The conservative treatment of ankle osteoarthritis
Witteveen, A.G.H.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)
CHAPTER 8

General Discussion
General Discussion

Conservative treatment or non-surgical treatment for ankle osteoarthritis (OA) is used in an early phase of OA. Surgical treatment is specifically reserved for end stage arthritis. It is not considered as first choice treatment 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\textsuperscript{[1-6]}. Non-surgical treatment is aimed to postpone surgical treatment by treating or relieving symptoms of ankle OA, like pain and functional loss.

Ankle trauma occurs in many patients at a relatively young age\textsuperscript{[7,8]}. Consequently, the expected life span of many patients with ankle OA is significantly longer than the life span of hip or knee OA patients. Keeping them active could reduce costs caused for instance by job loss, sickness and hospital treatment. A good algorithm for conservative treatment is required in order to retrieve this goal.

Evidence for conservative treatment is limited. The research described in this thesis was aimed to find evidence for the efficacy and dose regimen of hyaluronic acid (HA) for ankle OA. In order to enhance efficacy of HA and reduce the amount of adverse events, attempts were made to find the optimum injection technique for ankle OA. The impact of ankle OA on daily life comparing the opinion of patients to orthopedic surgeons was investigated. A systematic review of the literature was undertaken to find evidence for existing conservative treatments for ankle OA. In order to explore the current use of conservative therapy for ankle OA, a cohort of ankle OA patients was investigated for the use of conservative treatment before referral to the hospital, for the stage of ankle OA at which patients were referred and for the treatments that could be offered to them, specifically where it concerned the conservative options.

The potential benefit of Hyaluronic acid for ankle OA

The potential benefit of hyaluronic acid (HA) in treating ankle OA is pain reduction\textsuperscript{[1,9-12]}. Salk et al and Sun et al used a dosing regimen as used for knee OA in their studies\textsuperscript{[11,12]}. The ankle joint, however, is much smaller than the knee and has a different shape. It is likely that less hyaluronic acid is required to be effective in a smaller joint. For some HA brands dose-finding studies for usage in the knee were performed
and published\textsuperscript{[13,14]}. However, for the ankle no dose finding studies are published. Since there are several types of HA, varying in molecular weight and composition (sodium hyaluronate or a cross linked combination of different types of sodium hyaluronates), it is not unlikely that each type of hyaluronic acid has a different optimum in efficacy.

The potential benefit of a single injection of 2 ml of Hylan GF-20 (a low molecular weight combination of crosslinked hylan A and B) in the hip was already demonstrated, leading to the question if a single injection in the ankle could be safe and effective as well\textsuperscript{[15,16]}. The results of the efficacy and safety of a single injection of 2 ml of Hylan GF-20 in the arthritic ankle are described in chapter 2.

It was demonstrated that a single injection of 2 ml Hylan GF-20 with an optional second injection after 1, 2 or 3 months was effective in significantly reducing the pain associated with ankle OA. Pain reduction was maintained up to six months in the majority of the patients. The study was an open label study; no comparison to placebo was made, so no definite conclusions about the efficacy can be made. Adverse events were mild and moderate in intensity and consisted of transient pain and or swelling. A significant percentage of patients were affected by such an adverse event (30,9\%). This finding was consistent with findings demonstrated by Salk et al (29\%)\textsuperscript{[11]}. It is not likely that these adverse events are correlated with the use of HA. It is more likely that such adverse events are correlated with extra articular placement of the injection since the same amount of adverse events occurred for placebo injections when compared to HA\textsuperscript{[11]}.

The results of a dose finding study for HA are described in chapter 3 for a high molecular weight sodium hyaluronate (Orthovisc\textsuperscript{a}). Four different dosages were compared, the 3x1 ml regimen showed the best results for pain on walking. For a single dose application of Orthovisc\textsuperscript{a} no effectiveness was shown. Sample sizes were small, so more research needs to be done to support this finding and make a definite conclusion. Adverse events were reported by 27\% of the patients, again these were mild or moderate in intensity and consisted of transient pain and swelling, all resolved within a few days.

Different hyaluronic acids might need different dosing regimens to be effective; more studies to investigate different types of HA are required.

As stated before adverse events may be associated with extra-articular placement of the injections. Abate et al stated that the poor efficacy of HA for the use in ankle OA
could be associated by extra-articular placement of the injection\cite{17}. In order to reduce the chance of extra articular placement of ankle injections, two injection techniques were compared; one using the injection technique that is commonly used for the ankle joint and one using a traction device that is commonly used for ankle arthroscopy. The traction device is believed to open up the joint, which might facilitate the injection\cite{18,19}. The primary outcome was the needlepoint position. The position of the injection was determined by fluoroscopy. The location of the injected contrast was registered as either inside (success) or outside (failure) the joint. No significant difference between these two injection techniques was demonstrated. Neither of the two could be assigned as better than the other. There was a failure rate of 24\% in both groups. Despite the fact that HA was only administered after intra-articular placement of the needle a large number of adverse events were noted. These adverse events were all mild or moderate in severity. They consisted mainly of temporary pain and swelling and all resolved within a couple of days. Walking on crutches or taking pain medication reduced the symptoms. No satisfactory explanation for the amount of adverse events could be found. Possibly the contrast fluid caused some irritation as well as the HA itself. HA in itself is known to induce temporary benign side effects like pain, swelling, and warmth\cite{1,9,20,21}. Better injection techniques need to be investigated to reduce this complication. Several suggestions have been made in literature to test placement of intra-articular injections using some form of alternative imaging\cite{22-25}. At this point the best way to inject the ankle is with the aid of the fluoroscope. It is therefore advisable to inject the ankle using contrast-aided fluoroscopy until other techniques have proven themselves.

Interestingly enough HA in itself is not primarily meant to reduce pain, but more to restore the natural protective function of the joint, like shock absorption and lubrication of the joint during gait\cite{14,26}. This raises the question if we are not measuring the wrong outcome. It is a nice side effect that pain is reduced, more interesting however is question whether the process of cartilage deterioration is delayed or not? So maybe we need to follow these patients by X-ray or for instance dGEMRIC MRI (delayed Gadolinium Enhanced Magnetic Resonance imaging of Cartilage) This is a special MRI technique which is used to evaluate the amount and quality of the cartilage\cite{27}. Questions that need to be answered in the future.
Based on the current evidence hyaluronic acid for ankle OA seems to be effective in pain reduction. Better results were found compared to placebo. However sample sizes are small and different HA and dosing schedules were used. More high quality studies are needed to support the evidence. Recently it was demonstrated that bioengineered HA intra-articular injections in treating knee OA compared to conventional care including non-steroidal and anti-inflammatory drugs and analgesics was more effective and less costly than conventional care. This is an interesting phenomenon and needs to be investigated for ankle OA as well[28].

**Measure the effect of conservative treatment (PROMs)**

Since there is no cure yet for ankle OA, the conservative treatment of symptomatic ankle OA mainly focuses on treating symptoms like pain and stiffness, to improve or maintain function with prevention of further deterioration of the joint[29]. To monitor the effect of conservative treatment for ankle OA six scoring systems are used in the current literature; 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), the Foot and Ankle Outcome Score (FAOS) and the Foot Function Index (FFI)[30-43].

Physicians created most of these outcome scores with no or little input of the target patient group. 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 the needs and demands of patients are. In order to find an answer to this question the impact of ankle OA on daily life and function was investigated comparing the difference in opinion between patients and orthopedic surgeons.

The results and outcome are reported in chapter 5. A modified Delphi method in two rounds was used. Several significant differences in opinion between patients and orthopedic surgeons were demonstrated. One of the most important differences is the
The conservative treatment of ankle osteoarthritis

fact that patients have difficulty to perform certain activities; this prevents them from engaging in social activities, which in return might even isolate them. Another important difference is the fact that patients really feel that their ankle stiffness is hindering them in performing daily activities. The orthopedic surgeons appreciated this less. The surgeons also less appreciated the unstable sensation patients experience in their ankle as well. Orthopedic surgeons also are less aware of the fact that patients have difficulty standing still due to their ankle OA. Pain is considered the most important symptom by surgeon and patient.

A Patient reported outcome (PROM) should incorporate the needs and demands of the individual patient as well as the outcome that is important to the clinician. This study showed that next to pain, the participation in different kind of activities is a major concern to patients.

The outcome measures that are currently used (AAOS, AOFAS, AOS, FAAM, FAOS and FFI) are too general and do not meet the demands and expectations of the individual patient with ankle OA. An item that is missing in most scoring systems for instance is walking pace. Patients might be able to ascend or descend stairs, but might need a rail, or a crutch, or have a high or low pace.

When a PROM is to be designed from scratch, not considering existing PROMs, this study provides the elements that could be incorporated. Besides a VAS-score for pain, achieving functional goals might be a worthy addition to a new PROM. The Global Attainment Scaling (GAS) is such a tool, which evaluates a specific goal of a patient and can compare the outcome scales of different patients. The GAS is part of the International Classification of Functioning Disability and Health (ICF), developed by the World Health Organization (WHO)[44-46].

The next step is to create, test and validate a new PROM for ankle OA patients.

Is evidence of conservative treatment of ankle OA still lacking?

Nowadays many treatment modalities are offered. 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[29,47-52]. However, since ankle OA may be caused by a different mechanism, it is not unthinkable that these patients need a different treatment.
At this point there is no evidence based treatment algorithm for ankle OA. Several papers have been published concerning the cause of ankle OA and the possible conservative and operative treatment strategies. The conservative section mainly sums up the possibilities, however no algorithm is suggested[53-57].

To assess the benefits and harms of any conservative treatment for ankle OA in adults in order to provide a synthesis of the evidence as a base for future treatment guidelines a Cochrane review of the existing literature was performed (chapter 6).

Only 6 highly qualified studies were identified[9,11,58-61]. The studies retrieved were all randomized controlled trials (RCT), analyzing the use of hyaluronic acid for ankle osteoarthritis (OA). No other RCT concerning any other conservative treatment was identified.

It was concluded that up to date there is insufficient data to create a synthesis of the evidence as a base for future guidelines for ankle osteoarthritis. Hyaluronic acid as treatment for ankle osteoarthritis appears to be safe and more effective than placebo at 6 months for pain and disability as evaluated by the based on the Ankle Osteoarthritis Score (AOS). It remains unclear which patients (age and grade of ankle osteoarthritis) benefit the most from hyaluronic acid injections and which dosage schedule should be used.

The amount of studies and reviews concerning the use of hyaluronic acid for ankle osteoarthritis is very limited. Three reviews were identified[1, 17,62]. One study was included in all these reviews and was not eligible in our review, since hyaluronic acid was administered arthroscopically after arthroscopic debridement[63]. All randomized controlled trials that were included in these 3 reviews were included in our review as well. Abate reviewed 4 randomised controlled trials and 5 case series[17]. They concluded that there was no evidence on the efficacy of hyaluronic acid in reducing pain and improving function in ankle OA. Their advices for future research was to look at an adequate dose regimen, a good outcome measure, identify which patients and grade of OA benefit best of hyaluronic acid injections. Chang included 4 randomised controlled trials, 1 double arm and 4 single arm prospective studies[11]. All studies were pooled based on improvement scores from baseline. A significant pain reduction was found for hyaluronic acid. A not significant difference was found in favour for Hyaluronic acid comparing hyaluronic acid to placebo. Migliore included 3 randomised trials and 4 single arm studies[62]. Due to the
heterogeneity of studies, data could not be pooled. Every study and the conclusion were individually described. The overall conclusion was that visco supplementation is useful in ankle OA and that future prospective studies need to use standardized outcomes.

The next study question was what treatment patients were subjected to before referral to the orthopedic surgeon as an evaluation of what is used as conservative treatment of ankle OA by primary care doctors. We also investigated the stage of ankle OA at referral and the possible options left for the patients after referral. Patients were mainly referred at an end stage of the disease. Fifty three percent of the patients were referred at stage 2B Van Dijk classification or Van Dijk classification 3, some even 20-30 years after their initial diagnosis\[64\]. Their age varied from a mean age of 40 in the grade 1 (Van Dijk classification) ankle OA group to a mean age of 60 years in the grade 3 group (the minimum age was 19.5 and the maximum 81.2 years). Before referral, patients that were treated were treated in different ways without the use of a protocol or guideline. Treatment, if given, consisted mainly of an assistive device (84%), like a brace, shoe adjustment (inlay, or rocker sole) or cane/crutch, physical therapy (57%) and pain medication (48%). The majority of grade 3 patients (71%) were offered surgical therapy after their referral, mostly consisting of ankle fusion or ankle replacement. Some patients were treated with an orthopedic shoe or other non-operative measures because they suffered from severe general health problems, which increased the risk of complications by the use of surgery.

It is unclear why patients are referred in such a late stage. Patients mention that they were told to wait until they needed surgical treatment. A probable explanation might be that knowledge about conservative treatment options is still insufficient and that it might be difficult to recognize the process of OA.

Up to date only limited evidence concerning the conservative treatment for ankle OA exists and knowledge about the possibilities seems to be insufficient.

In search for evidence for the most efficacious conservative treatment high-quality studies are needed to find evidence for every stage of the disease. It is important to recognize patients at risk of developing ankle OA in order to treat them in an early stage of the disease.
How do we recognize OA and what do we know?

To recognize ankle OA in order to start early treatment it is important to be aware of the process that is going on. At this point the process of osteoarthritis is not clearly understood. Most likely it starts with the damage of cartilage\cite{65}.

Articular cartilage is aneural and avascular, yet it is a metabolically active tissue. Cartilage is poor in tissue healing when damaged and repair tissue, if any is formed, often consists of fibrous tissue. The most important limiting factor in cartilage repair is the lack of blood supply. When the subchondral bone is involved in the primary lesion a fibrin clot can be formed leading to tissue repair, which results in the formation of fibrocartilage. This tissue has less mechanical resistance than normal hyaline cartilage.\cite{66-68} This could lead to easier damage during loading, followed by a progressive deterioration of the joint.

It remains a challenge to find a moment, if this is even possible in which we can reverse, stop or slowdown the process of OA. It is unclear when the point of no return, if such a point exists, has been reached leading to the inevitable OA of the joint involved.

Pain is a symptom of OA\cite{29}. However, before pain becomes a symptom the process is more advanced than just cartilage damage since cartilage is aneural. It is important to recognize the potential start of OA in order to possibly interfere in the process of OA. Once we know the mechanism of OA and how we can recognize the early onset, we might even be able to find a disease modifying treatment. At this point we can only treat symptoms.

It is however important that symptoms like pain and stiffness in the ankle are recognized as an expression of ankle OA, in order to refer patients for conservative treatment.

It is known that the cause of ankle OA is posttraumatic in 70-78% of the patients\cite{8,69}. Our cohort showed a higher number (84%) of posttraumatic origin. This 84% percent could be divided in instability in 36% and a fracture of either the ankle or lower leg as a potential cause of ankle OA in 48% of these patients. A traumatic event can cause a direct cartilage lesion leading to a relative fast deterioration of the joint as described above. Insufficient fracture reduction can lead to an incongruent joint, which can lead to the development of ankle OA within 2.8 years\cite{70}. In ankle OA however, a lot of patients develop OA in a slower fashion, some even after 20 years, as was demonstrated in our cohort. Persisting ligamentous instability may cause this OA\cite{71}. Another reason might be
a traumatically induced varus or valgus malalignment of the hindfoot, which in turn may lead to an overload of the joint\textsuperscript{[72]}. Stufkens et al showed in his biomechanical study that a varus or valgus deformity of the distal tibia causes significant changes in the contact area of the tibiotalar joint of up to 36\textsuperscript{o}\textsuperscript{[73]}.

At this point the process of ankle osteoarthritis is not clear, it is also unclear if early treatment of instability and varus and valgus alignment will slow or halt the development of ankle OA. Symptoms like pain and stiffness are a relative late sign of the development of OA. Up to date scientific knowledge only provides us with limited evidence to treat symptoms of ankle OA.

**Future recommendations**

More high quality studies need to be done to find evidence for conservative treatment of early ankle OA. These studies are required to create a future guideline. Due to the higher volume of patients and other available resources it is preferable to perform this research in a hospital setting. Primary care physicians and other professionals involved in treatment of ankle OA patients have to be aware of the process of the development of ankle OA in order to recognize patients that are at risk.

Future research should be aimed at the prevention of the development of ankle OA. Possible subjects might be:

- Restoring the natural protective function of the joint soon after the initial trauma by possibly administrating HA injections.
- Investigate the possible effects of bodyweight on the development of ankle OA.
- A more aggressive treatment of persistent instability and valgus or varus deformities of the hind foot.

**Conclusions**

Up to date there are insufficient data to create a synthesis of the evidence as a base for future guidelines for ankle osteoarthritis (OA).

Hyaluronic acid as treatment for ankle OA appears to be safe and more effective than placebo at 6 months for pain and disability. It remains unclear which patients (age and grade of ankle OA) benefit the most from hyaluronic acid injections and which dosage schedule should be used.
For intra-articular HA therapy, it is recommended to inject the ankle using contrast-aided fluoroscopy until other techniques have proven themselves.

The outcome measures that are currently used to monitor the effect of conservative treatment of ankle OA (AAOS, AOFAS, AOS, FAAM, FAOS and FFI) are too general and do not meet the demands and expectations of the individual patient with ankle OA.

There is a significant difference in the opinion between patients and orthopedic surgeons concerning specific symptoms of ankle OA.

A patient reported outcome measure (PROM) should incorporate the needs and demands of the individual patient as well as the outcome that is important to the clinician. It was demonstrated that next to pain, the participation in different kind of activities is a major concern to patients.

Patients are referred to the orthopedic surgeon at a late stage of ankle OA. To find evidence for different conservative treatment options and to understand the process of ankle OA it is essential that patients be referred at an early phase of ankle OA.
The conservative treatment of ankle osteoarthritis

References:


The conservative treatment of ankle osteoarthritis


