Inflammation as a target for treatment in hand osteoarthritis

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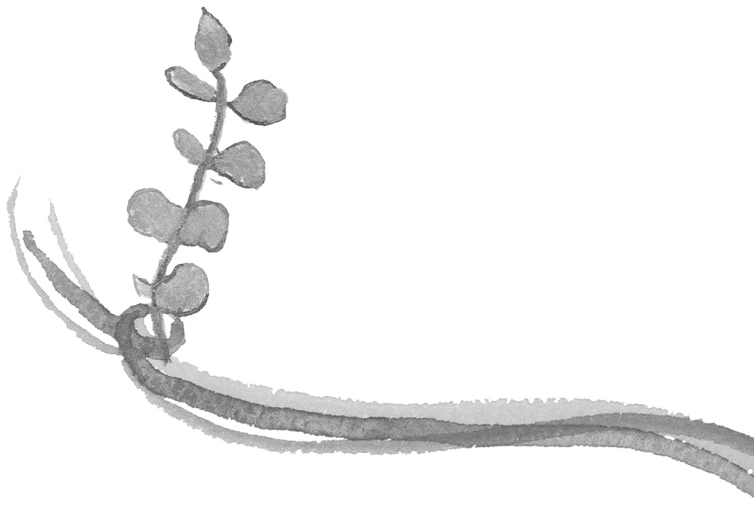
CHAPTER 17

Summary and discussion



SUMMARY AND DISCUSSION

Osteoarthritis is a prevalent chronic rheumatic disease that is associated with a high personal and societal burden of disease.[1] The hand is one of the most commonly affected joint sites. Hand osteoarthritis leads to hand pain, stiffness, functional limitation, decreased grip strength and a reduced quality of life.[2-4] Clinical hallmarks of the disease include bony enlargement and deformities of the hand joints, at times accompanied by soft tissue swelling.[5] Despite the high prevalence and substantial disease-burden, there is an unmet need for effective therapies for patients suffering from hand osteoarthritis. Currently, available treatment options are limited. No disease-modifying treatments exist, and therapies to offer symptom relief are moderately effective at best.

While for a long time hand osteoarthritis was a "forgotten disease", it has gained more interest in recent years. But although the number of studies in the field has increased, thus far progress in finding new therapeutic options for patients with hand osteoarthritis has been disappointing. Several difficulties can be identified that stand in the way of a real breakthrough. An important challenge is that it is yet unclear which tissue to target by treatment, largely caused by omissions in our understanding of the underlying mechanisms leading to osteoarthritis development. Second, evidence is accruing that hand osteoarthritis is a heterogeneous disease, and that a differential approach is warranted for different hand osteoarthritis phenotypes. A third challenge lies in shortcomings in outcome measurement in hand osteoarthritis studies, precluding adequate assessment of potential treatment effects. In this chapter we will summarise the main findings of the studies described in this thesis, which addressed aspects of these challenges and made a start towards facilitating the development of new treatment options for patients with hand osteoarthritis.

Current treatment options in hand osteoarthritis

In **part I** of this thesis we wished to gain insight in the current state of treatment for patients with hand osteoarthritis. **Chapters 2-3** provide an overview of the currently available therapeutic options, which range from non-pharmacological to pharmacological and even surgical modalities. Data from multiple trials, summarised in these chapters, show that hand exercises and prolonged splinting of the thumb base are non-pharmacological therapies resulting in symptom relief. Additionally, single trials have shown positive results for joint protection strategies and the use of assistive devices (including for example cutlery with built-up handles, ergonomic pens and devices to facilitate opening bottles, cans or jars). Pharmacological therapies that most evidently proved to be efficacious in relieving symptoms were non-steroidal anti-inflammatory drugs (NSAIDs), both topical and oral preparations. Moreover, single trials have reported beneficial results for chondroitin sulfate and intra-articular injections of glucocorticoids in interphalangeal osteoarthritis.

Besides providing an overview of available therapies for patients with hand osteoarthritis, there are other important things to be learned from **chapters 2-3**. Although the number of trials since the previous evidence synthesis for the 2007 EULAR recommendations for the management of hand osteoarthritis had steeply increased (i.e., 39 out of 50 and 43 out of 64 included trials of non-pharmacological and pharmacological therapies in **chapter 3**, respectively, were published in 2007 or later), their quality was not consistent. The risk of bias in many trials was judged to be high, especially in trials of non-pharmacological therapies, mainly due to a lack of blinding or the use of an inadequate method of randomisation. Evidence from trials with a high risk of bias should be interpreted with caution, since bias in a trial can produce misleading results.

Furthermore, effect sizes of effective therapies were modest. For example, the effect of oral NSAIDs on pain was the largest consistent effect observed, yet the effect size only reached 0.4, which is generally regarded a small effect.[6] Only the effects of prolonged thumb base splinting, oral NSAIDs and intra-articular glucocorticoid injections in interphalangeal joints, the last only evaluated in one study, crossed the margin of clinical meaningful difference. Moreover, almost all trials focussed on symptom alleviation, and the few trials that did investigate structure modification found no evidence for disease-modification.

Finally, this data synthesis did not only show us what evidence had been collected, but also what is lacking. Indeed, important questions remain, and, amongst others, well-performed (placebo-controlled) trials of paracetamol and surgical interventions are warranted, as are replications of the single positive trials of, for example, topical NSAIDs, intra-articular glucocorticoid injections in interphalangeal joints and chondroitin sulfate. An example of a trial that could answer a combination of research questions would be a three-armed trial comparing paracetamol, topical NSAIDs and placebo. This type of trial would be a good example of an efficiency study ("*doelmatigheidsonderzoek*"), a research type becoming more and more important with the rising demand for care and increasing costs. While paracetamol is a cheap and commonly used analgesic in daily clinical practice, through prescription by health care providers but definitely also by self-care by patients, it has barely been investigated in clinical trials, limiting the ability to properly advise on its use in treatment recommendations (**chapter 4**). Furthermore, topical NSAIDs are now advised as first-line drug treatment to relieve hand osteoarthritis symptoms based on efficacy in one placebo-controlled trial (**chapter 4**), but it is unknown whether its benefits outweigh the higher costs of these drugs, and since the advice is based on only one trial, it needs to be replicated.

Because of the large number of new trials performed since the first EULAR recommendations for the management of hand osteoarthritis published in 2007, it was timely to update these with the newly accrued evidence. **Chapter 4** presents the 2018 update of the EULAR recommendations for the management of hand osteoarthritis, based on a review of the literature (**chapter 3**) and expert opinion from an international task force of experts in the field. The task force, consisting of 19 physicians, health care professionals and patients from 10 European countries, agreed upon five overarching principles and 10 recommendations. The overarching principles covered treatment goals, information provision, individualisation of treatment, shared decision-making and the need to consider multidisciplinary and multimodal (non-

pharmacological, pharmacological and surgical) treatment approaches. The role of different non-pharmacological therapies is covered in the first three recommendations, where the provision and use of education and assistive devices is discussed (#1), as well as hand exercises (#2), and orthoses (#3). Several pharmacological therapies are the topic of recommendations 4-8. Topical treatments are preferred over systemic treatments, with topical NSAIDs as the first-line choice (#4), while oral analgesics, particularly NSAIDs, are to be considered for symptom relief, as long as the risk-benefit-ratio is taken into account and prescription is of limited duration (#5). Chondroitin sulfate may be considered for symptom relief (#6). Intra-articular injections of glucocorticoids are generally not recommended, except in particular cases, for example in patients with painful interphalangeal osteoarthritis (#7). Prescription of conventional or biologic disease-modifying antirheumatic drugs is discouraged (#8). Considerations for surgery are discussed in recommendation #9. The last recommendation (#10) pertains to follow-up.

The recommendations presented in **chapter 4** provide up-to-date guidance on the management of patients with hand osteoarthritis. The major changes in comparison with the 2007 recommendations show that we have gained new insights into the management of this disease in the last decade. Recommendations and guidelines are important tools to facilitate the integration of research findings into daily clinical practice. However, in order to substantially influence daily clinical practice and care for patients with hand osteoarthritis, dissemination and implementation of recommendations is crucial. Uptake of guidelines in clinical practice has proven to be a challenge. While there are many published guidelines for osteoarthritis, research has shown that a gap exists between the care that is recommended versus the care that patients receive.[7-9] This problem is not unique for the field of osteoarthritis: the same holds true for the uptake of recommendations in other chronic rheumatic diseases, such as rheumatoid arthritis.[10]

When comparing recommended with delivered health care in daily clinical practice, an interesting paradox becomes apparent: the failure to deliver needed services, while continuing to deliver unnecessary services. These two concepts are referred to as "underuse" and "overuse" of health care.[11] It has been shown that underuse of simple and effective interventions, as well as overuse of ineffective services occur often and simultaneously.[12,13] Both concepts are equally problematic: underuse leads to avoidable suffering from disease, while overuse may lead to avoidable physical harms from adverse events and financial harms from wasted resources. Underuse can arise from several sources, including poor access to health care, lack of availability in the health care system, failure of providers to deliver the service and failure of patients to use it.[13] Factors that drive overuse are also numerous, including, for example, effects of money flow on incentives and integration of care, knowledge gaps, misleading psychological tendencies and erroneous beliefs.[14] Examples of under- and overuse can also be found in osteoarthritis health care.

A compelling example of underuse in osteoarthritis care was demonstrated in a trial in which health care providers caring for patients with hip or knee osteoarthritis were randomised to receiving evidence-based treatment recommendations by a study team versus usual care.[15] While many providers in the intervention group were recommended by the study team to provide simple interventions such as physical therapy (49%), knee braces (41%) or topical

NSAIDs (50%), only part of the providers actually advised or prescribed these to the patient in question (physical therapy: 20%, knee brace: 36%, topical NSAIDs not reported) and even fewer patients actually received the treatment (7%, 9% and 15%, respectively). The same authors found similar results in a larger trial with a similar intervention.[16] These results illustrate how underuse originates from multiple sources, increasing the magnitude of the problem: recommended care was not provided by the health care provider and patients failed to adhere to the prescribed care. While the first can likely be improved by efforts in dissemination and implementation of recommendations, the second deserves at least as much attention, and is crucial for any treatment to succeed.

As an example of overuse in osteoarthritis care, the same trials also showed that the number of patients in whom joint injections were provided outnumbered the instances in which injections were actually recommended.[15,16] Other studies have reported the rate of inappropriate total knee replacement in Spain and the United States to be 26% and 34%, respectively.[12] More indirect evidence of overuse within osteoarthritis health care comes from otherwise unexplained inter- and across country variations in certain interventions, such as a 13-fold regional variation in the rate of arthroscopic knee lavage in England.[12]

Examples of steps that have already been taken to gain awareness of the updated recommendations presented in **chapter 4** are presentations by members of the task force at national and international rheumatology conferences. In addition, a EULAR Health Professional project that aims at implementing best practice for hand osteoarthritis, for example by making short instruction videos which hand exercises patients can do, is ongoing. Other methods to aid dissemination of these recommendation to health care providers who see patients with hand osteoarthritis in daily clinical practice in the Dutch situation could encompass publication of a Dutch translation by relevant national societies, such as the Dutch rheumatology society (Nederlandse Vereniging voor Reumatologie, NVR) but also the Dutch general practice society (Nederlandse Huisartsen Genootschap, NHG). Ideally, this should not only be a literal textual translation, but also a translation to Dutch clinical practice, acknowledging barriers for implementation of the recommended care. For example, while topical NSAIDs are advised as first-line pharmacological treatment in these new recommendations, in the current Dutch health care system topical NSAIDs are not available free of charge. For some patients paying for medication will be an important barrier to adherence, and a risk for underuse.

In conclusion, updating the recommendations for the management of hand osteoarthritis alone is not enough. Care should be taken to support the uptake of these recommendations in daily clinical practice, and to be aware of over- and underuse in osteoarthritis care.

Inflammation as treatment target

From the studies in **part I** we learned that available treatment options for hand osteoarthritis are currently unsatisfactory, and new treatment options are warranted. To develop novel therapies, it is crucial to know which tissue to target by treatment. However, at this moment important omissions in our understanding of the aetiology of hand osteoarthritis hamper the search for such a treatment target.

Studying the pathogenesis of hand osteoarthritis is difficult for several reasons. Due to the localisation of the disease in the small hand joints, it is difficult to obtain samples of diseased tissue for researchers, and the quantities of obtained tissue are small. Also, existing animal models of osteoarthritis are more reflective of osteoarthritis of weight-bearing joints, such as the knees or hips, than of the hands, of which no animal models exist. Our understanding of hand osteoarthritis pathogenesis therefore largely comes from epidemiological studies of genetic data, advanced imaging data and clinical trials. In the next paragraphs, we will focus on the latter two.

Since the introduction of ultrasound and magnetic resonance imaging (MRI) our knowledge of hand osteoarthritis has vastly increased. In contrast to conventional radiographs, these imaging modalities provide us with the opportunity to visualise other joint structures than bone, including the collateral ligaments, cartilage and synovium, and on MRI the subchondral bone can be assessed. Studies using ultrasound and MRI showed that inflammatory changes are often present in hand joints affected with osteoarthritis.[17-19] Inflammatory signs that can be assessed on ultrasound include synovitis, effusion and power Doppler signal (PDS; a sign of increased vascularisation). Synovitis can also be assessed on MRI. Besides that, bone marrow lesions (BMLs; ill-defined lesions in the subchondral bone with high signal intensity on T2-weighted fat-suppressed images) can be seen with MRI, which in osteoarthritis may primarily be a sign of increased bone remodelling.[20] Subsequent studies have demonstrated that these inflammatory signs are associated with clinical features, particularly joint tenderness.[17-19,21] Furthermore, longitudinal studies have demonstrated that presence of inflammation in a joint was associated with radiographic progression,[22-25] as well as erosive progression in the same joint.[23,26,27] Interestingly, inflammation was associated with radiographic progression even after adjustment for the amount of radiographic damage at baseline, which is known to be a predictor for future radiographic damage.[28] Finally, it was also shown that an increase in inflammatory signs on MRI is associated with the development of joint tenderness, independent of structural progression.[29,30] Interestingly, one of these studies also demonstrated the opposite: an association between decreasing synovial inflammation and less joint tenderness.[30]

Evidence from these imaging studies led us to believe that inflammation plays an important role in hand osteoarthritis, and that it may be a viable target for treatment.

To investigate this hypothesis, we set up a proof-of-concept study. In the HOPE study, a fourteen-week placebo-controlled randomised clinical trial, we investigated the effectiveness of short-term low-dose oral prednisolone in patients with painful hand osteoarthritis who had evidence of synovial inflammation. The well-known potent anti-inflammatory characteristics of prednisolone provided us with the opportunity to investigate whether inflammatory signs in patients with hand osteoarthritis can be modulated, and whether this consequently has beneficial effects on their signs and symptoms. In this trial, of which the results are presented in **chapter 5**, we found that six-week treatment with prednisolone led to a substantial improvement in finger pain, which was our primary outcome. Secondary outcome measures of pain and function were also consistently more improved in the prednisolone group, and a remarkable higher proportion

of patients in the intervention group fulfilled the OMERACT-OARSI responder criteria. To put these results into context, we can compare the effect sizes of different therapies. The effect size is a way to quantify the magnitude of an effect. Cohen's d, a commonly used type of effect size, is calculated by dividing the difference of the mean of the two intervention groups by the standard deviation. As described in **part I**, most therapeutic options in hand osteoarthritis that are considered to effectively relieve pain, have an effect size of around 0.2, which can be considered a small effect.[6] NSAIDs have one of the largest effects, with an effect size of 0.4 on pain. In the HOPE study, we found an effect size of 0.7 on pain. The same comparison can be made for function, for which the effect size of 0.6 in the HOPE study substantially exceeds the effect sizes of all other interventions, which lie around 0.2.

Another, at least as important finding, is the effect we found on clinical and imaging measures of inflammation. Showing that inflammation in hand osteoarthritis can be modulated is an important first step towards targeted treatment in hand osteoarthritis. Interestingly, while prednisolone had a significant beneficial effect on ultrasound synovitis and MRI BMLs, between-group differences in the other imaging parameters of inflammation (ultrasound PDS, MRI synovitis) were small. Possibly, the prevalence, particularly of PDS, was too low to detect change. Alternatively, PDS and MRI synovitis may not be sensitive-to-change, which can either be a characteristic of the feature itself or a shortcoming in the scoring method that was used, and these imaging features may represent different aspects of inflammation. Another noteworthy finding was that in contrast to the other imaging features, the between-group difference in MRI BMLs primarily stemmed from a deterioration in the placebo group. Few other studies assessed the effects of anti-inflammatory therapies on inflammation on ultrasound or MRI in hand osteoarthritis, generally with negative results.[31-34] None of the studies that included MRI synovitis as an outcome measure could detect a change in this feature,[31,33,34] while one trial observed a significant decrease in MRI BMLs.[33] The trials that used ultrasound were all negative, though variable quality of ultrasound machines and a generally limited reproducibility of scores hindered the detection of between-group differences by ultrasound in many studies.[32,33] Furthermore, it is important to realise that comparison with these studies is hampered by the concurrent negative results for clinical outcome measures of those studies. In other words: those interventions were not effective in the first place, so a change in joint inflammation may also not be expected.

After tapering the study medication, beneficial effects on signs and symptoms were not sustained and resumed baseline values. While the observed symptomatic effect at week six was substantial, it is unknown whether continued treatment with prednisolone would have led to further improvements. Future studies to investigate the optimal dosage and duration of treatment are warranted. This could be done in trials employing treat-to-target strategies. One could for example consider to perform a trial with multiple arms with a range of initial prednisolone dosages to find an optimal dosage, but also trial designs with a step-down-step-up protocol dependent on the fulfilment of a certain definition of low and high disease activity as treatment target are of interest, and possibly a combination of these. Trials with treat-to-target strategies are highly dependent on the choice of a suitable definition for low and high disease activity on which treatment decisions are subsequently based, so this would first warrant further investigation, possibly using data acquired in the HOPE study.

The HOPE study provides evidence for the efficacy and safety of short-term treatment with low-dose prednisolone in patients who experience a flare of their disease. Prednisolone is an inexpensive, widely available drug, providing ample opportunity to directly apply these findings in daily clinical practice. However, we included hand osteoarthritis patients with specific characteristics, and therefore the results of this study cannot be generalised to all patients with hand osteoarthritis. It is likely that joint inflammation is a prerequisite for the effectiveness of prednisolone. While in clinical practice confirmation of presence of inflammation on ultrasound is impractical for many reasons, such as the availability of an ultrasound machine, time constraints, and lack of expertise, doctors who consider prescribing prednisolone to a patient with hand osteoarthritis should at least confirm that there is clinical evidence of joint inflammation. Also, this study only provides evidence for treatment for a short and clearly limited period of time.

Besides the interesting results of the efficacy and safety of prednisolone, the HOPE study also taught us other, more general lessons regarding clinical trials in hand osteoarthritis.

We employed stringent inclusion criteria and selected a specific subset of hand osteoarthritis patients. While this could be viewed as a limitation, since it limited the generalisability of the results as discussed above, it is also an important strength of the study. Osteoarthritis is a heterogeneous disease. Clear patient stratification is therefore essential to select patients who will most likely benefit from treatment. Failure to select the appropriate patient population may have been a reason that so many previous trials in hand osteoarthritis were negative. Moreover, the proof-of-concept nature of the trial, to evaluate inflammation as treatment target, made it essential to include patients with evidence of joint inflammation. In other words, we performed an explanatory trial, as opposed to a pragmatic trial, a distinction first proposed by Schwartz and Lellouch.[35] Explanatory trials are designed to confirm a physiological or clinical hypothesis, whereas pragmatic trials inform clinical or policy decision by providing evidence for adoption of the intervention into real-world clinical practice.[36] While explanatory or mechanistic trials often have higher internal validity, pragmatic trials often have the advantage of improved external validity. Therefore, the ideal time to perform a pragmatic trial would be during the implementation stage of an intervention, and only after we have any real understanding of treatment benefit and potential adverse effects.

One of our inclusion criteria was the presence of a flare in hand pain after analgesic washout of at least 20 mm on a visual analogue scale (VAS). It has been suggested that flare designs, which are especially common in NSAID trials, are efficient, because it would lead to larger treatment effects and selection of patients with an "inflammatory" phenotype. However, during the course of the HOPE study, the flare criterion appeared difficult to assess and a reason for ineligibility of a substantial number of patients, despite a clinical presentation with "inflammatory" hand osteoarthritis and fulfilling other inclusion criteria. Therefore, during the course of the trial we decided to also include patients who did not experience a flare after analgesic washout. In accordance with a study published at that time, sensitivity analyses excluding those patients led to highly comparable between-group differences in the primary endpoint as the main analysis.[37] In hindsight, it is debatable whether a flare design was needed in our trial.

Finally, observed differences in the HOPE study between the results of different instruments all measuring the same domain, for example, comparing the treatment effect on pain measured by the VAS or by the Michigan Hand outcomes Questionnaire (MHQ) pain subscale, stresses the necessity of using instruments that are sensitive-to-change, as will be further discussed in one of the next paragraphs of this chapter.

While we were able to demonstrate an effect on pain and inflammation on the short-term, a question that remained unanswered in the HOPE study was whether suppression of inflammation may also modify the disease course of hand osteoarthritis on the long-term. Radiographic progression is a slow process, so to investigate whether suppression of inflammation may retard radiographic progression, studies with long-term follow-up are needed. Future studies investigating long-term effects of treatment with prednisolone on radiographic disease progression are therefore of interest, although, in comparison with short-term studies, the risk-benefit-ratio of prolonged glucocorticoid treatment becomes even more important to consider.

Systemic blockade of tumour necrosis factor (TNF) is also a potent method of suppressing inflammation, which is widely used in other chronic rheumatic diseases, such as rheumatoid arthritis. TNF-alpha is an important proinflammatory cytokine, produced in the inflamed synovium in osteoarthritis and implicated in several processes of osteoarthritis pathophysiology.[38] The clinical efficacy of TNF-inhibitors in patients with hand osteoarthritis has been investigated in several randomised clinical trials.[31,33,39,40] Generally, these trials failed to show beneficial effects on symptom relief, which suggests that, in contrast to for example rheumatoid arthritis, targeting a single cytokine may not be sufficient in osteoarthritis.

Osteoarthritis does not only lead to signs and symptoms such as pain, functional disability and reduced grip strength, but also causes progressive structural joint damage. While short-term clinical trials are ideal to investigate the clinical effects of anti-inflammatory medication, studies with long-term treatment and follow-up are needed to evaluate effects on structural damage. To investigate long-term effects of anti-inflammatory treatment in hand osteoarthritis, we and others took the opportunity to use ten-year follow-up data from the BeST study.[41] The BeST study is a randomised clinical trial originally designed to compare the efficacy of four treatment strategies in recent-onset rheumatoid arthritis patients, including treatment with TNF-inhibitors. Hand osteoarthritis is often present in these patients, either due to co-occurrence of primary osteoarthritis (predominantly in the distal and proximal interphalangeal (DIP and PIP) joints) or due to secondary osteoarthritis (predominantly in the PIP joints). Using data from the BeST study, we analysed the effect of prolonged treatment with TNF-inhibitors on incidental and progressive radiographic osteoarthritis in DIP and PIP joints.[42] We found that treatment with TNF-inhibitors was associated with a reduced risk, albeit small, of osteoarthritis progression in DIP joints after 10-year follow-up in patients with recent-onset rheumatoid arthritis, in line with findings in the same cohort after three-year follow-up.[43] While the study design may not have been ideal, data from that study suggest a role for TNF in the development of joint damage in osteoarthritis.

Interestingly, two clinical trials with a longer follow-up have performed subgroup analyses of the effect of anti-TNF in joints with active joint inflammation at baseline, and demonstrated a reduction in erosive progression after one year in inflamed joints of patients in the active treatment

arm compared to placebo, supporting our observations in the BeST cohort.[33,40] One of these trials further showed that BMLs decreased upon anti-TNF treatment, though no treatment response was seen on synovitis.[33] Further stratification revealed that this reduction of BMLs was primarily present in joints with synovitis at baseline. This apparent contradiction – no effect on synovitis itself, but a more pronounced reduction of radiographic erosive damage and BMLs in joints with inflammation – suggests that the interrelation between synovitis, subchondral bone marrow changes and structural damage is not straightforward. It suggests interplay between synovitis and the subchondral bone, possibly via cytokines like TNF-alpha. There are several pathways through which TNF-alpha can affect the subchondral bone, for example by induction of the production of other proinflammatory cytokines such as IL-6 and IL-8, through induction of the synthesis of matrix metalloproteinases (MMP) by chondrocytes and synovial cells, by activation of the cyclooxygenase-pathway, and by upregulation of the production of nitric oxide.[38] In a biomarker substudy of this trial, MMP-3 was indeed suppressed in the anti-TNF treated group.[44] Furthermore, in-vitro studies have shown that TNF-alpha can induce bone resorption by osteoclasts, and treatment with anti-TNF appeared to improve subchondral bone structure in animal models of osteoarthritis.[45,46] If it is true that TNF produced by inflamed synovium is a link between synovitis and bone processes in osteoarthritis, then inhibition of TNF may have an effect on the subchondral bone without impacting synovitis. Following this line of thought, it is conceivable that omnipotent suppression of inflammation through prednisolone (**chapter 5**) may reduce synovitis, subsequently decrease TNF production, and in this way also have an effect on subchondral bone. Moreover, observational studies have suggested that BMLs have an additive effect on pain when present in combination with synovitis, but that in absence of synovitis, BMLs have little effect on pain.[21,30] If synovitis is the main driver of pain in hand osteoarthritis, this would further explain why an intervention that does not impact synovitis but does reduce BMLs (anti-TNF) does not lead to clinical improvements, while an intervention that impacts synovitis as well as reducing BMLs (prednisolone) does invoke substantial symptom relief.

Future studies are warranted to elucidate this proposed interaction between the synovium and subchondral bone in hand osteoarthritis. As discussed above, while long-term studies of treatment with glucocorticoids would be of interest in this respect, prolonged glucocorticoid treatment is known to be associated with adverse effects that may outweigh the possible benefits. Other interventions also capable of general suppression of inflammation are the recently developed group of janus kinase (JAK) inhibitors, of which the first are now approved for the treatment of several chronic inflammatory rheumatic diseases. JAK inhibitors interfere with cytokine signalling by inhibiting the activity of one or more enzymes of the JAK family, which are crucial for signal transduction of several cytokine receptors. Since this signalling pathway is involved in many different cytokines, the activity of multiple cytokines is suppressed simultaneously. Therefore, a long-term clinical trial with a JAK inhibitor may be an interesting alternative.

In **chapter 9** we zoomed out, and looked at the role of inflammation in osteoarthritis from a completely different perspective, focussing on the systemic low-grade inflammation as is known to be present in obesity. Previous studies had provided evidence that not only mechanical, but also systemic factors are involved in the observed association between obesity and osteoarthritis

(figure 1, **chapter 1**). In the study described in **chapter 9**, we investigated the role of adipokines, bioactive factors produced by adipose tissue, as one of these systemic factors. We observed that increased leptin levels were associated with higher odds of knee and hand osteoarthritis, while adiponectin levels were not associated with osteoarthritis. Thereafter, we performed mediation analyses to investigate whether leptin could be one of the systemic factors connecting adiposity and osteoarthritis. In other words, we questioned whether part of the observed association between adiposity and osteoarthritis was in fact explained by a pathway of associations going from adiposity via leptin to osteoarthritis. Here, leptin is the so-called mediator. We found that leptin was a partial mediator in the association with knee and hand osteoarthritis. Sex-stratified analyses showed that the interrelations between adiposity, leptin and osteoarthritis were generally stronger in women than in men. These sex differences are in line with previous research showing that the aetiology of knee osteoarthritis in men is mainly biomechanical in nature, while in women there is a larger systemic or inflammatory component.[47,48] Another interesting observation was that when we adjusted the knee osteoarthritis analyses for body weight, as a proxy for the mechanical component of adiposity, the mediating effect of leptin only remained present in the lowest weight category. This suggests that in participants with a high body weight the detrimental effect of increased load is the most important determinant of osteoarthritis, while in those with a lower body weight the biomechanical effect is smaller and systemic effects play a larger role. Though this study supports the growing body of evidence for systemic effects of adipose tissue in osteoarthritis, adipokines are likely not the sole systemic factors by which adiposity contributes to osteoarthritis, but just one of the many mechanisms activated in the systemic inflammatory state that is present in obesity.

Thumb base osteoarthritis: a distinct hand osteoarthritis subset

Evidence is accruing that hand osteoarthritis is a heterogeneous disease. Any hand joint can be affected, though it most commonly occurs in the DIP, PIP and first carpometacarpal (CMC-1) joints. Besides the localisation of osteoarthritis in the hand, other factors that can vary between patients include, for example, the associated symptoms, speed of progression, and development of joint erosions. The heterogeneity of the disease is one of the challenges in hand osteoarthritis research.

Different hand osteoarthritis subsets have been proposed, based on their association with distinct risk factor profiles and disease outcomes.[49] The most important subsets include interphalangeal osteoarthritis (with or without nodes), thumb base osteoarthritis and erosive osteoarthritis. Data from studies described in **chapter 6-8** provide support for thumb base osteoarthritis as a distinct hand osteoarthritis subset, as will be discussed below.

A widely used intervention for thumb base osteoarthritis is intra-articular injection with glucocorticoids. However, from a meta-analysis of studies comparing these injections with placebo, presented in **chapter 6**, we had to conclude that intra-articular injection with glucocorticoids is not efficacious in thumb base osteoarthritis. Although the glucocorticoid and placebo groups both improved from baseline, there was no between-group difference. However, a placebo-controlled study of intra-articular glucocorticoid injections in interphalangeal joints did show promising effects on pain upon movement and joint swelling

in the injected joint, although not all endpoints were met.[50] Since the main mechanism of action of glucocorticoids is based on its anti-inflammatory properties, as discussed earlier in this chapter, we hypothesised a different role of inflammation in thumb base compared to finger osteoarthritis.

To explore this hypothesis, we investigated the relation between inflammation, radiographic damage and pain in thumb base osteoarthritis (**chapter 7 and 8**). We observed that, like in other hand joints with osteoarthritis, inflammatory signs on ultrasound and MRI were often present in the thumb base (**chapter 7**). While these inflammatory features were associated with joint tenderness, radiographic damage was a more important determinant, and after adjustment for radiographic damage the relation between inflammation and pain attenuated considerably. This is in contrast to what has been found in interphalangeal osteoarthritis, where the association between inflammation and pain is independent of radiographic damage.[17,21] Yet, to conclude that inflammation is not important in thumb base osteoarthritis is too simple, because additional analyses showed that the combined presence of inflammation and structural damage in a thumb base joint had an additive effect on pain, or in other words: the whole is greater than the sum of its parts (**chapter 7**).

Next, we set out to investigate whether a change in inflammation affects the course of joint pain in the thumb base. From interphalangeal osteoarthritis we knew that more synovitis was associated with more pain, and that vice versa less synovitis was associated with less pain, and also that fluctuation in BMLs amplified this effect of synovitis on change in pain.[29,30] In the thumb base we saw that an increase in synovitis and BMLs was associated with an increase in pain, particularly in joints with osteophytes at baseline (**chapter 8**). The number of joints with decrease in synovitis was too small to assess its relation to decrease in pain. A decrease in BMLs was associated with a decrease in pain.

Taking the results of **chapters 7 and 8** together, radiographic damage is the most important predictor of pain in thumb base osteoarthritis cross-sectionally, yet a change in inflammatory features may still be relevant. This is of interest for clinical trials. The inclusion criteria used in the trials of intra-articular glucocorticoid injections in thumb base osteoarthritis focussed on the presence of radiographic damage and/or pain, disregarding whether inflammation was present. If the trials would have selected patients with radiographic damage and concurrent joint inflammation, the trials may have led to different results. In the HOPE study (**chapter 5**) we deliberately excluded patients with predominantly thumb base complaints. Still, we observed an improvement in thumb base pain in the prednisolone group compared with placebo, albeit less than the observed effect on finger pain. This difference with the trials of intra-articular glucocorticoids may have been caused by the selection of patients with an "inflammatory" osteoarthritis phenotype, and therefore a higher prevalence of inflammation in the thumb base. It is also likely that patients in the HOPE study had less severe thumb base osteoarthritis, especially less radiographic damage, than the patients included in the trials of intra-articular glucocorticoid injections, which has an important influence on (change in) pain as we saw in **chapters 7 and 8**. Since the analyses described in **chapter 8** were hampered by the low amount of change in both inflammatory features and pain, it would be interesting to repeat these analyses in a positive clinical trial such as the HOPE study.

Even though inflammation also plays a role in thumb base osteoarthritis, it seems to be of less importance than in interphalangeal osteoarthritis, and intertwined with radiographic damage. Differences in underlying aetiology may explain this. The thumb base is a unique joint complex within the hand. It has to bear higher loads than finger joints and has a significantly larger, multidirectional range of motion, at the cost of joint stability.[51] Results from several studies have demonstrated the importance of these mechanical factors. For example, CMC-1 subluxation, higher maximal grip strength and hypermobility are all associated with CMC-1 osteoarthritis, but not with DIP osteoarthritis.[52-55] In the development of thumb base osteoarthritis these mechanical influences likely play a crucial role.

The studies described in **chapter 6-8** underline the importance of separate assessment of hand osteoarthritis subsets. If the relative effect of structural damage on pain is so much larger than that of inflammation in thumb base osteoarthritis, it is reasonable to focus on other types of interventions in thumb base osteoarthritis than those targeting inflammation. It may well be true that assessment of hand osteoarthritis as a whole, with disregard of the existence of specific subsets or phenotypes, has a large effect on study results. Pooling effects of heterogeneous subgroups may lead to null findings, despite a true intervention effect in one of the subgroups included.

While some trials have investigated interventions in certain hand osteoarthritis subsets, such as thumb base splints in thumb base osteoarthritis and anti-inflammatory type medication in so-called "activated" (interphalangeal) osteoarthritis,[56,57] many hand osteoarthritis trials use a clinical diagnosis of hand osteoarthritis or ACR classification criteria as their main inclusion criterion.[58] The ACR classification criteria, however, do not distinguish between osteoarthritis in interphalangeal and thumb base joints. Even more so, patients with isolated thumb base osteoarthritis, without concurrent involvement of interphalangeal joints, do not fulfil the ACR criteria for hand osteoarthritis. Currently, no separate classification criteria for thumb base and interphalangeal osteoarthritis exist. Separate classification criteria for interphalangeal and thumb base osteoarthritis could aid the development of therapies directed specifically at patients suffering from either one of these subsets. However, it is important to realise that osteoarthritis of the interphalangeal and thumb base joints often co-occurs and hand osteoarthritis subsets regularly overlap.[59]

Besides consideration of including the intended patient group in a study, it is important to be able to measure relevant outcomes in these patients. For example, the development of an MRI scoring system for interphalangeal osteoarthritis fuelled our ability to study the role of inflammation in the DIP and PIP joints, which led to increased insights in the disease.[60,61] Investigation of thumb base osteoarthritis with MRI, however, had rarely been done up to recently. This was, among other reasons, due to lack of an MRI scoring system for thumb base osteoarthritis. While ultrasound has been available, MRI has specific advantages over ultrasound in the case of the thumb base, including the ability to evaluate less superficially located joints and the ability to visualise both the radial and ulnar side of the joint. In addition, with MRI the subchondral bone can be assessed. Therefore, we developed the Outcome Measures in Rheumatology

(OMERACT) Thumb base Osteoarthritis MRI Scoring system (TOMS) in collaboration with the OMERACT MRI working group (**chapters 15-16**). The studies presented in **chapter 7 and 8** could only have been performed after development of the OMERACT TOMS.

Outcome measurement

As described in **chapter 1** of this thesis, high-quality outcome measurement is another prerequisite to advance our understanding of this disease. Below are two examples from studies described in **part I and II** of this thesis to illustrate this.

The overview of the available hand osteoarthritis trials (**chapter 2 and 3**) shows that outcome measurement in trials in hand osteoarthritis is still diverse and of variable quality. When several studies investigate the same intervention, but measure either different endpoints or use different instruments to measure the same endpoint, it becomes difficult to synthesise the evidence. In **chapter 3**, despite the inclusion of many trials, meta-analysis was often not possible for this reason. Trials that are performed, but of which results cannot be used, may be considered a form of research waste. Development of core domain sets is a way to reduce this research waste, if they are consistently used. Therefore, it is important to determine the uptake of a core domain set (and avoid that it becomes research waste itself). Although generally the recently published trials included in the systematic review (**chapter 3**) often assessed a larger part of the OMERACT core domain set for hand osteoarthritis than older studies did, uptake of the core domain set in hand osteoarthritis trials has not been formally investigated before, as has been done in some other rheumatic diseases.[62,63]

Another example of the importance of outcome measurement comes from the clinical trial described in **chapter 5**. In this trial we assessed several endpoints with multiple instruments. For example, pain was assessed using the VAS, the Australian/Canadian Hand Osteoarthritis Index (AUSCAN) and the MHQ. While the VAS pain and the AUSCAN pain showed a large between-group difference in pain in favour of the intervention group, the between-group difference on the MHQ pain was much smaller. Expressed as a percentage relative change from baseline, the patients in the prednisolone group improved by around 40% on the VAS and AUSCAN, while they relatively improved around 16% on the MHQ. This demonstrates that the choice of measurement instrument can have a large influence on the conclusions of a study. When a trial with an effective intervention uses a measurement instrument that is less sensitive-to-change to measure its primary outcome, effective interventions may be overlooked.

The underlying aim of the studies described in the last part of this thesis was therefore to further outcome measurement in the field of hand osteoarthritis. Research in outcome measurement can roughly be divided into two aspects, which are highly interrelated. First, meaningful endpoints have to be chosen to measure relevant outcomes, which should then be measured in all studies. For this purpose the OMERACT hand osteoarthritis working group presented a core domain set of outcomes to be measured in three settings: clinical trials of symptom modification, clinical trials of structure modification, and observational studies (figure 2, **chapter 1**).[64] Secondly, suitable instruments to measure these endpoints (core domains) have to be chosen and subsequently used in all studies. Before a decision can be made which instrument is most

suitable, the properties of potential instruments have to be compared. The studies in **part III** of this thesis primarily focussed on this second aspect of outcome measurement.

Chapter 10 presents age- and sex-specific reference curves for the AUSCAN, developed in analogy to the famous growth curves for children, in an effort to better interpret scores of this frequently used questionnaire for hand pain, function and stiffness. The reference curves can for example be used to compare AUSCAN scores across different populations, to compare scores of the same population on different occasions or to detect aberrant individual scores.

In **chapter 11 and 12**, we compared the clinimetric properties of several instruments that measure the core domains pain and function (**chapter 11**), and hand mobility (**chapter 12**), in preparation of selection of the most suitable instruments for these domains, as explained earlier in this paragraph. In these studies, assessment was guided by the OMERACT filter, evaluating truth ('Does the instrument measure what it intends to measure?'), discrimination ('Can the instrument discriminate across disease stages?', 'Can the instrument identify change over time?' (often referred to as responsiveness), 'Can the instrument pick up difference between treatment groups in a clinical trial?'), and feasibility ('Can the instrument be applied easily, given constraints of time, money, and interpretability?').[65]

In **chapter 11** we evaluated the MHQ, a questionnaire of hand complaints that was not validated for use in hand osteoarthritis before, and showed that it has several advantages justifying its use in hand osteoarthritis studies. It consists of multiple subscales, which measure different domains. Some of these subscales measure unique domains (work performance, aesthetics and satisfaction), other subscales assess the domains pain and function. The three domains unique for the MHQ were demonstrated to be valid, and can provide useful insights in aspects which are likely of importance for patients with hand osteoarthritis, but are currently understudied in absence of valid measurement instruments. The subscales measuring pain and function were compared to more widely used pain and function questionnaires in hand osteoarthritis (AUSCAN, Functional Index for Hand Osteoarthritis (FIHOA), VAS). Comparison of the individual items of the different questionnaires revealed that each assessed partly the same, but partly also rather different aspects of pain and function. With respect to discrimination and responsiveness, the MHQ generally performed at least as good as the reference instruments. An important advantage of the MHQ with respect to feasibility is that it is freely available, in contrast to the AUSCAN. Disadvantages are that the questionnaire is longer, and that different directions of effect of different subscales may negatively impact its interpretability. Taking all aspects together, none of the instruments was clearly superior to another. In the setting of the cohort in which the analyses of **chapter 11** were performed, sensitivity-to-change could not be investigated. Interestingly, as discussed above, in **chapter 5** we could see that the MHQ pain subscale, as well as the MHQ function subscales, were not as good in discriminating between the treatment groups as other pain and function instruments. This observation warrants a more detailed investigation.

We compared several instruments to measure hand mobility in **chapter 12**, including the Hand Mobility in Scleroderma test (HAMIS), fingertip-to-palm distance during maximal finger flexion and modified Kapandji index, and concluded that HAMIS had slightly more favourable properties. The reliability, feasibility and correlations with other outcome measures were similar

for the various hand mobility tests. However, although all tests could measure finger mobility, only HAMIS could distinguish between patients with and without reduced thumb mobility. HAMIS also appeared the most responsive, though generally the change in hand mobility over the two-year timeframe that was assessed, was small for all tests. The observed low progression rate in hand mobility could mean that the tests are not sensitive enough to measure change over time, in other words, that it is a problem of the instrument. On the other hand, it could also indicate that changes in hand mobility do not occur within a two-year timeframe, which is a problem of the domain. The latter would suggest that this domain is not useful to assess in (usually short-term) clinical trials. To further investigate these remaining research questions, we can again take advantage of data collected in the HOPE study (**chapter 5**), which included assessment of hand mobility, where we know that a change over time occurred in the intervention group in other domains.

In contrast to **chapters 10-11**, **chapter 12** focussed on a domain for clinical trials of structure modification. Besides hand mobility, structural damage, which includes subdomains radiographic damage, aesthetic damage, bony damage and deformity, is another domain intended to be measured in clinical trials of structure modification. From the studies described in **part I** of this thesis, we learned that few trials in hand osteoarthritis so far focussed on structure modification, and those that did found no evidence for disease-modification. In light of the studies on outcome measurement discussed here, it is important to realise that, although it may well be true that these interventions do indeed not have a structure modifying effect, it could also be a problem of the used measurement instruments. This is illustrated by the results presented in **chapter 12** for the domain hand mobility, as discussed above, but the same holds true for the domain structural damage. Put differently, as long as we do not have good measurement instruments to assess the domains of structure modification, finding a disease-modifying drug will be difficult.

When the OMERACT core domain set for hand osteoarthritis studies was endorsed in 2014, a preliminary proposal for suitable instruments was also presented.[64] Those instruments included VAS or numeric rating scale (NRS) to measure pain, FIHOA to measure function, tender joint count to measure joint activity and grip or pinch strength to measure hand strength. However, for several domains (patient global assessment, health-related quality of life, hand mobility) no instrument could be proposed, and several aspects of the proposed instruments also needed to be investigated further before these could be selected as core instruments for those domains. Therefore, a research agenda was compiled, in which the working group summarised the work that still needed to be done to progress selection of instruments for each of the core domains. **Chapter 13** presents the report of the progress made by the OMERACT hand osteoarthritis working group in instrument selection for each of the core domains since that time, as discussed at the 2018 OMERACT conference. Besides an overview of the progress in instrument selection, it presents an updated research agenda to guide future research. An important next step for this working group is to present a set of suitable instruments for domains for which enough data has accrued to be able to compare the properties of the available instruments and make a well-informed decision. Likely, the domains pain and physical function will be the first domains for which instruments can be selected.

One of domains for which instrument development would likely advance hand osteoarthritis research, but which at the same time is one of the most difficult domains to select an appropriate instrument for, is the domain 'joint activity'. Insufficient knowledge about the underlying pathophysiological process and lack of a well-accepted definition for this domain are the main problems hampering instrument development. Nevertheless, the ability to measure whether there is an active osteoarthritis disease process going on in a joint, may be pivotal in interfering in the disease before irreversible joint damage occurs. It could also be helpful in selection of suitable patients for clinical trials. Potential instruments that have been proposed and/or researched for this domain include inflammation on imaging (ultrasound or MRI), joint pain upon palpation ("joint tenderness"), self-reported joint pain, soft tissue swelling and pain while gripping. While individually none of these instruments were satisfactory, it is possible that these instruments complement each other and that a combination of (some of) these instruments may be a better reflection of joint activity. Future studies to investigate combinations of instruments to measure joint activity are warranted. Taking prediction of radiological progression as an anchor to assess suitable instruments may be a useful approach in these studies.

In contrast to the other chapters in **part III** of this thesis, evolving around the investigation of properties of existing measurement instruments, the studies in **chapter 14-16** describe the work done in development of the OMERACT TOMS. As discussed in one of the previous paragraphs of this chapter, thumb base osteoarthritis is an important hand osteoarthritis subset, which deserves separate attention. The development of this MRI scoring system made it possible to investigate the role of inflammation in thumb base osteoarthritis, and to increase our understanding of osteoarthritis in this unique hand joint (**chapter 7 and 8**). Besides the development (**chapter 14**) of the scoring system, in collaboration with the OMERACT MRI working group, we also investigated the reliability of scoring MRIs with this system cross-sectionally (**chapter 14**) and longitudinally (**chapter 16**), and developed an atlas to facilitate the use of the scoring system (**chapter 15**). To further validate the scoring system, a study comparing thumb base MRI with other imaging methods (ultrasound, radiography) that can (partly) visualise similar features would be of interest. Due to the differences in imaging techniques, it is conceivable that MRI is more sensitive than radiography. Whether features, for example small osteophytes or erosions, that can be seen on MRI but not on radiography, are of interest (i.e., can predict disease progression or are associated with complaints) has to be subject of investigation.

Future perspectives

In this chapter we summarised and discussed the findings of the studies described in this thesis, and addressed some of the major challenges in hand osteoarthritis research. First of all, this thesis provides an overview of the current state of treatment options in hand osteoarthritis, including a set of up-to-date recommendations for the management of this disease in daily clinical practice. Furthermore, this thesis contributes to the development of new treatment options for patients with hand osteoarthritis by providing evidence for inflammation as a suitable target for

treatment. Ultimately, this may contribute to the development of treatments that can alter the disease course of osteoarthritis. Moreover, this thesis advances the optimisation of outcome measurement in hand osteoarthritis research.

The HOPE study (**chapter 5**) is at the center of this thesis, and a unique trial in hand osteoarthritis. Besides its clinical application, providing evidence for a new treatment option to relieve symptoms of patients with hand osteoarthritis, this trial also advances the field in two other aspects. Not only does it provide more insights in the disease pathogenesis, showing that inflammation can be modulated in hand osteoarthritis, for many of the proposed follow-up studies, especially those with regard to outcome measurement, data collected in the HOPE study are invaluable.

Although the studies described in this thesis provide us with new insights in different aspects of hand osteoarthritis, many questions remain or were raised by the studies that were conducted, warranting future research. Throughout this chapter we have discussed how these studies may affect our current thinking about pathophysiology and clinical care for patients with hand osteoarthritis, and how they may provide guidance to future studies.

REFERENCES

1. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. *Nat Rev Rheumatol* 2014;10:437-41.
2. Marshall M, Watt FE, Vincent TL, et al. Hand osteoarthritis: clinical phenotypes, molecular mechanisms and disease management. *Nat Rev Rheumatol* 2018;14:641-56.
3. Michon M, Maheu E, Berenbaum F. Assessing health-related quality of life in hand osteoarthritis: a literature review. *Ann Rheum Dis* 2011;70:921-8.
4. Zhang Y, Niu J, Kelly-Hayes M, et al. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. *Am J Epidemiol* 2002;156:1021-7.
5. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. *Ann Rheum Dis* 2009;68:8-17.
6. Cohen J. *Statistical power analysis for the behavioral sciences*, 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988.
7. Denoeud L, Mazieres B, Payen-Champenois C, et al. First line treatment of knee osteoarthritis in outpatients in France: adherence to the EULAR 2000 recommendations and factors influencing adherence. *Ann Rheum Dis* 2005;64:70-4.
8. Porcheret M, Jordan K, Jinks C, et al. Primary care treatment of knee pain--a survey in older adults. *Rheumatology* 2007;46:1694-700.
9. Steel N, Bachmann M, Maisey S, et al. Self reported receipt of care consistent with 32 quality indicators: national population survey of adults aged 50 or more in England. *BMJ* 2008;337:a957.
10. Gvozdenovic E, Allaart CF, van der Heijde D, et al. When rheumatologists report that they agree with a guideline, does this mean that they practise the guideline in clinical practice? Results of the International Recommendation Implementation Study (IRIS). *RMD Open* 2016;2:e000221.
11. Saini V, Brownlee S, Elshaug AG, et al. Addressing overuse and underuse around the world. *Lancet* 2017;390:105-07.
12. Brownlee S, Chalkidou K, Doust J, et al. Evidence for overuse of medical services around the world. *Lancet* 2017;390:156-68.
13. Glasziou P, Straus S, Brownlee S, et al. Evidence for underuse of effective medical services around the world. *Lancet* 2017;390:169-77.
14. Saini V, Garcia-Armesto S, Klemperer D, et al. Drivers of poor medical care. *Lancet* 2017;390:178-90.
15. Allen KD, Yancy WS, Bosworth HB, et al. A combined patient and provider intervention for management of osteoarthritis in veterans: a randomized clinical trial. *Ann Intern Med* 2016;164:73-83.
16. Allen KD, Oddone EZ, Coffman CJ, et al. Patient, provider, and combined interventions for managing osteoarthritis in primary care: a cluster randomized trial. *Ann Intern Med* 2017;166:401-11.
17. Haugen IK, Bøyesen P, Slatkowsky-Christensen B, et al. Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis. *Ann Rheum Dis* 2012;71:899-904.
18. Keen HI, Wakefield RJ, Grainger AJ, et al. An ultrasonographic study of osteoarthritis of the hand: synovitis and its relationship to structural pathology and symptoms. *Arthritis Rheum* 2008;59:1756-63.
19. Kortekaas MC, Kwok WY, Reijnierse M, et al. Pain in hand osteoarthritis is associated with inflammation: the value of ultrasound. *Ann Rheum Dis* 2010;69:1367-9.
20. Loef M, van Beest S, Kroon FPB, et al. Comparison of histological and morphometrical changes underlying subchondral bone abnormalities in inflammatory and degenerative musculoskeletal disorders: a systematic review. *Osteoarthritis Cartilage* 2018;26:992-1002.
21. Liu R, Damman W, Reijnierse M, et al. Bone marrow lesions on magnetic resonance imaging in hand osteoarthritis are associated with pain and interact with synovitis. *Osteoarthritis Cartilage* 2017;25:1093-99.
22. Damman W, Liu R, Bloem JL, et al. Bone marrow lesions and synovitis on MRI associate with radiographic progression after 2 years in hand osteoarthritis. *Ann Rheum Dis* 2017;76:214-17.
23. Haugen IK, Slatkowsky-Christensen B, Bøyesen P, et al. MRI findings predict radiographic progression and development of erosions in hand osteoarthritis. *Ann Rheum Dis* 2016;75:117-23.
24. Kortekaas MC, Kwok WY, Reijnierse M, et al. Inflammatory ultrasound features show independent associations with progression of structural damage after over 2 years of follow-up in patients with hand osteoarthritis. *Ann Rheum Dis* 2015;74:1720-4.
25. Mathiessen A, Slatkowsky-Christensen B, Kvien TK, et al. Ultrasound-detected inflammation predicts radiographic progression in hand osteoarthritis after 5 years. *Ann Rheum Dis* 2016;75:825-30.
26. Mancarella L, Addimanda O, Pelotti P, et al. Ultrasound detected inflammation is associated with the development of new bone erosions in hand osteoarthritis: a longitudinal study over 3.9 years. *Osteoarthritis Cartilage* 2015;23:1925-32.

27. Kortekaas MC, Kwok WY, Reijnierse M, et al. Brief report: association of inflammation with development of erosions in patients with hand osteoarthritis: a prospective ultrasonography study. *Arthritis Rheumatol* 2016;68:392-7.
28. Bijsterbosch J, Watt I, Meulenbelt I, et al. Clinical and radiographic disease course of hand osteoarthritis and determinants of outcome after 6 years. *Ann Rheum Dis* 2011;70:68-73.
29. Haugen IK, Slatkowsky-Christensen B, Bøyesen P, et al. Increasing synovitis and bone marrow lesions are associated with incident joint tenderness in hand osteoarthritis. *Ann Rheum Dis* 2016;75:702-8.
30. Van Beest S, Damman W, Liu R, et al. In finger osteoarthritis, change in synovitis is associated with change in pain on a joint-level; a longitudinal magnetic resonance imaging study. *Osteoarthritis Cartilage* 2019;27:1048-56.
31. Aitken D, Pan F, Laslett L, et al. A randomised double-blind placebo-controlled crossover trial of humira (adalimumab) for erosive hand osteoarthritis: the HUMOR trial. *Osteoarthritis Cartilage* 2017;25:S9.
32. Keen HI, Wakefield RJ, Hensor EM, et al. Response of symptoms and synovitis to intra-muscular methylprednisolone in osteoarthritis of the hand: an ultrasonographic study. *Rheumatology* 2010;49:1093-100.
33. Kloppenburg M, Ramonda R, Bobacz K, et al. Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2018;77:1757-64.
34. Wenham CYJ, Hensor EMA, Grainger AJ, et al. A randomized, double-blind, placebo-controlled trial of low-dose oral prednisolone for treating painful hand osteoarthritis. *Rheumatology* 2012;51:2286-94.
35. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Chronic Dis* 1967;20:637-48.
36. Ford I, Norrie J. Pragmatic trials. *N Engl J Med* 2016;375:454-63.
37. Smith TO, Zou K, Abdullah N, et al. Does flare trial design affect the effect size of non-steroidal anti-inflammatory drugs in symptomatic osteoarthritis? A systematic review and meta-analysis. *Ann Rheum Dis* 2016;75:1971-78.
38. Kapoor M, Martel-Pelletier J, Lajeunesse D, et al. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol* 2011;7:33-42.
39. Chevalier X, Ravaud P, Maheu E, et al. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2015;74:1697-705.
40. Verbruggen G, Wittoek R, Vander Cruyssen B, et al. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: A double blind, randomised trial on structure modification. *Ann Rheum Dis* 2012;71:891-8.
41. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007;146:406-15.
42. Loef M, Kroon FPB, Bergstra SA, et al. TNF-inhibitor treatment is associated with lower risk of hand osteoarthritis progression in rheumatoid arthritis patients after 10 years. *Rheumatology* 2018;57:1917-24.
43. Güler-Yuksel M, Allaart CF, Watt I, et al. Treatment with TNF-alpha inhibitor infliximab might reduce hand osteoarthritis in patients with rheumatoid arthritis. *Osteoarthritis Cartilage* 2010;18:1256-62.
44. Kroon F, Bay-Jensen AC, Wittoek R, Verbruggen G, Smolen JS, Kloppenburg M, Ramonda R. Etanercept therapy leads to reductions in matrix metalloproteinase-3 in patients with erosive hand osteoarthritis. *Scand J Rheumatol* 2020;49:167-68.
45. Bertolini DR, Nedwin GE, Bringman TS, et al. Stimulation of bone resorption and inhibition of bone formation in vitro by human tumour necrosis factors. *Nature* 1986;319:516-8.
46. Ma CH, Lv Q, Yu YX, et al. Protective effects of tumor necrosis factor-alpha blockade by adalimumab on articular cartilage and subchondral bone in a rat model of osteoarthritis. *Braz J Med Biol Res* 2015;48:863-70.
47. Kellgren JH, Lawrence JS. Osteo-arthrosis and disk degeneration in an urban population. *Ann Rheum Dis* 1958;17:388-97.
48. Visser AW, de Mutsert R, Loef M, et al. The role of fat mass and skeletal muscle mass in knee osteoarthritis is different for men and women: the NEO study. *Osteoarthritis Cartilage* 2014;22:197-202.
49. Kloppenburg M, Kwok WY. Hand osteoarthritis--a heterogeneous disorder. *Nat Rev Rheumatol* 2011;8:22-31.
50. Spolidoro Paschoal Nde O, Natour J, Machado FS, et al. Effectiveness of triamcinolone hexacetonide intraarticular injection in interphalangeal joints: a 12-week randomized controlled trial in patients with hand osteoarthritis. *J Rheumatol* 2015;42:1869-77.
51. Kloppenburg M, van Beest S, Kroon FPB. Thumb base osteoarthritis: A hand osteoarthritis subset requiring a distinct approach. *Best Pract Res Clin Rheumatol* 2017;31:649-60.
52. Chaisson CE, Zhang Y, Sharma L, et al. Grip strength and the risk of developing radiographic hand osteoarthritis: results from the Framingham Study. *Arthritis Rheum* 1999;42:33-8.

53. Hunter DJ, Zhang Y, Sokolove J, et al. Trapeziometacarpal subluxation predisposes to incident trapeziometacarpal osteoarthritis (OA): the Framingham Study. *Osteoarthritis Cartilage* 2005;13:953-7.
54. Jonsson H, Valtysdottir ST. Hypermobility features in patients with hand osteoarthritis. Osteoarthritis Cartilage. *Osteoarthritis Cartilage* 1995;3:1-5.
55. Jonsson H, Valtysdottir ST, Kjartansson O, et al. Hypermobility associated with osteoarthritis of the thumb base: a clinical and radiological subset of hand osteoarthritis. *Ann Rheum Dis* 1996;55:540-3.
56. Talke M. Treatment of Heberden and Bouchard types of finger osteoarthritis. Comparison between local etofenamate and oral indomethacin. *Therapiewoche* 1985;35:3948-54.
57. Zacher J, Burger KJ, Farber L, et al. Topical diclofenac versus oral ibuprofen: A double blind, randomized clinical trial to demonstrate efficacy and tolerability in patients with activated osteoarthritis of the finger joints (Heberden and/or Bouchard arthritis). [German]. *Aktuel Rheumatol*. 2001;26:7-14.
58. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601-10.
59. Marshall M, Peat G, Nicholls E, et al. Subsets of symptomatic hand osteoarthritis in community-dwelling older adults in the United Kingdom: prevalence, inter-relationships, risk factor profiles and clinical characteristics at baseline and 3-years. *Osteoarthritis Cartilage* 2013;21:1674-84.
60. Haugen IK, Lillegraven S, Slatkowsky-Christensen B, 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.
61. Haugen IK, Østergaard M, Eshed I, et al. Iterative development and reliability of the OMERACT hand osteoarthritis MRI scoring system. *J Rheumatol* 2014;41:386-91.
62. Bautista-Molano W, Navarro-Compan V, Landewé RB, et al. How well are the ASAS/OMERACT core outcome sets for ankylosing spondylitis implemented in randomized clinical trials? A systematic literature review. *Clin Rheumatol* 2014;33:1313-22.
63. Kirkham JJ, Clarke M, Williamson PR. A methodological approach for assessing the uptake of core outcome sets using ClinicalTrials.gov: findings from a review of randomised controlled trials of rheumatoid arthritis. *BMJ* 2017;357:j2262.
64. Kloppenburg M, Bøyesen P, Visser AW, et al. Report from the OMERACT hand osteoarthritis working group: set of core domains and preliminary set of instruments for use in clinical trials and observational studies. *J Rheumatol* 2015;42:2190-7.
65. Boers M, Brooks P, Strand CV, et al. The OMERACT filter for outcome measures in rheumatology. *J Rheumatol* 1998;25:198-9.