Osteoarthritis: the role of synovitis

Kortekaas, M.C.

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Summary and discussion

Osteoarthritis (OA) is the most common musculoskeletal disorder, characterized by cartilage degradation and changes in subchondral bone. It often leads to pain and disability. It is an increasing burden for society, especially with the aging of the population. The hand is one of the most frequently involved sites.

The etiology of pain and structural progression in hand OA has not been fully understood up till now, and the role of inflammatory features have not been thouroughly investigated.

This thesis presents the results of the ECHO (= ultrasound (US) in hand OA) study. In this study 63 patients with symptomatic hand OA according to the American College of Rheumatology (ACR) criteria were recruited from the rheumatology department of the Leiden University Medical Center and followed for 2.3 years. At baseline, after 3 months and 2.3 years, an US examination, physical examination and global pain score were performed. The baseline and 2.3 year follow-up visits also included radiographs and questionnaires on demographics and selfreported outcome measures. In this cohort we investigated the association between inflammatory US features and clinical outcomes, the evolvement over time, and the association with progression of structural abnormalities, such as osteophytes, joint space narrowing (JSN) and erosions. The association of structural abnormalities and clinical outcomes were also investigated since earlier studies gave conflicting results. In the latter analyses we especially focussed on results on patient level versus joint level. The role of inflammatory features in the subset erosive OA was studied separately cross-sectionally as well as prospectively after 2,3 years of follow-up.

In addition two studies are presented looking into the value of MRI in OA.

The association of OA features with pain

The association of pain and OA features has been studied much more frequently in knee OA than in hand OA. For this reason, a systematic review of 22 studies that associated MRI features and pain in knee OA patients was described in Chapter 2. We identified a moderate level of evidence for a positive association for bone marrow lesions (BMLs) and effusion/synovitis with pain in knee OA. The level of evidence was limited for a positive association for knee ligamentous abnormalities with pain, and limited for no association for osteophytes and subchondral cysts with pain.

In our review, we used an a priori defined qualitative level of evidence to summarize the results. More robust results could have been obtained by performing a meta-analysis, but due to the heterogeneity of the included studies, it was not possible to perform these analyses. The assignment of a level of evidence to studies results in counting positive and negative studies taking in account the design and quality of the study. This has some limitations. First of all, sizes of studies cannot be taken into account, and the cut-off point for the decision of ‘positive or negative’ studies is only

based on statistical significance. Also, the use of a selected quality score set to assess the methodological quality of the studies is a potential limitation. It is possible that when a different quality score set is used, the interpretation of the results could be influenced.

Other limitations of this review mostly reflect the limitations of the studies investigated. First, no publication bias could be investigated due to the limited number of studies that reported their results in relative risks or odds ratio's. Second, the quality of included studies was not excellent.

Thus, additional high-quality research is needed to further explore the associations of BML and effusion/synovitis with pain in knee OA.

In Chapter 3 the first results of the ECHO study were presented. It was demonstrated that the majority of patients had inflammatory US features. In the present study 96% of patients showed grayscale (GS) synovitis (a composite measure of synovial thickening and effusion), 91% effusion, 86% power Doppler signal (PDS) and 73% synovial thickening.

Dose dependent associations of inflammatory US features and pain were found in individual joints taking into account patient effects and confounders. In addition it was shown that these associations were all independent of the other inflammatory features, although the association with PDS did not reach significance, probably due to insufficient power. Associations on patient level were found for GS synovitis with the patient reported outcomes AUSCAN pain and stiffness and the SF-36 physical component scale, and for effusion with AUSCAN pain.

In earlier studies of hand OA[1,2] and in the manuscript by Keen et al.,[3] defining a preliminary scoring system for US, only GS synovitis was investigated. The separate scoring of effusion and synovial thickening was not proposed. The choice for a composite measure GS synovitis is due to the assumption that effusion and synovial thickening are difficult to distinguish separately. In the present study it was demonstrated that it is technically possible and clinically relevant to study effusion and synovial thickening as separate entities, since both effusion and synovial thickening can be scored reliable and it is shown that both features associate independently of each other with pain and progression.

Up till now, structural abnormalities assessed on radiographs, such as osteophytes and JSN, are frequently used as outcome measure in research to study associations with clinical features in hand OA. Using radiography, conflicting results have been reported on these associations. [4] We hypothesized that the lack of association between structural abnormalities and pain in hand OA might be caused by the choice of the imaging modality. A few studies have shown that radiographs are less sensitive in

detecting osteophytes compared to US.[5,6] Therefore, we compared the sensitivity for the detection of osteophytes using radiography and US. In addition, we investigated the association between structural abnormalities and pain using both imaging modalities. In Chapter 4 it is demonstrated that more osteophytes were found using US compared to radiography. Also, it was shown that a strong dose-dependent association between pain and structural abnormalities assessed on joint level is present, taking into account patient effects in patients with symptomatic hand OA. These associations were found when structural abnormalities were assessed using US as well as radiographs. Associations were absent when summated scores of structural abnormalities and global pain scores were analysed. Both osteophytes and JSN are independent of each other associated with pain. Thus, although higher sensitivity of US is found for the detection of osteophytes compared to the detection on radiographs, both imaging modalities show equally strong associations with pain. It is therefore not sure whether the increased sensitivity of US is of clinical relevance. It is possible that the sensitivity is too high in US to reveal bony abnormalities.

The fact that JSN is independently associated with pain is especially interesting, since the cartilage in itself is aneural. Healthy cartilage absorbs mechanical forces that are imposed on the joint. With the thinning of the cartilage, these forces are loaded increasingly on the subchondral bone, which does contain nerve fibres. It is possible that the association found between cartilage loss and pain, is in fact an association between increased loading of the subchondral bone. Further studies are necessary to investigate this hypothesis. Since US is incapable to access subchondral bone, for this research MRI would be the imaging modality of choice.

Results from both Chapter 3 and 4 reveal that analyses on joint level taking in account patient effects, such as genetic and psychosocial factors, are able to show associations between OA features and pain in hand OA, while analyses on patient level without taking these factors into considerations cannot always support these associations.

An explanation for these differences could be that patients' effects in hand OA are predominantly responsible for patients reporting pain. It is possible that hard tissue and to a lesser extent soft tissue abnormalities are not of clinical relevance.

Another hypothesis could be raised by the complex nature of hand OA. Since multiple joints are involved in the hands and OA joint-specific features that showed to be associated with pain on joint level are differentially present within the joints of the hands (for instance structural abnormality in one joint, effusion in the other, JSN in yet another joint) it is much more difficult to show an association with a certain feature on patient level, even taking in account all these different OA joint-specific features in the analyses. Moreover, some joints, such as the 1st CMC joint, attribute more to overall pain and disability than other joints, making it even more difficult to capture the associations on patient level.

Finally, it is of course important to have a large enough patient population. The latter might by a problem in the present study for the analyses on patient level.

Follow-up studies

In Chapter 5 we present results of the 3 months follow-up study. In this study it is shown in hand OA patients, that total inflammatory US features remained stable over time. At joint level 19% of hand joints had persistent inflammatory features, while they fluctuated in 20%. Remarkably, overall pain reduced over time, while the associations of inflammatory features with pain on joint level remained and even tended to grow stronger after three months. This implies that the decrease in overall pain can't be explained by a decrease of inflammation. A possible explanation could be a decrease in psychosocial (i.e. anxiety) and mechanical causes of pain, (i.e. joint protection principles) which is not directly related to inflammation. This observation emphasized the multifactorial origin of pain yet again.

In Chapter 6 the prospective 2.3-year follow-up study in patients with hand OA from the ECHO cohort is described. In this study it was shown that baseline inflammatory US features in hand joints are positively associated with radiological progression in these joints, independently of each other and also independent of baseline radiological features. Repeated measurements of inflammatory US features revealed that the prevalence of joints with synovial thickening and effusion increased with 35 and 26%, respectively, after 2.3 years, while only a slight increase (2%) of joints with PDS was seen. The minority of joints showed persistent inflammatory US features at baseline and follow-up -2, 7 and 14% respectively for PDS, synovial thickening and effusion-while 14, 38 and 38% of joints showed fluctuating features. Especially persistent inflammatory US features were associated with radiological progression after 2.3 years. Joints with both persistent and fluctuating PDS had an increased risk to progress radiologically over 2.3 years.

In the present study, especially the presence of PDS, reflecting active synovitis, appears to be a predictor of radiological progression. Synovial thickening and to a lesser extent effusion are also of importance, but these features are especially associated with radiological progression when they persist over time.

After 2.3 years, a large increase of inflammatory features was seen for effusion and synovial thickening. It is possible that this is the natural course of the disease. Since hand OA has not been studied after long-term follow-up with ultrasound or MRI up till now, the natural course on the long-term of inflammatory features is not known. The study population consisted of severe hand OA patients, as supported by the presence of 18 patients with erosive hand OA at baseline and with a fairly high VAS hand pain. More longitudinal studies in different patient populations are warranted to understand the natural course of these inflammatory features.

Studies in erosive hand OA

Chapter 7 describes that interphalangeal joints of patients with erosive OA demonstrate more PDS, GS synovitis and effusion, but not more synovial thickening, in comparison to interphalangeal joints from patients with non-erosive hand OA. Further detailed investigation revealed that especially erosive interphalangeal joints show inflammatory features. Remarkably, also interphalangeal joints without erosions in patients with erosive OA demonstrated more inflammatory US signs in comparison to interphalangeal joints of patients with non-erosive hand OA. The anatomical phases S, J, E and R showed more signs of inflammation compared to interphalangeal joints in N-phase, but PDS was only significantly associated to the E-phase.

These findings support our hypothesis that inflammatory signs might be implicated in erosive evolution. The present study suggests that erosive OA is a phenotype affecting all interphalangeal joints 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. To fully understand the role of inflammatory features in erosive evolution longitudinal studies have to be done.

Further investigation revealed that especially the E-phases were associated with active synovitis as reflected by positive PDS. In contrast, synovial thickening, which is frequently found in hand OA, does not distinguish between the different hand OA anatomical phases.

The diagnosis of erosive OA is based on subchondral erosions on radiographs in interphalangeal joints. The number of erosive interphalangeal joints necessary to diagnose erosive OA is not clear. Often it is stated that more than one erosive interphalangeal joint is needed. In this study we investigated both erosive OA as defined by at least one or by more than one erosive interphalangeal joint. The results were the same for both definitions, confirming that one erosive interphalangeal joint is enough to define a patient as erosive OA.

In the present study the clinical burden of patients with erosive OA was compared to patients with non-erosive hand OA. This study confirms the results of earlier studies that patients with erosive OA patients have a higher clinical burden.[7]

In conclusion, this study shows that erosive OA demonstrates more inflammatory features compared to non-erosive hand OA, even in interphalangeal joints that are not erosive. This is already true when erosive OA is defined as the presence of one erosive interphalangeal joint. Whether inflammation in erosive OA is a cause of erosive evolution or a result of extensive destruction in particular joints is not known; the finding that inflammatory features are also demonstrated more often in non-erosive joints in erosive OA suggests that inflammation is a cause.

In Chapter 8 we investigated associations between inflammatory US features and erosive development in hand OA. This study shows that erosive development is associated with moderate/severe synovial thickening, effusion and PDS at baseline in the same joints, however after adjustment for baseline structural abnormalities only synovial thickening and PDS remained associated. In addition, all inflammatory US features were associated with erosive development when present at baseline and follow-up. This implicates a role for inflammation in the pathogenesis of EOA and it might render new therapeutic options that can halt erosive evolution.

Reliability and validity of MRI in hand OA

In Chapter 9 we performed a reliability and validity study of MRI features in a severe hand OA population. In this severe, (pre)erosive, hand OA population MRI was found to be a reliable method to investigate OA characteristics in hand OA, as shown by substantial to almost perfect intra-reader reliability of all MRI features.

MRI was shown to be a valid method: Criterion validaty was tested by comparison with ultrasonography, radiography and clinical features and showed good correlations varying between 0.40 and 0.80 except for erosions.

Erosions detected on MRI versus radiographs showed however a lower correlation then expected (0.32). This might be explained by the fact that erosions on MRI were not identified as such on radiographs, but were classified as cysts, as we observed when the presence of cysts and/or erosions on radiographs and MRI was compared on joint level.

Comparison with physical examination showed that MRI abnormalities such as synovitis, osteophytes, but also abnormal collateral ligaments, BMLs, and bone erosions, 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 and validate MRI with clinical features. We showed that presence of moderate/severe synovitis and BMLs were positively associated with pain, suggesting that inflammation is an underlying cause of pain in hand OA.

Future recommendations

In this thesis the role of inflammatory features in OA has been investigated. Based on the studies described in this thesis, we conclude that inflammatory features appear to be important and of clinical relevance, since they are involved in the perception of symptoms and in progression of structural damage over time.

This conclusion was partly based on the results of the systematic review we performed for the association of pain and inflammatory features in knee OA. However, the level of evidence was only moderate. Therefore, more research is needed in order to further strengthen these findings. High-quality epidemiological studies investigating BML and effusion/synovitis are especially warranted. An ideal epidemiological study design would be a case-crossover study where individual MRI findings in the presence of knee pain at one time point will be compared with MRI findings in the same patient without knee pain at another time point. The ideal data analysis would provide an association size and permit adjustment for confounders, including age, sex and BMI, and also for other MRI features when multiple MRI findings are studied simultaneously.

Since the performance of the review, more studies have been published on this issue and an update of the present review will follow in the near future.

An important conclusion that has implication for future research on pain in hand OA, is the multifactorial nature of pain. Independent associations were found on joint level of both hard tissue and soft tissue abnormalities. However, on patient level these effects are more difficult to discern. Probably this is due to the multiple causes, such as hard and soft tissue abnormalities simultaneaously, but also psychological and genetical factors, that are present within a patient. It is therefore important to study hand OA on joint level taking into account patients effects.

More longitudinal studies investigating inflammatory US features in hand OA are warranted. Because the studied population in the ECHO study appeared to be a rather severe hand OA population, these studies should be repeated, also in different and larger hand OA populations. In addition to the present study, a follow-up cohort study was started in the Leiden University Medical Center in 2009, where all consecuitive patients who were diagnosed with hand osteoarthritis by their rheumatologist are included. In this study MR images and radiographs of the hands are obtained. To understand more fully the role of soft tissue abnormalities it would be recommended to incorporate US as well. This would give the opportunity to investigate inflammatory features in a larger, less severe hand OA population.

In our studies we found that at follow-up some inflammatory US features are persistent, whereas others are fluctuating. Recently, several clinical trials have been performed with a follow-up duration of around 3 months including inflammatory features as outcomes.[8,9] It is important to realize when performing such trials that inflammatory features fluctuate due to their natural course of disease. These fluctuations should not be mistaken for a possible treatment effect. Therefore, we recommend, first, to undertake large observational studies in hand OA populations to acquire detailed knowledge on the natural course of hand OA. Second, to perform a randomized trial with a placebo group as control .

This thesis shows that US has contributed greatly in our search after the pathogenesis of hand OA and has increased our knowledge on the etiology of pain and structural progression in hand OA. An important task for the future is yet to define more exact criteria for OA features in imaging modalities. In several studies it was shown that the features described as “slight” were not clinically relevant. Also, we have shown that although US descerned far more osteophytes then radiographs, association with pain were found with both modalities, thereby questioning the relevance of the increased sensitivity of US for osteophytes. Also, recently it has become clear that in the knee using MRI in normal subject an astonishing amount of abnormalities can be found that are considered to be OA abnormalities. It has high priority therefore to develop good definitions what is considered to be normal and what abnormal using imaging modalities. The same is true for the definition of what is considered hand OA, since no satisfactory definition is present at this time. In 2010 we started a working group within the OMERACT (Outcome Measures in Rheumatology) with these themes amoung it’s objectives. Within this working group definitions for MRI and US are being defined and validity and reliability exercizes performed. This work is still ongoing.

In the subset erosive hand OA, more inflammatory features were found, not only in the erosive joints, but also in the non-erosive joints of erosive patients. Moreover, strong associations were found between inflammatory US features and erosive development. These findings suggest that in erosive OA systemic underlying mechanisms are implicated.

Finally, to understand the clinical relevance of inflammatory features in hand OA, a proof-of-concept study with an anti-inflammatory drug in patient with hand OA could be very helpful.

There have been three studies that have investigated the effect of corticosteroids in hand OA. These studies did not came to equivocal results.[8,10,11] However, these studies had limitations. One study did not investigate inflammatory features by imaging modalities as US or MRI making it difficult to evaluate the effect on inflammation.[10] Two studies included small patient populations and analyses were done on patient level only, not taking into account patient effects.[8,11] One study had an open study design and lacked a placebo group,[8] the other did only perform 0.2 Tesla MRI without contrast enhencement at baseline and at 4 weeks in the most painfull hand.[11] An ideal proof-of-concept study would be a randomized trial comparing placebo with oral prednisolon during at least one year with evaluation of both clinical outcomes and inflammatory signs. Osteophytes, JSN and erosions should be evaluated as well by radiography and MRI or US.

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