High resolution CT imaging of finger joints

VALORISATION

Valorisation of research is defined as "the process of creating value from knowledge, by making this knowledge available and suitable for economic and social exploitation and to translate this knowledge into products, services, processes, and new business". Or, how can society benefit from the knowledge acquired with research? In this chapter I aimed to describe the clinical relevance of this thesis and relevance of future research of high-resolution peripheral quantitative computed tomography (HR-pQCT) imaging.

During my research I have only seen a fraction of patients suffering from rheumatoid arthritis (RA). Some of the patients were not able to get in or out of the bed or dress themselves. These limitations will probably be there for the rest of their lives. Since there is no cure for RA, the treatment of the patients is directed at achieving symptom improvement, a low disease activity state or remission, and to inhibit damage to bone, ligaments and tendons. However, despite achieving clinical remission, bone damage can still occur or progress, and bone damage is considered largely irreversible. To reduce the development of this bone damage, current treatment recommendations for RA support early and aggressive treatment. Would it therefore not be great if we could diagnose patients, of whom the bone is still deteriorating, at an earlier stage in order to initiate or change the treatment which may prevent progression of bone damage, and thus prevent loss of function and mobility? Besides the benefits on the individual level, improved diagnosis and monitoring of patients with RA could also benefit the society by reducing the costs that are related to RA, such as loss of productivity.

Imaging of peri-articular bone in RA in clinical practice is performed using conventional radiography (CR), but CR is not sensitive to detect bone damage at an early stage. More sensitive techniques, such as magnetic resonance imaging (MRI) or clinical CT, are suggested for monitoring disease activity and progression of bone damage. HR-pQCT is a novel three-dimensional imaging technique that allows *in vivo* evaluation of the bone at the micro-scale. HR-pQCT is proven to be a more sensitive technique in the detection of bone damage compared to CR, MRI and clinical CT. In this thesis, we further validated and improved the applicability of HR-pQCT imaging by introducing a more standardized and less time-consuming analysis of bone damage of finger joints. We showed that HR-pQCT imaging with our introduced algorithm is a valid, reliable and applicable tool in the detection of small cortical interruptions, bone density and micro-structure in finger joints, and can discriminate between patients with RA and healthy subjects both cross-sectionally and longitudinally.

Contributions of this thesis to society

The algorithm introduced in this thesis can be a significant contributor for further research, since it improves the reliability, applicability and discriminatory value of HR-pQCT imaging in research of peri-articular bone in RA.

We first showed that the HR-pQCT with our algorithm is able to detect smaller interruptions compared to CR, MRI and visual scoring of HR-pQCT images. Detection of small cortical interruptions is of importance since these small interruptions are more frequently present in patients with RA compared to healthy subjects. Therefore, HR-pQCT imaging with our algorithm was of added value over findings on CR and MRI in the discrimination between patients with RA and healthy subjects. Additionally, these small interruptions may play a role in the development of large (pathological) interruptions (i.e. erosions). When large interruptions indeed develop at the 'entry points' through small physiological interruptions (such as vascular channels), HR-pQCT imaging will enable to show and follow these bone changes and occurrence of new cortical interruptions over time. This monitoring may be of additional value after treatment initiation in clinical studies in order to assess the effect of treatment, even early in this process. Because HR-pQCT has a higher sensitivity to detect bone damage (small cortical interruptions) and structural bone changes over time compared to CR and MRI, it is expected that fewer participants will be needed in clinical trials with HR-pQCT to observe an effect of drug treatment. We already could identify differences in bone changes between patients treated with biological disease modifying anti-rheumatic drugs (bDMARDs) and synthetic DMARDs (sDMARDs).

Second, we showed a higher reliability of the algorithm compared to visual scoring. An improvement in reliability enables to better discriminate between patients and healthy subjects and to measure change over time. Therefore, compared to CR, MRI and visual scoring of HR-pQCT images, we expect that fewer participants will be needed in clinical trials using HR-pQCT with our algorithm to observe an effect of drug treatment.

Third, the use of our algorithm is more applicable compared to visual scoring. With our algorithm, corrections of the outer cortical contours are needed to assess the number and size of interruptions. However, these corrections were already necessary to determine the bone density and micro-structural parameters. Hence, compared to visual scoring no extra visual evaluation to score interruptions is necessary. Improvement in applicability can help larger studies using HR-pQCT to analyse the data, and improvement in applicability is needed for eventual use in clinical practice.

This thesis aimed to answer the filters of the OMERACT initiative (outcome measures of rheumatology), defined by "truth", "discrimination" and "feasibility". The SPECTRA (Study grouP for xtrEmeCT in RA) collaboration, in which we participated, strives to implement HR-pQCT as imaging tool in clinical practice. A new instrument such as HR-pQCT needs to meet these OMERACT filters, before it can be implemented in clinical practice. Other international scientific centres that are part of the SPECTRA initiative are interested to apply our cortical interruption detection algorithm. The results in this thesis form a solid base for further development and implementation of automated algorithms in the assessment of peri-articular bone damage in finger joints.

Future perspectives

Currently, HR-pQCT imaging has only been used in research settings. Further optimisation of the algorithm in reliability and applicability, and confirmation of our results are needed before studying the possibility of use in clinical settings. Studies that further answer the questions raised by the OMERACT filters, "truth", "discrimination" and "feasibility", to show that HR-pQCT imaging is valid, reliable, applicable tool which can discriminate between situations of interest.

HR-pQCT imaging may be applied in several future studies, for example for in randomized controlled clinical trials that compare different treatment strategies. Other studies compared sDMARDs to bDMARDs, or the additional effect of osteoporosis medication treatment (e.g. denosumab or alendronate) in addition to DMARD treatment. Partial repair of bone was regularly observed using HR-pQCT in patients primarily on bDMARD treatment. Differences could already be observed after 3 months of treatment. In view of the limited availability of HR-pQCT, such studies could be performed in the context of pilot studies, proof of concept studies or Phase IV monitoring studies.

Further HR-pQCT research may focus on better identification of patients that will develop severe, erosive RA, and a variety of factors can be investigated using HR-pQCT to identify those patients (e.g. the number, size, location, shape and distribution of cortical interruptions, which may be predictors for the development of erosions). The structural integrity of the bone tissue around a cortical interruption might be an additional predictor of bone damage progression that can be studied with HR-pQCT.

HR-pQCT imaging may also be used in the future as a diagnostic tool to identify those patients that will develop RA and might be used to monitor patients with RA to earlier detect bone damage progression. This might be an indication to alter the medication of these patients to prevent bone damage progression.

This thesis provides a solid basis for an algorithm based analysis of HR-pQCT images of peri-articular bone in finger joints of patients with RA and healthy subjects, which can be further explored in future research, including other diseases that affect finger joints, such as psoriatic arthritis and erosive osteoarthritis.

Current publicity

Results in this thesis have been submitted and published in scientific journals. Results have also been presented at national and international conferences. Oral presentations have been given at the national conferences of the Dutch and Belgian Rheumatology association (Nederlandse Vereniging voor Reumatologie (NVR) and Belgian Congress of Rheumatology (BCR) (NVR in 2014 and 2017, and BCR in 2014 and 2015). Posters have been presented at American Society of Bone Mineral Research (ASBMR 2014), the European League Against Rheumatism (EULAR 2015, 2016 and 2017) and American College of Rheumatology (2016).