EXTENDED REPORT

Research in hand osteoarthritis: time for reappraisal and demand for new strategies. An opinion paper

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Background: Osteoarthritis of the hands is a prevalent musculoskeletal disease with a considerable effect on patients' lives, but knowledge and research results in the field of hand osteoarthritis are limited. Therefore, the Disease Characteristics in Hand OA (DICHOA) initiative was founded in early 2005 with the aim of addressing key issues and facilitating research into hand osteoarthritis.
Objective: To review and discuss current knowledge on hand osteoarthritis with regard to aetiopathogenesis, diagnostic criteria, biomarkers and clinical outcome measures.
Methods: Recommendations were made based on a literature review.
Results: Outcomes of hand osteoarthritis should be explored, including patient perspective on the separate components of disease activity, damage and functioning. All imaging techniques should be cross-validated for hand osteoarthritis with clinical status, including disease activity, function and performance, biomarkers and long-term outcome. New imaging modalities are available and need scoring systems and validation. The role of biomarkers in hand osteoarthritis has to be defined.
Conclusion: Future research in hand osteoarthritis is warranted.

Osteoarthritis of the hands is one of the most prevalent musculoskeletal diseases. The disease leads to pain in and around affected joints and to swelling, stiffness, deformity and gradual loss of function.[1 2] Contrary to common belief, it is not necessarily a disease of older people, but can occur relatively early in life, impairing the patient's capacity to work. Currently, the detailed pathogenetic events are unknown, and therapy is confined to symptomatic treatment or surgical intervention. Because research activities in osteoarthritis have concentrated on the knee and hip in recent years, knowledge and research results for hand osteoarthritis are limited. Hand joints are frequently involved in combination with osteoarthritis elsewhere; however, such ''generalised osteoarthritis'' may be a function of age rather than representing a generalised nature of the disease.

Given the impact of hand osteoarthritis together with limited research data, the Disease Characteristics in Hand OA (DICHOA) initiative was founded in early 2005 with the aim of addressing key issues and facilitating research into hand osteoarthritis. In this article, we review and discuss current knowledge of the aetiopathogenesis, diagnostic criteria, biomarkers and outcome measures for clinical, epidemiological and follow-up studies, and the therapeutic interventions for hand osteoarthritis to facilitate the development of strategies addressing these issues.

CURRENT DIAGNOSTIC CRITERIA FOR HAND OSTEOARTHRITIS

The criteria for hand osteoarthritis are not clear. In hand osteoarthritis studies, especially epidemiological studies, several sets of criteria are used, none scientifically tested. Both radiographic and clinical criteria sets are applied. Some criteria sets are based on the involvement of various or a particular number of joint groups comprising proximal interphalangeal joints (PIPs), distal interphalangeal joints (DIPs) or first carpometacarpal joints (CMCs), whereas others require the involvement of only one hand joint with osteoarthritis.

A validated criteria set for hand osteoarthritis is the classification defined by the committee on Diagnostic and Therapeutic Criteria of the American College of Rheumatology (ACR).[3] These criteria were developed by comparing patients with clinical hand osteoarthritis, as determined by experts, with patients suffering from other rheumatic disorders causing hand pain such as rheumatoid arthritis (box 1).

These classification criteria have a sensitivity of 0.94 and a specificity of 0.87 in this setting. Pain had to be present on most days of the month before the analysis to fulfil these criteria. However, for epidemiological studies, the need for pain on most

Box 1: American College of Rheumatology criteria for osteoarthritis of the hand

Hand pain, aching or stiffness for most days of the prior month plus 3 of the following 4 criteria:

- Hard tissue enlargement of ⩾2 of 10 selected hand joints*
- Metacarpophalangeal joint swelling in ⩽2 joints
- Hard tissue enlargement of ⩾2 distal interphalangeal joint joints
- Deformity of ⩾1 of 10 selected hand joints

*The 10 selected hand joints include bilateral second and third DIP joints, second and third proximal interphalangeal joints and first carpometacarpal joints.

Abbreviations: ACR, American College of Rheumatology; AUSCAN, Australian/Canadian Osteoarthritis Hand Index; CMC, carpometacarpal joints; DICHOA, Disease Characteristics in Hand OA; DIP, distal interphalangeal joint; MCP, metacarpophalangeal joints; PIP, proximal interphalangeal joint; SACRAH, Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands

days of the previous month may lead to lack of sensitivity and instability of the diagnosis. If clear-cut changes of hand osteoarthritis are clinically evident, the frequent presence of pain would suggest a certain degree of disease activity rather than being a defining diagnostic criterion. Another discussion point is that the ACR classification criteria for hand osteoarthritis combined all joint groups in the hand, so that patients with only two DIPs with two first CMCs affected fulfil the criteria, even though these patients may represent different disease entities, requiring different treatment strategies. Hence, it may be more accurate if all (affected) joints in the hand were to be described separately and that, depending on the research question or intervention under study, the assessment of changes observed in specific hand joints might be required. The requirement for the presence of a certain number of affected joints, as per the ACR classification criteria, is not supported by other research data. From a clinical point of view, it has been suggested that in therapeutic studies of hand osteoarthritis patients with one painful osteoarthritic hand joint could be included.

Although radiographs did not add information for the clinical patient population used for the ACR classification of hand osteoarthritis, it has been suggested that this could be different in other study populations. Moreover, Heberden nodes on physical examination are not always equivalent to osteophytes at DIPs on radiographs. Hence, it may be valuable to add radiographs to collect extra information. Recently a European League Against Rheumatism task force was set up to define a diagnostic criteria set for hand osteoarthritis, which it is hoped will resolve these problems.

Although most studies in osteoarthritis investigate one affected joint site in any given patient, often more joint sites are affected simultaneously.[4 5] A concept of generalised osteoarthritis was suggested from data showing that multiple joint involvement was observed more frequently than expected by chance[6–9] and that joints are not affected at random.[10 11] This can be seen in the hands themselves but also in all the other joints. How hand osteoarthritis is related to osteoarthritis in other joint sites is unclear. Kellgren and Moore defined in 1952 a distinct clinical entity for which they suggested the name of primary generalised osteoarthritis, which was associated with Heberden nodes.[12] To define this entity, radiographic osteoarthritis in 13 joint groups was assessed and a cut-off point was set rather arbitrarily as involvement of at least 3 or 5 affected joint groups.[13] This definition is still widely used.[14] When using this definition, hand osteoarthritis can be defined as generalised osteoarthritis. Alternative definitions for generalised osteoarthritis especially in epidemiological studies are the presence of Heberden nodes.

The generalised nature of osteoarthritis is underlined by data from a Norwegian hand osteoarthritis population, which comprised 199 patients, included in this study on the basis of clinically diagnosed hand osteoarthritis. In total, 82% fulfilled the ACR classification criteria for hand osteoarthritis, 10% fulfilled the clinical and radiographic ACR classification criteria for hip osteoarthritis and 11 patients had undergone a hip replacement. Most (75%) fulfilled the clinical ACR classification criteria for knee osteoarthritis, and 7 patients had undergone a knee replacement.[15] This stresses the importance of incorporating information concerning all joint groups in a patient when investigating hand osteoarthritis and in defining the osteoarthritis phenotype.

RISK FACTORS FOR DEVELOPMENT OF HAND OSTEOARTHRITIS

Much more is known about risk factors for development of osteoarthritis of the knees and hips than for osteoarthritis of the hands. However, some undisputable risk factors have been identified.[16] Age seems to be the strongest risk factor for both radiographic and symptomatic hand osteoarthritis,[17 18] although only up to the age of 75 years.[19] Body mass index is positively associated with osteoarthritis of the hand,[16 20 21] but the reason for this association is currently unknown. Biomechanical influences have been suggested as risk factors for hand osteoarthritis but the evidence is rather weak.[22 23] As for other subtypes of osteoarthritis of the peripheral joints, tobacco smoking seems to decrease the risk for development even after adjustment for body mass index.[16]

Familial aggregation of Heberden nodes was described as early as the 1940s[24] and has since been confirmed for hand osteoarthritis by several studies.[16 25] Genetic factors important in the aetiopathogenesis were identified early in genetic research by linking the *COL2A1* gene to familial osteoarthritis developing at a young age.[16 26] An association between polymorphisms in the *matrilin-3* gene and different subtypes of hand osteoarthritis, idiopathic hand osteoarthritis and first CMC osteoarthritis, has recently been recognised in two separate study populations.[27 28]

IMAGING IN HAND OSTEOARTHRITIS

Plain radiographs are the initial method of choice to image the hands, as they are widely available, cheap and reproducible. The characteristic radiological features of osteoarthritis include joint space narrowing, osteophytes, sclerosis and deformity. It is not clear whether any or all these features are truly indicative of osteoarthritis. Osteophytosis, without joint space narrowing, can be present even after several years of follow-up, raising the question of whether this condition should be addressed as osteoarthritis.[29] Radiographic features of osteoarthritis are often seen in the hands, especially in elderly patients, in the absence of symptoms, and so may represent age-related changes.[30] Kessler *et al*[31] suggested a hand scale for osteoarthritis in which radiological osteoarthritis is defined only when joint space narrowing is present.

To determine the nature and severity of osteoarthritis in hand joints, several standardised qualitative scoring methods can be used, including those described by Kellgren and Lawrence,[32] Kallman,[33] and Altman.[34] Many individual features can be scored, but none of these methods distinguishes between features of damage and repair.

The question arises as to which joints of the hands should be scored. Usually, DIPs, PIPs and first CMCs are assessed in published methods. Whether or not metacarpophalangeal joints (MCPs) should be included is not clear. Further, it has not been clarified whether erosive osteoarthritis is a distinct disease entity or an aggressive variant of hand osteoarthritis. Verbruggen and Veys[35 36] developed a scoring method in which erosive osteoarthritis is addressed. Currently, no validated quantitative scoring method is available for hand osteoarthritis. It is not clear which feature should be addressed, and with regard to joint space width, it is unclear which part of the interbone distance should be measured and how. Osteophytes have been quantified by microfocal radiographic techniques, but this method is not widely available.

MRI is a sensitive imaging method that has been extensively evaluated in the knee, but scarcely in the hand. Methods are being introduced to make the examination less uncomfortable for the patient. At this stage it is also uncertain which tissue types are the most relevant to examine (hyaline cartilage, chondrophytes and osteophytes, synovium, joint effusion, ligaments and capsule or bone-marrow oedema).[37] A scoring method has yet to be defined, tried and tested, although ''whole organ scores'' , such as the Whole Organ Magnetic Resonance imaging Score)[38] and the Knee Osteoarthritis Scoring System[39]

have been evaluated in the knee. It is still unknown which, if any, individual radiological signs indicate the likelihood of progression. Currently, it is felt that so-called bone-marrow oedema is important.[40] No tried and tested method of routinely quantifying hyaline cartilage volume and bone-marrow oedema in disease and health is currently available. The only imaging technique with a known positive and negative predictive value for progressive osteoarthritis is radionuclide imaging.[41] However, this method carries a whole-body radiation burden, and is not cheap or widely available. Currently, the development of ultrasonography techniques for hand osteoarthritis is necessary.[42]

BIOMARKERS

During processes leading to joint tissue destruction in osteoarthritis, extracellular matrix proteins in cartilage, bone and surrounding structures are degraded. Fragments are released into synovial fluid and may subsequently reach the circulation. Such fragments can be quantified by immunoassays, and these ''molecular markers'' have the potential to provide information on ongoing active processes in the tissue. Similarly, there are markers of protein formation within these structures, which may reflect an increase in turnover or attempted repair of damage. This technology has been increasingly used both in osteoarthritis and in rheumatoid arthritis as a means of diagnosis, for estimation of activity of the tissue-damaging process, to document treatment effects and, most importantly, to discover processes in the very early stages of the disease to aid in prognostic considerations.[43 44] Some of these applications have been more extensively studied in rheumatoid arthritis, such as monitoring treatment effects, as treatments with the potential to retard joint damage are available for this disease.[45] Table 1 shows some of the markers currently being explored.

In osteoarthritis, most biomarker studies so far have been performed on knee and to some extent in hip osteoarthritis, and the reports predominantly concern studies of serum/plasma or urine samples. Whether results from knee and hip osteoarthritis are applicable to osteoarthritis of the hands is unknown. Given the fact that hand osteoarthritis is frequently accompanied by osteoarthritis in larger joints, it is also not clear whether it is possible to discern changes reflecting processes in the hands against a background of fragments released into the circulation from other joints. A primary objective on the research agenda would therefore be to explore whether currently available markers and those in development may prove useful in detecting these changes in carefully selected patient groups. Novel markers with higher specificity for osteoarthritis and/or markers that are released only in disease states and not during normal turnover may prove particularly advantageous for monitoring hand osteoarthritis. It should also be emphasised that advances in techniques for analysis may allow future genetic studies, such as studies with gene arrays of tissues or cells, microfluidic cards of specific gene sets, and proteomic analysis of blood, synovial fluid or urine.

Table 1 Currently available cartilage and bone biomarkers

Cartilage	Biomarker
Aggrecan	G1 (hyaluronan-binding-region), chondroitin sulphate region, chondroitin sulphate epitopes, keratan sulphate, aggrecanase cleavage neoepitopes, matrix metalloproteinase cleavage neoepitopes
Type II collagen	C-terminal propeptide, cross-links, collagenase cleavage neoepitopes
Other matrix molecules	Cartilage oligomeric matrix protein (thrombospondin 5), cartilage intermediate layer protein, matrilin-1
Bone	
Type I collagen	N-procollagen and C-procollagen propeptides, N-telopeptides and C-telopeptides
Other matrix molecules	Osteocalcin, bone sialoprotein

Unless existing and promising novel approaches to biomarker identification and testing are applied to hand osteoarthritis, we will continue to have an imperfect appreciation of how useful markers may be in assessing progression of the disease, identifying patients who may benefit from potential disease-modifying therapy, and monitoring response to therapy.

CLINICAL ACTIVITY AND OUTCOME MEASURES

Clinical measures are essential to monitor the disease process and to evaluate the outcome. There is a lack of knowledge as to which outcomes are important to patients with osteoarthritis. If, from the perspective of patients, hand osteoarthritis is a separate entity, outcomes specific for hand osteoarthritis representing patient perspective should be defined. To date, recommendations about which outcomes should be measured have been derived from expert consensus. Clinical improvement criteria for osteoarthritis in general have been defined from clinical databases, but not specifically for hand osteoarthritis.[46] In osteoarthritis in general, the recommendations for assessments include pain, (physical) function and patient global assessment.[47–49] Specifically in hand osteoarthritis, measurements of pain, function, performance, mobility, stiffness, inflammation, deformity and aesthetic damage are recommended.[50]

Pain can be measured with a visual analogue scale or a Likert scale.[46] Function and performance are included as separate entities in the recommendations. Performance always requires measurement by a ''test'', whereas either a ''questionnaire'' or a ''test'' can be used to measure function.[46] For measurement of performance, a hand function test is suggested, such as the Backman hand function test,[51] or grip-strength measurement.[52] Questionnaires specifically developed and/or validated for measurement of function in hand osteoarthritis[53] include: the Health Assessment Questionnaire,[54] the Arthritis Impact Measurement Scales-2 questionnaire,[55] the Australian/Canadian Osteoarthritis Hand Index (AUSCAN),[56 57] the Cochin scale,[58 59] the Functional Index for Hand Osteoarthritis,[60 61] and the Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (SACRAH).[62 63] These questionnaires have mainly been developed from lists of possible items pre-selected by professionals and then scored by the patients, but not from qualitative studies exploring the perspective of patients with hand osteoarthritis. It would be particularly advantageous to see the AUSCAN questionnaire freely and publicly available for academic use. A limitation of all questionnaires is the necessity to translate and validate them for all regions with different languages.

It has been suggested that physical functioning might represent only one perspective of functioning, and a more comprehensive perspective of functioning could include ''participation'' in daily life as a key concept relevant to patients. ''Participation'' refers to a person's relationship to other people and involvement in societal institutions in the International Classification of Functioning, Disability and Health.[64] The ability to perform a given task in a daily life situation may be more important to a patient than their ability to perform a

specified task item in a test situation or on a questionnaire, which may not be at all important to that particular patient.[65 66]

For measurement of mobility, range of motion is usually assessed,[67] although our experience suggests that range of motion measurement may not have sufficient intra-rater reliability for finger joints (data not shown). If mobility is considered an issue important to the patients, a reliable tool or a standardised protocol to increase the reliability should be developed. Stiffness can be measured by the length of morning stiffness or the stiffness subscales of the AUSCAN[56 57] and the SACRAH[62 63] questionnaires, although it is not currently clear whether stiffness is an outcome relevant to patients with hand osteoarthritis.

Inflammation is assessed by joint swelling, night pain, duration of morning stiffness or local erythema, regardless of their clinical relevance, reliability or responsiveness.[46] With similarly questionable relevance, reliability and responsiveness, measurement of deformity includes the presence or absence of bone enlargement, Herberden and Bouchard nodes, and squaring of first CMC or axial deviation. Measuring these variables may require either standard protocols or validated instruments.

Currently no tool exists for the measurement of aesthetic damage, but there seems to be evidence in the literature that this parameter is important to patients.[46]

Whether a domain represents the perspective of the patient or the professional might influence the choice of instrument and both should probably be included in any composite score. Composite questionnaires, such as the AUSCAN[56 57] or the SACRAH,[62 63] which include pain, stiffness and function, represent only the perspective of the patient. Moreover, they appear to combine aspects of long-term outcome and disease activity. It may be more appropriate to separate measures of disease activity from those of long-term outcome, and such instruments need to be developed. Such scores should ideally be multidimensional, composed of both subjective and objective components. Examples of a multidimensional approach, using evaluation of disease activity, functional impairment and imaging, can be found in other diseases, especially rheumatoid arthritis, but also psoriatic arthritis and ankylosing spondylitis,[68] and have proven to be highly useful in linking aetiological, clinical and treatment aspects.

GENERAL CONSIDERATIONS AND RECOMMENDATIONS

We consider the following to be important for future research in the field of hand osteoarthritis:

- Outcomes of hand osteoarthritis should be explored, including the separate components of disease activity, damage and functioning from a disease-specific and generic health status perspective.
- All imaging modalities should be cross-validated in hand osteoarthritis and related to clinical status, including disease activity, function and performance, biomarkers and long-term outcome.
- Several valid radiographic scoring systems exist: conclusive comparative studies are needed.
- New imaging modalities are available and need scoring systems and validation.
- Role of biomarkers in hand osteoarthritis has to be defined; in this context, the specificity of markers has to be evaluated in patients with osteoarthritis confined to the hands and compared with polyarticular (''generalised'') osteoarthritis.
- Which outcome measures address most adequately the outcomes important to patients with hand osteoarthritis?

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