The conservative treatment of ankle osteoarthritis
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CHAPTER 1

General introduction
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Ankle osteoarthritis

Osteoarthritis (OA) is a chronic and degenerative disorder associated with joint pain and loss of joint function. OA can affect any synovial joint but is found most frequently in the hip, knee and hand. The majority of these patients present with primary OA (idiopathic disease)[1,2]. Reliable figures on the prevalence of OA in other joints are not readily available but estimates suggest that the incidence of symptomatic ankle OA is 1% to 4% in the adult population[3,4]. In contrast to knee and hip OA, where the main cause of OA is primary; knee 67% and hip 58%, 70% to 78% of patients with ankle OA present themselves with the sequelae of an traumatic event in the past[5]. The remainder is primary OA as well as OA caused by an inflammatory disease, such as rheumatoid arthritis and gout[6,7]. Ankle trauma occurs in many patients at a relatively young age[6,8]. Consequently, the expected life span of many patients with ankle OA is significantly longer than the life span of hip or knee OA patients; their quality of life is effected for a substantial amount, Saltzman demonstrated that the self reported physical function in patients with symptomatic ankle OA quantified using the Short Form-36 (SF-36) questionnaire was equivalent to or worse than that of patients with end-stage kidney disease or congestive heart failure suggesting that these patients are seriously impaired[9].

Considerations for treatment

Lots of treatment modalities are offered, however no clear-cut treatment algorithm for ankle OA is used. The choice of treatment depends on the severity of the disease, the patients’ age, medical and social history and the level of physical activity to be demanded of the joint. For knee and hip OA several treatment algorithms are advocated[10,11,15]. However, since ankle OA may be caused by a different mechanism, it is not unthinkable that these patients need to be treated differently. The conservative treatment of symptomatic ankle OA, like general OA, consists mainly of treating symptoms like pain and stiffness. Since no cure is available at this point another treatment goal is preventing deterioration of the joint[11]. To treat OA and prevent joint deterioration it is important to understand the pathogenesis of OA.
Pathogenesis of OA

Osteoarthritis (OA) results from articular cartilage failure induced by a complex interplay of genetic, metabolic, biochemical and biomechanical factors with secondary components of inflammation. The process involves interactive degradation and repair processes of cartilage, bone and synovium\(^{16}\).

The cause of OA is divided in two mechanisms; primary and secondary OA. Primary OA means that the process seems to originate in the joint itself, the cause is thought to be multifactorial. Risk factors that could contribute to the development of OA are genetic, age, being overweight, heavy physical workload or high level of sport activities\(^{17-22}\). Secondary OA means the process of OA is activated by another process; e.g. reumatoid arthritis, gout, or post-traumatic OA.

In case of post traumatic OA, joint incongruency, cartilage lesions or alignment issues create a different loading pattern of the joint, which leads to cartilage loss. Despite the cause, the process of OA is relatively uniform. Progressive cartilage loss takes place leading to changes in subchondral bone (cyst formation and sclerosis) and the formation of osteophytes. Peri-articular tissues changes (synovitis and fibrosis of ligaments) take place as well, all these changes lead to symptoms like pain, loss of function and stiffness\(^{1,23}\).

Current treatment possibilities

In clinical practice, patients diagnosed with end-stage OA (Kellgren Lawrence 3 or 4 and van Dijk 3) are offered operative treatment if they have significant clinical symptoms\(^{24,25}\). These patients are treated by arthrodesis, ankle replacement or osteotomy\(^{26-28}\). Surgical treatment is specifically reserved for end stage arthritis. It is considered to be harmful due to short and long term complications. Complications consist of wound healing problems, infectious disease, non or delayed union and OA of adjacent joints due to overloading\(^{26-31}\). Operative treatment is therefore not considered in an early phase of OA. An exception to perform surgery in an earlier stage of OA is the reason to perform a corrective osteotomy at the level of the proximal tibia, supramalleolar or at the calcaneus, to unload a part of the joint or to correct an alignment problem\(^{32,33}\). Arthroscopy can be used to clean the joint of loose bodies or treatment of cartilage lesions is used when complaints are more specific to either a loose body or a local defect.
It remains a challenge to treat patients that are diagnosed with a low grade OA of the ankle (Kellgren Lawrence 1, 2 or 3 and Van Dijk 1 or 2)\(^{24,25}\). They are often young and experience serious disabilities, which prevent these patients from participating in more heavily laboured work as well as sports activities. Several conservative treatment options are available, however evidence of the benefits and harms of these options are still lacking.

Non-pharmacological therapy is to be considered the foundation for the successful medical management of general OA.\(^{14,15,34}\) Ankle OA pain can be reduced by off loading the joint through rest, wearing a brace or using a cane. A cane can reduce the amount of bodyweight going through the ankle joint by 25%\(^{35}\). Rockersoles are thought to off load the ankle joint by decreasing the ankle motion at heel strike to push off during walking\(^{36}\). Weight loss by dietary adjustments or exercises are thought to off load a joint as well\(^{37-39}\). Messier showed that each pound of weight loss created a 4-fold reduction in the load exerted by step at the knee during daily activities\(^{40}\). Shoe adjustment like inlays can correct alignment issues and in this way off load a part of the joint thus creating pain reduction\(^{41,42}\). It is possible that in this way the joint can be preserved from further deteriorating.

If the above mentioned measures are not successful a painkiller can be added. Several analgesics are available. They either act as a simple analgesic (acetaminophen), have anti inflammatory effects (intra articular/oral or topical steroids/non steroidal anti-inflammatory drugs (NSAIDs)), a sedative effect (opioids) or a combination. Recommendations for hip, knee or hand OA are well described\(^{11,34,43-45}\). No recommendations exist for ankle OA.

**Hyaluronic Acid**

Hyaluronic acid (visco-supplementation) is thought to restore rheologic properties of the osteoarthritic joint by creating a more viscoelastic synovial fluid, which improves mobility and restores the natural protective function of the joint, like shock absorption during gait\(^{46,47}\).

In an osteoarthritic joint, the amount of hyaluronic acid in the synovial fluid diminishes and the hyaluronic acid chains are smaller in size, which leads to less water absorption, which in its turn makes the joint fluid less viscous. Shock absorption of the joint is diminished. Injection of hyaluronan stimulates the synovial membrane to synthesize new
chains of hyaluronic acid, shock absorption and joint lubrication is enhanced. Several studies have shown pain reduction as well.

Visco-supplementation is a well-established treatment option in knee OA and is included in the professional guidelines for treatment of the disease in this joint. The potential for treating osteoarthritis of the ankle joint by visco-supplementation has been suggested in the literature. Evidence for efficacy and safety in the ankle is limited but two studies showed that five weekly HA injections in the ankle joint seem to be well tolerated and can improve pain and function.

Dosing in the ankle joint remains an area for discussion as no dosing studies have been published up to this thesis. Anecdotal evidence suggests that some clinicians simply follow the dosing regimen for knee OA, which varies from 3 to 5 weekly injections of 1-2ml.

The safety of hyaluronic acid is measured by the amount of adverse events. Adverse events mainly consist of swelling and pain, they are mainly contributed to extra-articular placements. Poor efficacy of hyaluronic acid is also contributed to extra-articular placement. To diminish the amount of adverse events and enhance the efficacy of hyaluronic acid an optimal injection technique is needed. Osteoarthritis might stiffen the ankle joint and osteophytes might block the way of the needle, which will make injecting the joint even more difficult.

Measure the effect of conservative treatment (PROMs)

To monitor the effect of conservative treatment modalities for ankle OA, different scoring systems are used. The Arbeitsgemeinschaft für Osteosynthesefragen Handbook on Musculoskeletal Outcomes Measures and Instruments describes 42 ankle scores. Seventeen of these are validated. Five are used for monitoring the conservative treatment of ankle OA, i.e. the American Academy of Orthopedic Surgeons (AAOS) foot and ankle scale, the American Orthopedic Foot and Ankle Society Scale (AOFAS) score, the Ankle Osteoarthritis scale (AOS), the Foot and Ankle Ability Measure (FAAM), and the Foot and Ankle Outcome Score (FAOS). The Foot Function Index (FFI) is mentioned in the book as a foot score, but is often used as an outcome measure for ankle problems.

The AOFAS scale has been used more frequently in orthopedic literature than the FFI, the AOS, and the Visual Analogue Score (VAS) for pain. Other, more general
outcome measures are the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Short Form 36 (SF-36)\textsuperscript{[75–77]}. The former is normally used and validated to evaluate the condition of patients with hip or knee OA, but it is also applied to patients with an arthritic condition of the ankle\textsuperscript{[73]}. The latter is used to evaluate individual health status\textsuperscript{[76]}.

In order to get an outcome measure that monitors clinical outcome in ankle OA patients, it is imperative to know what is considered relevant for the target patient group\textsuperscript{[78]}. Most outcome scores were made by physicians and validated for one specific disease.

It seems logical to use terms and outcomes that are important to the target group if constructing a useful outcome measure that can be used as a patient reported outcome measure (PROM). PROMs are mandatory nowadays to evaluate the quality and effect of treatments. For the development of a future guideline it is important that the right outcome has been used.

Little is known about the disabilities and symptoms patients experience at an early stage of ankle OA. It is difficult to measure efficacy of conservative treatment if one does not know what needs to be improved.

**Why is evidence of conservative treatment of ankle OA lacking?**

The question remains why the evidence for the conservative treatment of ankle OA is lacking. Patients are referred to the hospital mostly for surgical treatment once their symptoms are intolerable and/or when possible conservative treatment options are exhausted. The conservative treatment, if any has been used, is mostly prescribed by primary care physicians. Since there is no guideline for ankle OA, treatment might be prescribed according to the hip or knee guideline. It is unclear if there is enough knowledge about treatment options. No information, how choices to use a certain conservative treatment are made, is available.

At this point it is unclear if and how often ankle OA is recognized at an early stage, maybe the incidence is larger than the current numbers show us. Recognizing the presence of an early stage of ankle OA might be the first step in order to test any conservative treatment. Combined with a sufficient prom, this could lead to a useful guideline in order to treat patients in an earlier stage of the disease, which could maybe prevent the
joint from further deteriorating and maybe even diminish health care costs by simply preventing or postponing the necessity for surgery. This remains to be investigated.

Aims and outline of this thesis

There is no treatment algorithm for ankle OA. Evidence for conservative treatment for ankle OA is lacking. Hyaluronic acid injections might be an alternative to treat pain and may slow down the process of ankle OA. Dosing in the ankle joint is unclear often the dose regimen of the knee is followed. The ankle joint is smaller than the knee, it is not logical to simply follow existing regimens that are made for larger joints. No dosing studies have been published to date.

Different treatments need to be compared to decide which is the optimum in efficacy and safety in order to make guidelines. It is important to decide what is efficacious? If we decide we want to make our patients satisfied, do we not need to know how they think and feel about their disease? What is the impact of ankle OA on daily life?

In this thesis we address the efficacy and safety of hyaluronic acid injections for ankle OA, what dosage schedule to use, how to inject the osteoarthritic ankle, the impact of ankle OA on daily life, the evidence for conservative treatment of ankle OA and at what stage ankle OA are referred to a tertiary center, what treatment they underwent, what the cause of their ankle OA was and what treatment was prescribed.

Outline of this thesis

To investigate the efficacy and safety of hyaluronic acid injections for ankle OA; a prospective study to investigate the safety and efficacy of hylan G-F-20 (Synvisc) in patients with symptomatic ankle OA was carried out, chapter 2.

The exact dosage schedule of hyaluronic acid for ankle OA is unclear, to find an answer to this question, the effects, safety and dose dependency of hyaluronic acid were investigated, chapter 3. The former two studies showed a significant amount of adverse events and a varying efficacy of the injections, this outcome maybe caused by extra articular placement of the injection.

The efficacy of intra-articular injections can possibly be enhanced if they truly reach the joint cavity and the amount of adverse events might be diminished if the Hyaluronic acid truly is injected in the joint. The ankle is difficult to inject and osteophytes might
The conservative treatment of ankle osteoarthritis block the way in case of OA. In chapter 4 the optimum injection technique for ankle osteoarthritis was investigated by means of a cross-over trial.

It is unclear what the impact of ankle OA is on daily life, to judge the treatment effect of any therapy, as a patient reported outcome (PROM), we need to know what a patient considers the most important limitations. The difference between the opinion on the impact of ankle OA between patient and orthopedic surgeons was investigated and results are displayed in chapter 5. To find evidence for conservative treatment for ankle OA a systematic review of the literature was carried out, chapter 6.

At this point it is unclear if and how often ankle OA is recognized at an early stage, maybe the incidence is larger than the current numbers show us. Recognizing the presence of an early stage of ankle OA, might be the first step in order to test any conservative treatment. It is also unclear what and if any conservative treatment has been used before patients are referred to the hospital.

A cohort of ankle OA patients that was referred to the hospital was investigated to see at what stage patients are referred for treatment of their ankle OA and what kind of conservative treatment was offered to them, in order to get a global idea what is used as conservative treatment, chapter 7.
References:


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