectively. In the NorStOP Study, the prevalence for erosions in the IPJS in a symptomatic radiographic hand OA population was 10.0%. The true population estimate was 2.4% for the total population aged ≥ 50 years. Before these studies were performed, a relatively small Italian study reported that 7% of 200 symptomatic hand OA subjects (aged ≥ 40 years) had erosive OA[25,26]. The results in **chapter 6** confirmed with a high degree of consistency, previous estimates of the prevalence of erosive OA in **chapter 5**. Furthermore, the first estimates of the prevalence of erosive disease in the thumb base were provided in **chapter 7**, which was not possible in **chapter 5** due to the design of the sample drawing.

Participants with erosive OA had substantially more pain and disability than those with non-erosive OA in both the general and radiographic hand OA populations. In **chapter 5**, pain was reported in 16% (n=551) of the general population and in 19% (n=371) of the radiographic HOA population. In participants with erosive OA, 40% (n=38) had pain. In the total population, erosive OA was associated with hand pain (adjusted OR 3.6, 95%CI 2.4-5.6). In radiographic hand OA, participants with erosions have more pain (adjusted OR 3.1, 95%CI 2.0-4.8) than those without. The presence of one single erosion contributes to more pain than persons with non-erosive hand OA. This is an important finding since ≥2 erosions are often proposed as a cut-off value for the definition of erosive OA[26], suggesting that the prevalence of erosions is infrequent and that even the presence of one single erosion has clinical consequences.

Chapter 6 gave us the opportunity to quantify the pain functional limitation and health status in erosive OA in the interphalangeal joints in a general population with hand symptoms, since detailed assessments of the hand were collected (e.g. clinical examination, AUSCAN, Artritis Impact Measurement Scales questionnaire (AIMS-2)[27] and Short Form-12[28]) in contrast to the Rotterdam Study. Also, it was possible to investigate the clincial impact of erosive OA compared to inflammatory diseases, in order to place the clinical burden of erosive OA into the spectrum of the clinical burden of other inflammatory rheumatic diseases of patients drawn from the same population. Persons with erosive OA reported significantly more pain, stiffness and functional limitations than persons with symptomatic non-erosive radiographic hand OA on both AUSCAN and AIMS-2 questionnaires in **chapter 6**. Scores of the AUSCAN subscales in this study were slightly lower than reported for persons with erosive OA in secondary care, where persons with symptomatic OA at multiple sites were included[29]. Regardless of the study population, all these studies confirm that persons with erosive OA have a higher clinical burden than persons with symptomatic radiographic hand OA. However, erosive OA does not appear to impact as strongly on pain and function as prevalent inflammatory disease identified from the same population.

Chapter 7 describes the prevalence of erosive disease in 1st CMCJs, which is prevalence is 2.2% in persons from the general population with hand symptoms. Only

a few persons do have both interphalangeal erosive OA combined with erosive disease in the 1st CMCJs, while the rest have erosive lesions in 1st CMCJs or in IPJs exclusively. Persons with erosive disease in the 1st CMCJs have significantly higher sum scores of the KL-grade in 1st CMCJs. It appears like males are more often affected by erosive disease in the 1st CMCJs in contrast to erosive OA in IPJs. Age could confound the results, however strenuous manual activities have previously been linked to thumb base OA[30] and those occupational exposures prevalent in the local population (e.g. occupations in the pottery industry) could also explain the sex difference. Although significantly more persons with erosive disease of 1st CMCJs reported pain in their TB than persons with radiographic TB OA, AUSCAN pain/function was not significantly different. Further studies are needed to confirm these findings.

Inflammation in hand OA

The role of inflammation in hand OA is unclear. Earlier reports suggest that inflammation especially plays a role in erosive OA[26,31]. But what the role of inflammation is in hand OA in general is unknown and needs to be elucidated first. **Chapter 8** showed that the majority of patients with hand OA show inflammation on ultrasound. In individual joints, a dose-dependent association between inflammatory features and pain was seen. In addition, GS synovitis, effusion and synovial thickening were independently associated; PDS was not. GS synovitis was also associated with AUSCAN pain and stiffness and with the physical component summary score of the Short-Form 36[32], as was effusion with AUSCAN pain. In our study, 96% of patients showed GS synovitis, 91% effusion, 86% PDS and 73% synovial thickening. GS synovitis is often chosen because it is thought that separation of effusion and synovial thickening is not straightforward[33]. We showed that it is technically possible to study effusion and synovial thickening as separate entities. Strong dose-dependent associations were found between inflammatory ultrasound features and pain in separate hand joints. These findings are promising for elucidating the aetiology of pain in hand OA. The association between ultrasound features and pain may give rise to further research for therapeutic strategies. However, repeat studies to confirm the association of ultrasound features and pain are needed.

In **chapter 9** we focused on the role of inflammation in erosive and non-erosive hand OA separately. We showed that IPJs of patients with erosive OA demonstrate more Power Doppler signal (PDS), Greyscale (GS) synovitis and effusion, but not more synovial thickening, in comparison to IPJs from patients with non-erosive hand OA. Further detailed investigation revealed that especially erosive IPJs show inflammatory signs. Remarkably, also IPJs without erosions in patients with erosive OA demonstrated more PDS, GS synovitis and effusion, but not more synovial thickening, in comparison to IPJs of patients with non-erosive hand OA. It confirms our hypothesis that inflammatory signs might be implicated in erosive evolution. This study suggests that erosive OA is a phenotype affecting all IPJs in a patient, not only the erosive ones, and could explain why erosive evolution is more often seen in those patients that already have erosions[19]. Whether it means that non-erosive joints with PDS, GS synovitis or effusion in patients with erosive OA are at an increased risk to develop erosions in the future cannot be answered, due

to the cross-sectional design of the study. To answer that question longitudinal studies are necessary. Inflammation was also more frequently seen in erosive OA at physical examination, since soft tissue swelling was present during physical examination in erosive OA. These results underscore the earlier observations of erosive OA as inflammatory hand OA[26,34,35]. In contrast, synovial thickening, which is frequently found in hand OA, does not distinguish between the different hand OA subsets[33,36-39].

Methodological studies in hand OA

Chapter 10 compares the joint space width (JSW) in millimeters of finger joints in a large population of patients with hand OA with visual grading score for joint space narrowing (JSN) and JSW measurements of controls. It showed that quantitative JSW measurements and the visual grading method for JSN are both associated with self-reported pain and functional ability, pain on palpation and the presence of osteophytes, nodes and erosions. This implies that JSW measurement is a valid method to evaluate loss of joint space in finger joints of hand OA patients. However, the role of measuring the JSW in hand OA patients needs to be investigated in longitudinal studies to determine if it can discriminate progression in hand OA in an earlier stage than the JSN scoring and to assess its relationship to change in symptoms over time. We confirmed the expectation that the mean JSW in patients with hand OA would be smaller than in controls without hand complaints. The radiographs and JSW measurements of these controls were judged by the same expert and measured in the same hospital with identical semi-automated method as in the present study minimizing confounding factors.

Older age was associated with a lower JSW in controls, but no association between age and JSW was seen in hand OA patients. This could be explained by the small age range between 50 and 85 years in hand OA patients which could lead to a biased (positive) association of age and JSW in this population. Alternatively, the positive association between age and JSW in hand OA patients could be explained by thickening of the cartilage in early stages of OA reflecting a larger JSW on radiographs[40].

A possible way to investigate whether synovial thickening reflects any inflammation in hand OA is to perform MRI studies with contrast enhancement. Chapter 11 performed one of the first steps in MRI studies in hand OA to investigate the reproducibility of the Oslo Hand OA (OHOA) MRI scoring method[41] and correlation of MRI features with pain, radiographs, and ultrasound in patients with hand OA. The OHOA-MRI scoring method showed to be reproducible when compared to US and conventional radiographs in a severe hand OA population. In this severe, predominantly erosive, hand OA population many MRI abnormalities were present; synovitis, abnormal collateral ligaments, bone marrow lesions (BMLs), bone erosions and osteophytes were associated with pain upon palpation in individual joints.

The association between MRI features with pain was also investigated to increase the understanding of causes of pain in hand OA. We showed that presence of moderate/severe synovitis and BMLs were positively associated with pain, suggesting that inflammation is an underlying cause for pain in hand OA. No earlier MRI studies in hand OA reported this association, but this finding is in line with an US study in hand

OA[36], showing that GS synovitis and PDS are associated with more pain per joint, and with MRI studies in knee OA[42]. Presence of BMLs is associated with a higher chance to be in a radiographic pre-erosive (J phase) or erosive phase (E phase), but not in remodelled phases (R phase) after the erosive process of the joint. Also cysts are more associated with the presence of an radiographic erosive phase. This finding suggests that erosive OA is mainly a disease starting from the subchondral bone with possible inflammatory signs and may give lead to future studies that gives more insight in understanding processes in OA pathogenesis.

Treatment in hand OA

Chapter 12 evaluated the role of clinical nurse specialists in daily clinical practice in the management of hand OA in a proof-of-concept study as part of usual care. This study explored the health-related quality of life, pain and daily activities of patients with hand OA after a single one-hour consultation and their satisfaction with this care. The conclusion was that the physical dimension of health-related quality of life improved after a single one-hour consultation and one telephone contact by the clinical nurse specialist in hand OA patients, although further controlled trials are needed to determine the added value of the clinical nurse specialist in the care for hand OA patients. The use of helping aids/devices and acetaminophen was increased after intervention, whereas the non-steroidal anti-inflammatory drug (NSAID) use showed a trend towards a decrease in usage. Most patients were satisfied with the education.

The expectation was that self-reported pain and function would improve after intervention, since the use of assistive devices and acetaminophen could influence these determinants. Surprisingly, no change was seen between baseline and follow-up regarding to pain and function. It could be that the intervention does not directly improve the disease-specific complaints of hand OA, but improves the health status in general after attention and information from the clinical nurse specialist. However, a single one-hour consultation by the clinical nurse specialist seems to be feasible and potentially effective in hand OA patients in a relatively short and cost-effective manner. Further randomized controlled studies should be done to understand the value of protocol-led consultation by a nurse specialist. Also cost-effectiveness of the intervention should be investigated.

Future perspectives

This thesis makes new contributions to the epidemiology of hand OA in secondary care and erosive OA. Also knowledge is added with methodological studies to understand how outcome could be measured in a better way over time and how to understand pain in hand OA in relation to structural abnormalities, in order to gain insight in the pathogenesis of hand OA. However, no disease-modifying treatment is available at the moment to lower the disease activity in hand OA, except symptomatic therapy such as analgesics and thumb splints[43].

As pointed out in this thesis, inflammatory signs are present in hand OA and could play a role in the pathogenesis and in the disease course of hand OA. The role of inflammatory components in OA, were demonstrated by findings of pro-inflammatory

cytokines in synovial fluids, and cellular infiltrates in synovial membranes, but also by a mild increase in C-reactive protein[44,45]. Inflammation can enhance pro-inflammatory cytokine production, including tumor necrosis factor-α (TNF- α), interleukin (IL)-1 and IL-6[46]. The pro-inflammatory cytokines can drive destructive events by activation of osteoclasts like in rheumatoid arthritis or induce synovial inflammation, which is associated with degradation of cartilage. Interestingly, preliminary results from a placebo-controlled phase-II study with adalimumab (a monoclonal anti-TNF-α antibody) can reduce the occurrence of erosive progression in joints showing palpable synovial effusion at baseline[47].

Thus, given that currently disease modification has not yet been established unequivocally and that the subset of erosive OA appears to be the form of hand OA with most radiographic and clinical burden, a randomized, double-blind, placebo-controlled trial has been designed to attempt to improve clinical and functional abnormalities and to halt or reverse radiographic changes by virtue of blocking a major pro-inflammatory cytokine, TNF-α. Therefore, patients with symptomatic erosive OA (n=90) were randomized in this multi-center study (Leiden, Ghent, Padua and Vienna) into placebo or etanercept subcutaneous weekly during one year. The preliminary results are being expected by 2013/2014.

Drug development in OA is hampered by the lack of measurable progression in the majority of the patients included in clinical studies. Besides clinical and radiographic markers for measuring the progressive course of hand OA, biochemical markers in synovial, blood and urine samples are of interest for this purpose. Biochemical markers for hand OA have more recently become the focus of intense research. It has been reported that C-telopeptide of type I collagen (CTX-I), a specific marker sensitive to bone resorption, was evaluated in the serum of patients with hand OA and controls[48]. The study showed increased levels of CTX-I in patients with erosive OA compared to nodal OA. Silvestri and colleagues demonstrated that significant increases of collagenase cleavage neoepitopes Col2-3/4C$_{short}$ level were noted in patients with hand OA[49]. Increased urinary C-telopeptide of type II collagen (CTX-II), a biochemical marker of cartilage degradation has also been reported in patients with clinical[50] and radiographic hand OA[51]. Recently, a cross-sectional study reported that high levels of adiponectin, a cytokine produced by adipocytes, were associated with progression of hand OA and could be another interesting potential target for intervention[52]. Cartilage in DIPJs and PIPJs represents only a small fraction of total cartilage in the body, making it particularly impressive that this limited damage can be detected in blood and urine by specific biochemical markers. However, more studies are needed to confirm the above data. Moreover, a longitudinal follow up of the changes of the biochemical markers would increase insight on the mechanism of disease for hand OA and provide opportunities to evaluate the specificity and sensitivity of these biomarkers.

Until present, conventional radiographs are commonly used for classifying radiographic OA, based on bony structural abnormalities. Unfortunately, this modality is not suitable to judge other anatomical structures and soft tissue that is involved in the process of OA besides subchondral bone. Another limitation of conventional radiographs is that joints can be viewed in limited angles and that reconstructing

three-dimensional images is not possible, in contrast to ultrasound or MRI. The MRI is able to visualize soft tissue and structures that are involved in OA and the whole joint, such as cartilage, synovium, capsule and ligaments. In knee OA, MRI has to be proven to be a valid imaging modality to visualize not only soft tissues, but also subchondral bone lesions, such as bone marrow lesions[53-55]. For hand OA, few studies used MRI to investigate abnormalities in soft tissue and subchondral bone[56-58]. Recently, the Oslo Hand OA MRI score is developed to assess MRI key features in hand OA[41] and facilitate research with MRI in hand OA. At the moment, patients with hand OA visiting the rheumatology outpatient clinic in Leiden are now consecutively included in an inception cohort, to study the utility of MRI in the diagnosis, association with patient outcomes, prognosis and sensitivity to change of hand OA. Furthermore, risk factors associated with and predict the diagnosis of hand OA and prognostic factors with the outcome are also studied in this cohort. The results from this study will hopefully give us new insights in the OA processes and answers whether MRI would be a better tool to detect OA in an earlier phase. At last, to learn more about who will progress in their hand OA, more high-quality research with longitudinal data in the future is needed, since the available evidence and knowledge is limited.

REFERENCE LIST

1. Busby J, Tobin J, Ettinger W, Roadarmel K, Plato CC. A longitudinal study of osteoarthritis of the hand: the effect of age. Ann Hum Biol 1991; 18:417-24.
2. Chaisson CE, Zhang Y, McAlindon TE, Hannan MT, Aliabadi P, Naimark A et al. Radiographic hand osteoarthritis: incidence, patterns, and influence of pre-existing disease in a population based sample. J Rheumatol 1997; 24:1337-43.
3. Kalichman L, Kobyliansky E, Seibel MJ, Livshits G. Repeated measurement study of hand osteoarthritis in an apparently healthy Caucasian population. Am J Hum Biol 2005; 17:611-21.
4. Lane NE, Michel B, Bjorkengren A, Oehlert J, Shi H, Bloch DA et al. The risk of osteoarthritis with running and aging: a 5-year longitudinal study. J Rheumatol 1993; 20:461-8.
5. McCarthy C, Cushnaghan J, Dieppe P. The predictive role of scintigraphy in radiographic osteoarthritis of the hand. Osteoarthritis Cartilage 1994; 2:25-8.
6. Paradowski PT, Lohmander LS, Englund M. Natural history of radiographic features of hand osteoarthritis over 10 years. Osteoarthritis Cartilage 2010; 18:917-22.
7. Plato CC, Norris AH. Osteoarthritis of the hand: longitudinal studies. Am J Epidemiol 1979; 110:740-6.
8. Balblanc JC, Mathieu P, Mathieu L, Tron AM, Conrozier T, Piperno M et al. Progression of digital osteoarthritis: a sequential scintigraphic and radiographic study. Osteoarthritis Cartilage 1995; 3:181-6.
9. Hutton CW, Higgs ER, Jackson PC, Watt I, Dieppe PA. 99mTc HMDP bone scanning in generalised nodal osteoarthritis. II. The four hour bone scan image predicts radiographic change. Ann Rheum Dis 1986; 45:622-6.
10. Macfarlane DG, Buckland-Wright JC, Emery P, Fogelman I, Clark B, Lynch J. Comparison of clinical, radionuclide, and radiographic features of osteoarthritis of the hands. Ann Rheum Dis 1991; 50:623-6.
11. Olejarova M, Kupka K, Pavelka K, Gatterova J, Stolfa J. Comparison of clinical, laboratory, radiographic, and scintigraphic findings in erosive and nonerosive hand osteoarthritis. Results of a two-year study. Joint Bone Spine 2000; 67:107-12.
12. Fogelman I. Skeletal uptake of diphosphonate: a review. Eur J Nucl Med 1980; 5:473-6.
13. Palosaari K, Vuotila J, Takalo R, Jartti A, Niemela RK, Karjalainen A et al. Bone oedema predicts erosive progression on wrist MRI in early RA--a 2-yr observational MRI and NC scintigraphy study. Rheumatology (Oxford) 2006; 45:1542-8.
14. Roimicher L, Lopes FP, de Souza SA, Mendes LF, Domingues RC, da Fonseca LM et al. 99mTc-anti-TNF-{alpha} scintigraphy in RA: a comparison pilot study with MRI and clinical examination. Rheumatology (Oxford) 2011; 50:2044-50.
15. Battafarano DF, West SG, Rak KM, Fortenbery EJ, Chantelois AE. Comparison of bone scan, computed tomography, and magnetic resonance imaging in the diagnosis of active sacroiliitis. Semin Arthritis Rheum 1993; 23:161-76.
16. Slatkowsky-Christensen B, Mowinckel P, Loge JH, Kvien TK. Health-related quality of life in women with symptomatic hand osteoarthritis: a comparison with rheumatoid arthritis patients, healthy controls, and normative data. Arthritis Rheum 2007; 57:1404-9.
17. Slatkowsky-Christensen B, Haugen I, Kvien TK. Distribution of joint involvement in women with hand osteoarthritis and associations between joint counts and patient-reported outcome measures. Ann Rheum Dis 2010; 69:198-201.
18. Bijsterbosch J, Visser W, Kroon HM, Stamm T, Meulenbelt I, Huizinga TW et al. Thumb base involvement in symptomatic hand osteoarthritis is associated with more pain and functional disability. Ann Rheum Dis 2010; 69:585-7.
19. Bijsterbosch J, van Bemmel JM, Watt I, Meulenbelt I, Rosendaal FR, Huizinga TW et al. Systemic and local factors are involved in the evolution of erosions in hand osteoarthritis. Ann Rheum Dis 2011; 70:326-30.
20. Bellamy N, Campbell J, Haraoui B, Gerecz-Simon E, Buchbinder R, Hobby K et al. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. Osteoarthritis Cartilage 2002; 10:863-9.
21. Hofman A, Breteler MM, van Duijn CM, Janssen HL, Krestin GP, Kuipers EJ et al. The Rotterdam Study: 2010 objectives and design update. Eur J Epidemiol 2009; 24:553-72.
22. Myers HL, Thomas E, Hay EM, Dziedzic KS. Hand assessment in older adults with musculoskeletal hand problems: a reliability study. BMC Musculoskelet Disord 2011; 12:3.

23. Peat G, Thomas E, Handy J, Wood L, Dziedzic K, Myers H et al. The Knee Clinical Assessment Study-CAS(K). A prospective study of knee pain and knee osteoarthritis in the general population: baseline recruitment and retention at 18 months. BMC Musculoskelet Disord 2006; 7:30.
24. Thomas E, Wilkie R, Peat G, Hill S, Dziedzic K, Croft P. The North Staffordshire Osteoarthritis Project--NorStOP: prospective, 3-year study of the epidemiology and management of clinical osteoarthritis in a general population of older adults. BMC Musculoskelet Disord 2004; 5:2.
25. Cavasin F, Punzi L, Ramonda R, Pianon M, Oliviero F, Sfriso P et al. [Prevalence of erosive osteoarthritis of the hand in a population from Venetian area]. Reumatismo 2004; 56:46-50.
26. Punzi L, Frigato M, Frallonardo P, Ramonda R. Inflammatory osteoarthritis of the hand. Best Pract Res Clin Rheumatol 2010; 24:301-12.
27. Meenan RF, Mason JH, Anderson JJ, Guccione AA, Kazis LE. AIMS2. The content and properties of a revised and expanded Arthritis Impact Measurement Scales Health Status Questionnaire. Arthritis Rheum 1992; 35:1-10.
28. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996; 34:220-33.
29. Bijsterbosch J, Watt I, Meulenbelt I, Rosendaal FR, Huizinga TW, Kloppenburg M. Clinical burden of erosive hand osteoarthritis and its relationship to nodes. Ann Rheum Dis 2010; 69:1784-8.
30. Lawrence JS. Rheumatism in cotton operatives. Br J Ind Med 1961; 18:270-6.
31. Peter JB, Pearson CM, Marmor L. Erosive osteoarthritis of the hands. Arthritis Rheum 1966; 9:365-88.
32. Ware JE. User's Manual for the SF-36v2 Health Survey, Second Edition. Chapter 7 ed. 2009; pp.81-84.
33. Keen HI, Lavie F, Wakefield RJ, D'Agostino MA, Hammer HB, Hensor E et al. The development of a preliminary ultrasonographic scoring system for features of hand osteoarthritis. Ann Rheum Dis 2008; 67:651-5.
34. Belhorn LR, Hess EV. Erosive osteoarthritis. Semin Arthritis Rheum 1993; 22:298-306.
35. Ehrlich GE. Inflammatory osteoarthritis. I. The clinical syndrome. J Chronic Dis 1972; 25:317-28.
36. Kortekaas MC, Kwok WY, Reijnierse M, Watt I, Huizinga TW, Kloppenburg M. Pain in hand osteoarthritis is associated with inflammation: the value of ultrasound. Ann Rheum Dis 2010; 69:1367-9.
37. Mancarella L, Magnani M, Addimanda O, Pignotti E, Galletti S, Meliconi R. Ultrasound-detected synovitis with power Doppler signal is associated with severe radiographic damage and reduced cartilage thickness in hand osteoarthritis. Osteoarthritis Cartilage 2010; 18:1263-8.
38. Vlychou M, Koutroumpas A, Malizos K, Sakkas LI. Ultrasonographic evidence of inflammation is frequent in hands of patients with erosive osteoarthritis. Osteoarthritis Cartilage 2009; 17:1283-7.
39. Wittoek R, Carron P, Verbruggen G. Structural and inflammatory sonographic findings in erosive and non-erosive osteoarthritis of the interphalangeal finger joints. Ann Rheum Dis 2010; 69:2173-6.
40. Bae DK, Yoon KH, Song SJ. Cartilage healing after microfracture in osteoarthritic knees. Arthroscopy 2006; 22:367-74.
41. Haugen IK, Lillegraven S, Slatkowsky-Christensen B, Haavardsholm EA, Sesseng S, Kvien TK et al. Hand osteoarthritis and MRI: development and first validation step of the proposed Oslo Hand Osteoarthritis MRI score. Ann Rheum Dis 2011; 70:1033-8.
42. Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. Ann Rheum Dis 2011; 70:60-7.
43. Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007; 66:377-88.
44. Bonnet CS, Walsh DA. Osteoarthritis, angiogenesis and inflammation. Rheumatology (Oxford) 2005; 44:7-16.
45. Walsh DA, Bonnet CS, Turner EL, Wilson D, Situ M, McWilliams DF. Angiogenesis in the synovium and at the osteochondral junction in osteoarthritis. Osteoarthritis Cartilage 2007; 15:743-51.
46. Wang J, Elewaut D, Veys EM, Verbruggen G. Insulin-like growth factor 1-induced interleukin-1 receptor II overrides the activity of interleukin-1 and controls the homeostasis of the extracellular matrix of cartilage. Arthritis Rheum 2003; 48:1281-91.

47. Verbruggen G, Wittoek R, Vander Cruyssen B, Elewaut D. Preliminary Results of a Phase II Placebo Controlled Trial with Adalimumab in Erosive Hand Osteoarthritis: Predictors of Erosive Evolution and the Potential Effect of Adalimumab in Specific Subgroups. Arthritis Rheum 60Suppl 10, 856. 2009.
48. Rovetta G, Monteforte P, Grignolo MC, Brignone A, Buffrini L. Hematic levels of type I collagen C-telopeptide in erosive versus nonerosive osteoarthritis of the hands. Int J Tissue React 2003; 25:25-8.
49. Silvestri T, Pulsatelli L, Dolzani P, Punzi L, Meliconi R. Analysis of cartilage biomarkers in erosive and non-erosive osteoarthritis of the hands. Osteoarthritis Cartilage 2004; 12:843-5.
50. Garnero P, Sornay-Rendu E, Arlot M, Christiansen C, Delmas PD. Association between spine disc degeneration and type II collagen degradation in postmenopausal women: the OFELY study. Arthritis Rheum 2004; 50:3137-44.
51. Meulenbelt I, Kloppenburg M, Kroon HM, Houwing-Duistermaat JJ, Garnero P, Hellio Le Graverand MP et al. Urinary CTX-II levels are associated with radiographic subtypes of osteoarthritis in hip, knee, hand, and facet joints in subject with familial osteoarthritis at multiple sites: the GARP study. Ann Rheum Dis 2006; 65:360-5.
52. Yusuf E, Ioan-Facsinay A, Bijsterbosch J, Klein-Wieringa I, Kwekkeboom J, Slagboom PE et al. Association between leptin, adiponectin and resistin and long-term progression of hand osteoarthritis. Ann Rheum Dis 2011; 70:1282-4.
53. Hunter DJ, Lo GH, Gale D, Grainger AJ, Guermazi A, Conaghan PG. The reliability of a new scoring system for knee osteoarthritis MRI and the validity of bone marrow lesion assessment: BLOKS (Boston Leeds Osteoarthritis Knee Score). Ann Rheum Dis 2008; 67:206-11.
54. Kornaat PR, Ceulemans RY, Kroon HM, Riyazi N, Kloppenburg M, Carter WO et al. MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS)--inter-observer and intra-observer reproducibility of a compartment-based scoring system. Skeletal Radiol 2005; 34:95-102.
55. Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage 2004; 12:177-90.
56. Grainger AJ, Farrant JM, O'Connor PJ, Tan AL, Tanner S, Emery P et al. MR imaging of erosions in interphalangeal joint osteoarthritis: is all osteoarthritis erosive? Skeletal Radiol 2007; 36:737-45.
57. Tan AL, Grainger AJ, Tanner SF, Shelley DM, Pease C, Emery P et al. High-resolution magnetic resonance imaging for the assessment of hand osteoarthritis. Arthritis Rheum 2005; 52:2355-65.
58. Wittoek R, Jans L, Lambrecht V, Carron P, Verstraete K, Verbruggen G. Reliability and construct validity of ultrasonography of soft tissue and destructive changes in erosive osteoarthritis of the interphalangeal finger joints: a comparison with MRI. Ann Rheum Dis 2011; 70:278-83.