Mortality and other outcome measures in osteoarthritis

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Chapter 1

General introduction

INTRODUCTION

Osteoarthritis (OA) is a common and heterogeneous disease, which can involve various movable joints. The hand, knee and hip joints are most commonly involved. OA is considered to be initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first at molecular level (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic abnormalities (characterized by cartilage degradation, osteophyte formation and bone remodelling, joint inflammation and loss of function), that can culminate in illness.[1] Pathologic abnormalities of soft tissue structures such as synovium, periarticular muscles, ligaments, meniscus may also occur.

Epidemiology

The prevalence of OA may differ depending on the definition that is used. Radiographic OA occurs more often than symptomatic OA. In the Netherlands, the prevalence of OA for patients visiting the general physician has been estimated to be 53.8 per 1 000 men and 88.5 per 1 000 women in 2011, resulting in a total estimate of well over one million patients in the whole country.[2] Knee OA has been reported to be the most prevalent, followed by hip OA and peripheral OA.
OA is a multifactorial disease and despite the discovery of many mechanical and systemic risk factors such as injury, mechanical stress and genetic factors, its precise pathogenesis has remained elusive.[3] What is, however, well recognised, is that age, sex and obesity are among the most well known risk factors.[4-6]

Osteoarthritis: clinical presentation

OA has a major impact on morbidity. The WHO Global Burden of Disease Study reported in their 2013 update that knee OA is the 13th cause of global years lived with disability (YLD).[7] In the Dutch population OA ranked sixth as contributor to disability with 122 400 YLDs.[8] YLDs equated disability adjusted life-years. Whether OA has an impact on mortality is less clear. In 2011 Nuesch et al published a study that suggested an association of OA with mortality.[9] In this population based cohort study using survey data from general practices in England, patients with radiographic OA were at higher risk of death than those in the general population. In addition, it was shown that a history of diabetes, cancer, or cardiovascular disease and the presence of walking disability were major risk factors.
Symptoms due to OA may be highly variable, since they depend upon factors such as the affected joint, the severity of OA and the number of affected joints.[4,10] Important clinical symptoms are pain, stiffness and disability. For an optimal evaluation of the outcome in OA, all domains of interest to patients should

be assessed. The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) has recently developed a new preliminary set of domains for hand OA, taking patient perspectives into account. The OMERACT has indicated that other factors such as hand strength, hand mobility and aesthetic damage should also be taken into account.[11]

OA as a biopsychosocial model

Two patients with the exact same diagnosis and similar objective clinical features may describe in a completely different way how the disorder impact their lives. Leventhal's Common Sense Model (CSM) offers a possible explanation for this phenomenon. In this model, situational stimuli as disease processes may influence the representation of the health threat or emotion as illness perceptions, which in turn may involve coping responses in the process and ultimately lead to appraisal of the clinical outcome**.** Feedback loops also interlink the different components in this self regulation model (Figure 1).[12] The CSM is supported by cross-sectional studies in which illness perceptions of OA patients were associated with limitations in daily activities and quality of life,[13-15] while longitudinal studies reported an association between changes in illness perceptions with changes in outcomes.[16,17] The role of coping in this model in OA has, however, not been studied well.

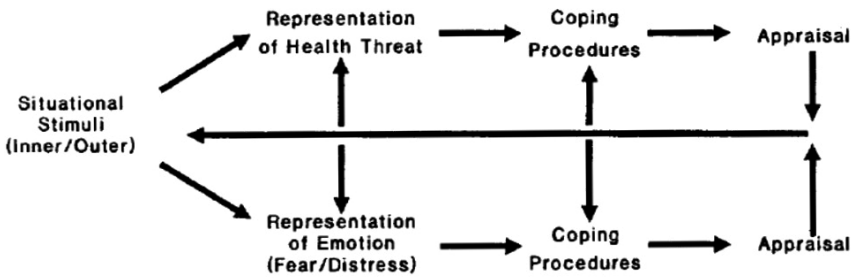

Figure 1. Leventhal's Common Sense Model (Leventhal 1992)

Imaging

Radiographs can be used to support the diagnosis of OA and to monitor the progression of the disease. Structural abnormalities of osteoarthritic joints, visualized as osteophytes and joint space narrowing on radiographs, are associated with hand pain, although this association is weak.[18,19]

Studies using ultrasonography have demonstrated that soft tissue abnormalities such as synovial thickening with positive Power Doppler signal is often present in the joint. Moreover, inflammatory ultrasound features have been shown to be associated with pain and radiographic damage, which support their potential

role in the disease process in hand OA. However, a difference remains between ultrasonography and clinical findings.[20,21]
Magnetic resonance (MR) imaging is a modern imaging method, which can visualize both hard and soft tissue abnormalities. In addition, abnormalities in subchondral bone, such as bone marrow lesions (BML), can be visualised (Figure 2). Studies have shown that BMLs are often present in knee OA and seem to play a role in pain[22], while in hand OA this abnormality has been rarely studied.

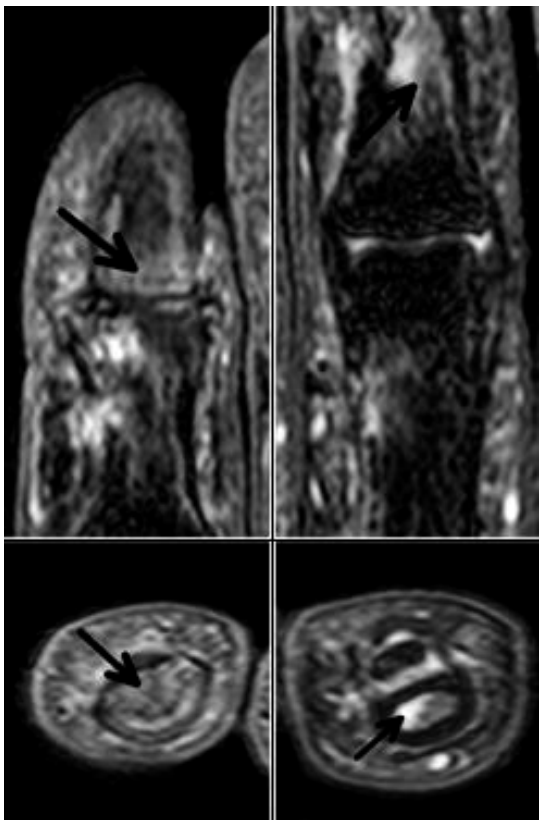

Figure 2. Magnetic Resonance Imaging: bone marrow lesions (arrow) were present in the second distal interphalangeal joint (A) and third proximal interphalangeal joint (B)

A MR imaging scoring method has been developed by Haugen et al as the first available scoring tool to assess OA abnormalities in the interphalangeal joints. This method incorporates important hand OA abnormalities such as synovitis, flexor tenosynovitis and BMLs and studies are now emerging for validation of this tool.[23,24] The use of MR imaging can improve our understanding of hand OA and the assessment of the burden of disease.

Aim of thesis

The aim of this thesis is:

1. To gain insights into the determinants of outcome in hand osteoarthritis
2. To investigate mortality in osteoarthritis

The HOSTAS study

Several of the studies presented in this thesis made use of the HOSTAS study. The Hand OSTeoArthritis in Secondary care (HOSTAS) study is an ongoing observational cohort study which has enrolled patients with hand OA consecutively since 2009. The study aims to investigate determinants of outcome in hand OA patients. Inclusion occurred when patients consulted a rheumatologist at the outpatient clinic of the Leiden University Medical Center for hand complaints and these hand complaints were diagnosed as primary hand OA. To reach a diagnosis, history, physical and radiographic examinations were used. Patients with secondary OA or hand complaints due to other disease causes were excluded. In total, over 500 patients are enrolled. Their OA status and its determinants are evaluated bi-annually during a visit to the LUMC and annually via questionnaires.

OUTLINE OF THE THESIS

In **part I** we investigate which determinants play a role in the clinical outcomes pain, disability, aesthetic damage and structural damage in hand OA, using the CSM model as a guide. **Chapter 2** we examine the role of joint-specific factors and coping styles on disability in hand OA patients. In **chapter 3** we describe the prevalence of aesthetic dissatisfaction in hand OA patients, its impact on daily life and their determinants such as osteoarthritic joint abnormalities, illness perceptions, anxiety and depression. In **chapter 4** we evaluate the presence of synovitis, tendon involvement and BMLs in hand OA, and their association with hand pain. **Chapter 5** concerns the association between BMLs and synovitis and radiographic progression of hand OA over 2 years.

Part II evaluates the association between OA and mortality. In **chapter 6** we investigate the mortality rates in patients with OA from two cohorts, the "Genetics ARthrosis and Progression"(GARP) cohort, including patients with primary familial OA at multiple sites, and the "Osteoarthritis Care Clinic", including patients with primary OA from the rheumatology outpatient clinic, in comparison to the general population. We also investigate specifically cardiovascular mortality. Many studies have investigated the association between OA and mortality with different conclusions. Therefore, we have performed a systematic literature review to summarise and determine the association between OA and mortality in **chapter 7**.

Finally, we provide a summary of the study results in the thesis and present a general discussion and future perspectives in **chapter 8**.

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