
Ankle Osteoarthritis
Impact and Interventions
Liam D. A. Paget

Propositions

“Patients with ankle osteoarthritis have a clinically relevant poorer mental and physical quality of life compared to the general population”
— This thesis

“Former professional football and rugby players have a higher prevalence of ankle osteoarthritis compared to the general population”
— This thesis

“PRP injections do not significantly improve ankle symptoms and function over 26 or 52 weeks. There is no support for the use of PRP injections for ankle osteoarthritis”
— This thesis

“When commercial promise speaks louder than clinical evidence, science must speak louder still”
— Inspired by this thesis

“The greatest gain from a good RCT is not always a new treatment, but sometimes the abandonment of an old habit”
— Inspired by this thesis

“Sport has the power to inspire. It has the power to unite people in a way that little else does. It has the power to change the world”
— Nelson Mandela

“It always seems impossible until it’s done”
— Nelson Mandela

“Leave the jersey in a better place. The jersey doesn’t belong to you; you are merely the caretaker for the next person”
— The All Blacks

“You miss 100% of the shots you don’t take”
— Wayne Gretzky

“In rugby, as in science, progress is rarely made without first taking a few knocks”
— Inspired by this thesis

“No captain can do very wrong if he places his ship alongside that of the enemy.”
— Admiral Horatio Nelson

“PRRRRIMA”
— Prof. Dr. J. L. Tol

Ankle Osteoarthritis

Impact & Interventions

LIAM D. A. PAGET

For Daphne, Zoë, Nikki and Chris

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Ankle Osteoarthritis

Impact and Interventions

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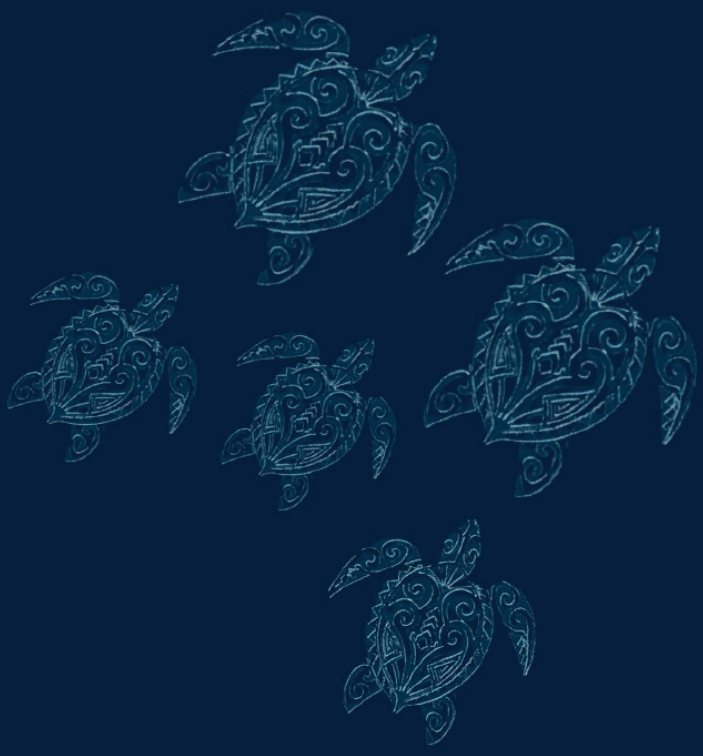
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CHAPTER

1

General Introduction



EPIDEMIOLOGY AND FINANCIAL AND SOCIAL IMPACT

Osteoarthritis (OA) is characterized by pain and disability, with pain being the biggest driving factor for consulting a health care professional.[1-3] OA is among the leading causes of global disability and is estimated to affect 250 million people world-wide.[4-6] In high-income countries it accounts for 1 – 2.5% of the gross national product.[7] Ankle OA is estimated to have a prevalence of 3.4% in the general population.[8] In 70-78% of ankle OA cases it has been preceded by trauma to the ankle, unlike knee and hip OA where the main cause is primary OA in 67% and 58% of cases, respectively.[9-11] As a result, patients with ankle OA are relatively younger with a longer projected life span than patients with knee and hip OA. Furthermore, the mental and physical quality of life of patients with ankle OA is significantly impacted and similar to patients with end-stage hip OA, end-stage kidney disease and even congestive heart failure.[12,13]

ANATOMY

The mortise structured talo-crural ankle joint, formed by the distal fibula and tibia together with the talus, is connected by four ligaments at the level of the syndesmosis (anterior and posterior tibio-fibular ligaments, the transverse (deep fibers) tibiofibular ligament and the interosseous membrane). The deltoid ligament runs from the tibia to the talus on the medial side. Distally, the talus articulates with the calcaneus forming the subtalar ankle joint and is attached through the medial, lateral and interosseus talocalcaneal ligaments. The lateral malleolus is connected to the talus through the anterior and posterior talofibular ligaments (ATFL and PTFL), which are capsular ligaments. The calcaneofibular ligament (CFL) attaches the distal fibula directly to the calcaneus, bridging both the talocrural and subtalar joint, and is extra capsular.[14] The talus is wider anteriorly than it is posteriorly. In dorsal flexion the wider part of the talus moves between the malleoli forming a stable congruent ankle position. In plantar flexion, the narrow part of the talus moves between the malleoli forming an unstable incongruent ankle position.[15] It is in this unstable plantar flexion position that the ankle is most prone to ankle sprains.

BIOMECHANICS

Rapid evolutionary changes, the transition from quadrupedal to bipedal walking, resulted in dramatic kinematic and energy expenditure changes, with some joints affected more than others.[16] Consequently, some joints are relatively underdesigned attributing to higher primary OA prevalence

due to the adoption of an upright position and bipedal walking, such as the development of OA on the superior margin of the femoral head that is relatively uncovered in bipedal primates.[16-18] The ankle surface cartilage is exposed to higher loads per unit surface area than the knee during normal walking.[19]

BIOLOGY OF THE ANKLE

At cartilage level, that of the ankle is stiffer and less permeable to water, due to a higher content of proteoglycans and lower water content.[20] The response of ankle cartilage chondrocytes to (catabolic) inflammatory cytokines (such as Interleukin-1) is also reduced compared to knee cartilage.[20] Furthermore, as the tensile fracture stress and tensile stiffness decrease significantly with age in knee and hip cartilage, the cartilage of the talus shows little change.[19] As a result primary ankle OA is only seen in a minority of cases with 70-78% of cases being posttraumatic of origin as described earlier.[9-11]

PATHOGENESIS OF OSTEOARTHRITIS

Although frequently wrongly described as a degenerative or “wear and tear” disease, OA is a significantly complex pathogenesis involving genetic, mechanical, inflammatory and metabolic factors.[21-23] These multiple factors facilitate a dynamic imbalanced state of repair and destruction of the bone, cartilage and synovium, enabling multiple pathways to joint destruction. Due to the wide range of underlying factors this heterogeneous disease is more of a syndrome.[24] The mechanisms of OA are divided into primary and secondary OA. Primary or idiopathic OA is thought to originate in the joint with a multifactorial etiology of which genetics, age, obesity and heavy physical workload are risk factors. Secondary OA is where another cause instigates the osteoarthritic process, such as rheumatoid arthritis or a trauma. For instance, in post-traumatic osteoarthritis (OA), malalignment and incongruency lead to a different loading pattern with subsequent cartilage loss. In the osteoarthritic process, the cartilage composition changes resulting in an increased susceptibility to mechanical forces. As the chondrocytes attempt to repair cartilage loss or fissures, pro-inflammatory factors are released that cause changes of the articular and peri-articular tissues. This results in further alteration of cartilage composition, synovitis, fibrosis of ligaments and vascular invasion from the subchondral bone to the cartilage. This process of bone remodeling and repair facilitates changes of the subchondral bone such as subchondral cysts or sclerosis.[25-28]

TREATMENT OPTIONS

Currently, surgical treatment is in particular reserved for end-stage ankle OA and includes arthrodesis, arthroplasty or osteotomy.[29-32] In general, patients with OA may benefit from weight loss thereby reducing joint load and therefore pain.[33,34] In knee OA, each pound of weight loss reduced the load on the knee during daily activities by a factor of four.[35] Although paracetamol and Non-Steroidal Anti-Inflammatory Drugs are frequently recommended in guidelines for the management of pain in OA, a meta-analysis concluded paracetamol to be of little use.[36,37] Oral NSAIDs have shown clinically relevant improvement.[37] However its use must be limited and carefully considered due to the gastrointestinal, cardiovascular and renal side-effects. A meta-analysis reported efficacy of topical NSAIDs without observations of gastrointestinal, cardiovascular or renal side-effects.[38] However, intra-articular injections may be a non-surgical intervention in the treatment of ankle OA.

PLATELET-RICH PLASMA

In the literature results have suggested efficacy of Platelet-rich plasma (PRP) in the treatment of OA.[39-41] PRP is defined as plasma containing over 1 000 000 platelets/ml.[42] Following activation, for instance through centrifugation, growth factors stored within the α-granules of the platelets are released. These growth factors are believed to provide the anti-inflammatory and regenerative effects of PRP through modulation of the intra-articular environment.[43] A review reports the ability of PRP to diminish interleukin-1 mediated effects and upregulate mRNA of proteoglycan core protein, thereby decreasing chondrocyte apoptosis and positively affecting the collagen and therefore cartilage composition.[43] Although no randomized clinical trials (RCT) are available concerning the efficacy of PRP in the treatment of ankle OA, 21 RCTs investigated the effect of PRP injections for knee OA.[39] Meta-analyses report some benefits for PRP injections in knee OA.[39-41] Additionally the global commercial market for PRP is rapidly growing and is forecast to increase to 1.2 billion US$ by 2028.[44]

PATIENT REPORTED OUTCOME MEASURES

As pain is the driving factor for clinical decision making, and there is only a moderate association between pain and structural OA on x-ray, measurement is of clinical importance. Patient reported outcome measures (PROMs) measure predetermined properties of a disease and can be used for individual or research purposes to evaluate treatment effect or deterioration. The American Orthopaedic Foot and Ankle Society (AOFAS) score is the most frequently used PROM for foot and ankle disorders. The AOFAS is a 9-item questionnaire and includes 5 items to be reported by the patient and 4 items to be determined by the physician. These 9 items cover 3 subscales, namely pain,

function and alignment and runs from 0 to 100. Higher scores indicate less pain and or symptoms. However the AOFAS has not been structurally and elaborately evaluated for ankle OA for its measurement properties. Furthermore, completely patient-reported PROMs are thought to be more patient friendly, less time-consuming and achieve more patient compliance.

AIMS AND VIEWS

The impact of ankle OA on the mental and physical quality of life is reportedly significant according to two North American studies. However patients with ankle OA have never been compared to a matched-control group from the general population. In **chapter 2** we looked at the impact of ankle OA on the mental and physical quality of life of patients with ankle OA and compared it to a matched-control group from the general population.

As a major portion of ankle OA is posttraumatic, sports with a higher risk of ankle trauma and at an elite level would be more at risk of developing ankle OA than the general population. In **chapter 3** we looked at the association of ankle injuries and ankle surgeries with ankle OA and the prevalence of ankle OA in former professional football and rugby players.

With treatment options limited for patients in the early phase of ankle OA, the promising effects of PRP may be a potential non-surgical treatment for ankle OA. In **chapter 4** we aim to determine the validity, reliability, interpretability, responsiveness and minimally important change of a completely patient-reported version of the AOFAS as well as the measurement properties of the original patient-reported and physician determined AOFAS in patients with ankle OA.

In **chapter 5** we present a protocol of double-blind, placebo-controlled, randomized trial to assess the efficacy of PRP in the treatment of ankle OA. In **chapter 6** we describe the results of this trial at 26 weeks. In **chapter 7** we describe the results of this trial at 52 weeks.

Injection therapies are widely used for OA, however evidence for their efficacy is limited. In **chapter 8** we systematically reviewed the literature for efficacy of injection therapies used for the treatment of ankle OA.
In **Chapter 9** the most important findings of these studies their limitations and implications for clinical practice and future research are discussed.

CHAPTER

2

Health-Related Quality of Life in Ankle Osteoarthritis

A Case-Control Study

Liam D. A. Paget, Johannes L. Tol, Gino M. M. J. Kerkhoffs, Gustaaf Reurink



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ABSTRACT

Objective – Ankle osteoarthritis (OA) has a prevalence of 3.4% in the general population of which 70% to 78% is posttraumatic, affecting younger patients with a longer projected life span compared with hip and knee OA. The current literature reports the physical and mental quality of life (QoL) of patients with ankle OA, to be similar to end-stage hip OA, end-stage kidney disease and congestive heart failure. However, the QoL of ankle OA patients has not yet been determined compared with a matched control group representing the general population. Our aim is to determine the physical and mental QoL compared with a matched control group.

Design – The Physical and Mental Component Summaries of the Short Form–36 of 100 patients with ankle OA were compared with 91 age- and gender-matched controls. This case-control study is a substudy of the PRIMA trial, in which the efficacy of platelet-rich plasma injections for ankle OA is determined.

Results – A clinically relevant difference was found for both the Physical (P=0.003; 95% CI −6.7 to −1.3) and Mental Component Summary scores ($P < 0.001$; 95% CI −10 to −6). Patients with ankle OA had a median of 45 points (matched controls 52 points) and 43 points (matched controls 53 points) for the Physical and Mental Component summary scores, respectively.

Conclusions – Patients with ankle OA had a clinically relevant poorer mental and physical QoL compared with matched controls from the general population. Furthermore, the physical QoL of patients with ankle OA from younger age categories was affected more than those in older age categories.

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease and is characterized by pain and disability.[3,5] The pathogenesis of OA involves mechanical, inflammatory, and metabolic factors and an imbalance between destruction and repair of the joint.[22,45] Clinically and radiographically determined ankle OA has a prevalence of 3.4% in the general population.[8] In former professional football and rugby players, the prevalence of ankle OA is 9% to 19% and 4.6%, respectively.[46-49] The majority of ankle OA cases are posttraumatic (70%-78%) and affect younger patients with a longer projected life span unlike hip and knee OA.[9,10] Other secondary causes (including rheumatoid arthritis [5%-12%], hemochromatosis [0%-3%] hemophiliac [1%-2%], septic [1%-2%], congenital [2%], and osteonecrosis [1%-2%]) and primary OA (7%-9%) are reported to be the underlying causes of the ankle OA cases that are not posttraumatic.[9,10]

Patients with ankle OA have a poor physical and mental quality of life according to 2 studies in North America.[12,13] The first study followed 195 patients (matched controlled to 95 subjects) with moderate to severe ankle OA at their clinic.[13] They found a similar quality of life as reported for end-stage kidney disease and congestive heart failure. The second study matched controlled 130 end-stage ankle OA patients with end-stage hip OA patients on the waiting list for a hip replacement.[12] They found a similar physical quality of life and a poorer mental quality of life compared with end-stage hip OA patients.

Currently, only one study in the United States compares the quality of life of ankle OA patients to the general population.[13] Generalization of quality of life outcomes to other population is limited, as differences in quality of life, measured with the Short Form–36 (SF-36), differs between countries for the same diseases.[50,51] Our aim is to complement the current literature and determine whether the results found in this study are reproducible and comparable to a Dutch population. We will determine the quality of life of ankle OA patients that are willing to participate in a trial on injection therapy. The quality of life was determined using the SF-36 and was compared with a matched control group from among the Dutch population. Our hypothesis is that patients with ankle OA have a poorer mental and physical quality of life compared with the control group.

METHODS

Study Design

This is a case-control study of ankle OA patients and matched controls from the general population. It is a substudy of the PRIMA trial, a randomized, double-blind, placebo-controlled, multicenter prospective study, designed to determine the efficacy of platelet-rich plasma injections in the management of ankle OA.[52] We used baseline SF-36 patient data from the PRIMA trial and matched controls from a database of the general population. The PRIMA trial is approved by the Medical Ethics Review Committee Amsterdam Medical Center, the Netherlands (ABR 2018-042, approved July 23, 2018) and registered in the Netherlands trial register (NTR7261). The study was sponsored by the Marti-Keuning Eckhardt Foundation, a nonprofit patient organization.

Study Population

Cases – Patients with ankle OA in 6 hospitals in the Netherlands (2 university medical centers, 2 teaching hospitals, a general hospital [Flevo Hospital], and a focus clinic [Bergman Clinic] were informed about the study. The SF-36 data of patients with ankle OA, acquired at baseline on participation in the PRIMA trial, was compared with a matched control group.

Controls – The data of the control group was obtained from the Netherlands Cancer Institute (NKI-AVL).[53] In 1996, the Netherlands Organization for Applied Scientific Research (TNO) conducted a nationwide survey in order to generate normative data for a study of patient with congenital heart defects. Questionnaires were sent to a randomly selected population from the telephone registry in the Netherlands. The telephone registry includes a smaller percentage of individuals between the ages of 15 and 25 years and a larger percentage of men. An effort was made to correct this imbalance by requesting (in the introductory letter) household members in the age category of 15 to 25 years, to fill in the questionnaire. In total, 1771 questionnaires were returned, a response rate of 68%. Compared with the Central bureau of Statistics, the national sample has a slightly greater percentage of men (56% vs. 49%). The male population was slightly skewed toward the younger age categories. The age distribution of the female population closely matched the total population. From this representative sample of the general Dutch population, controls were randomly matched with PRIMA participants for age and gender (maximum 5-year age difference). No information regarding comorbidities of the control patients was available and was therefore not considered in the analysis.

Eligibility Criteria

All participants signed an informed consent form before participating in the study. Patients were eligible for inclusion if they have a severity of ankle OA pain on a visual analogue scale (VAS 0-100

mm) ≥40 mm during daily activities, X-rays (anteroposterior [AP] and lateral views) indicating ≥grade 2 talocrural OA on the van Dijk classification (joint space narrowing, with or without osteophytes)[54] and are ≥18 years of age. Patients were excluded if they have received injection therapy for ankle OA in the previous 6 months, do not want to receive one of the 2 therapies, have clinical signs of concomitant OA of one or more other major joints of the lower extremities that negatively affects their daily activity level or have had a previous ankle surgery for OA or osteochondral defects <1 year (not including surgery for an ankle fracture in the past).

Study Measures

Outcome Measures – At baseline, before receiving the intervention of the PRIMA trial, the ankle OA patients completed the SF-36 questionnaire. The SF-36 is validated in the Dutch language and consists of 8 subscales.[53] All (sub)scales and summary scores go from 0 to 100, where 0 represents low quality of life or function and 100 represents high quality of life or function. These subscales can be summarized into 2 scores, the Physical Component Score and the Mental Component Score, which represent the physical and mental quality of life, respectively. The 4 SF-36 subscales that fall under the Physical Component Score are physical functioning, role limitation due to physical problems, bodily pain, and general health. The other 4 subscales, role limitation due to emotional problems, social functioning, mental health, and vitality, are summarized into the Mental Component Score. The minimal clinically important difference (MCID) of the SF-36 for both the Physical and Mental Component Scores is reported to be 3 points.[55]

Primary Outcome Measure – The primary outcome is the Physical and Mental Component Scores of ankle OA.

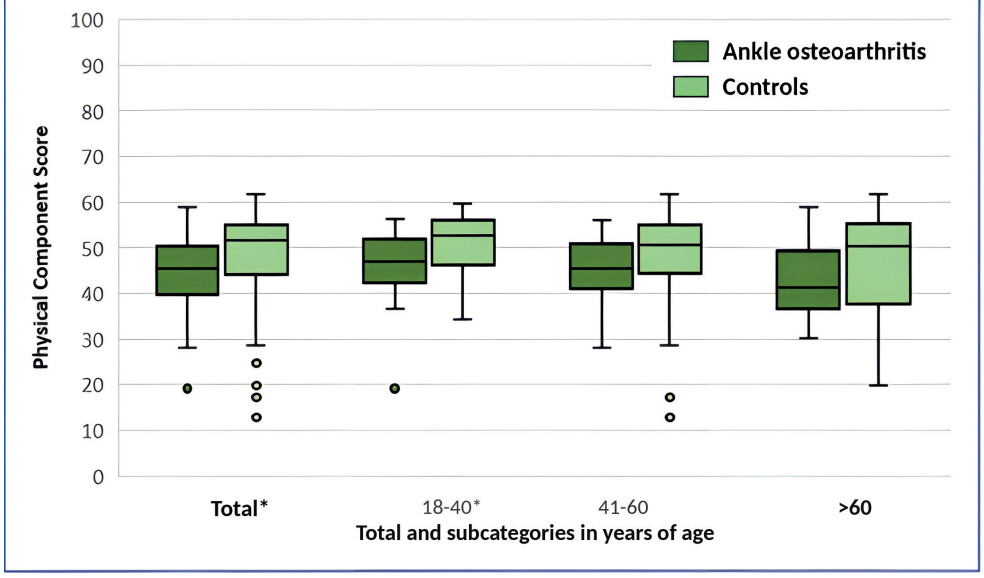
Statistical Analysis – Data analysis was performed using the statistical software IBM SPSS V.24.0 for Windows. Depending on normal or nonnormal distribution, data were expressed as means and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Baseline characteristics, including age and gender, were analyzed between groups using descriptive statistics. Physical and Mental Component Scores were calculated for all ankle OA patients and controls, as well as for the predetermined age categories (18-40, 41-60, and >60 years of age). Intergroup comparisons (ankle OA patients vs. controls) were determined using the paired Wilcoxon signed rank test. We considered $P < 0.05$ to be statistically significant.

RESULTS

Participants – In total SF-36 data from 100 patients from the PRIMA study were matched controlled with 91 patients from the Netherlands Cancer Institute (NKI-AVL). Of the original 100 matched controlled patients, 9 had missing values and could not be used. Unfortunately, no more matched controlled patients could be found in the database of the Netherlands Cancer Institute (NKI-AVL). In the ankle-OA group, there were 59 males and 41 females compared with the 56 males and 35 females of the control group. The average age was a median of 56 years (IQR: 44-64; min-max: 24-87) in the ankle OA group and a median of 56 years (IQR: 43-63; min-max: 23-90) in the control group.

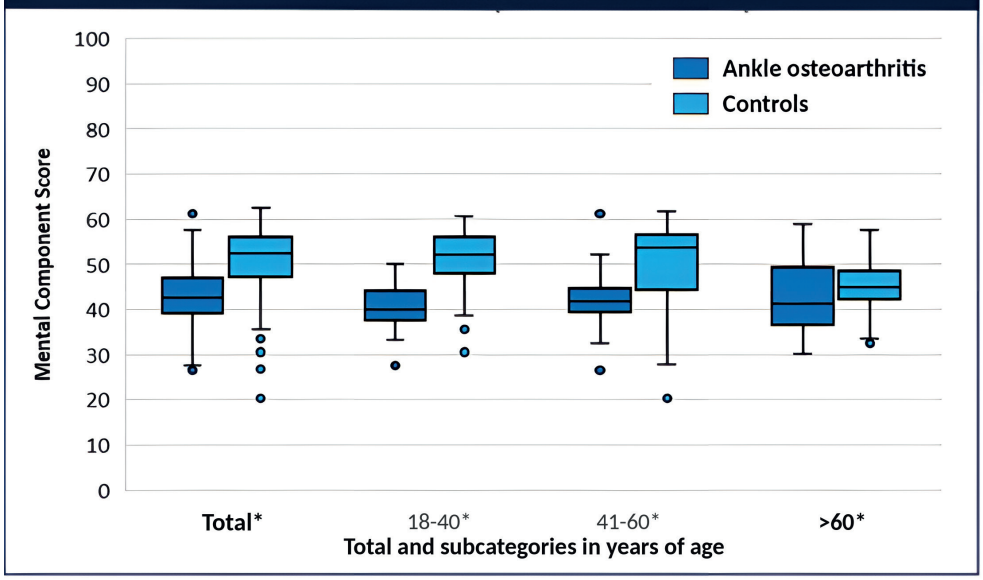
Mental and Physical Quality of Life – The Mental and Physical Component Scores of the SF-36 for all ankle OA patients and controls, as well as the predetermined age groups (18-40, 41-60, and >60 years) are presented in Figures 1 and 2, respectively (see also Table 1). A statistically significant, and clinically relevant difference was found for the Physical Component Score (P = 0.003; 95% CI −6.7 to −1.3), with a median of 45 points (IQR: 40-50; min-max: 19-59) for patients with ankle OA and a median of 52 points (IQR 44-55; min-max: 13-62) for the control group (Figure 1). For the Mental Component Score (Figure 2), a statistically significant and clinically relevant difference was found (P < 0.001; 95% CI −10 to−6) with a median of 43 points (IQR: 39-47; min-max: 27-61) for the patients with ankle OA and a median of 53 points (IQR: 47-56; min-max: 20-63) for the control group. For all predefined age categories, a statistically significant and clinically relevant difference was found between ankle OA patients and controls, except for the Physical Component Score of the subgroups 41 to 60 and >60 years of age (Figures 1 and 2).

Figure 1. SF-36 Physical Component Summary



Physical Component Score representing physical quality of life for patients with ankle osteoarthritis (OA) compared with the control group. Statistical significance is illustrated by * on the x-axis.

Figure 2. SF-36 Mental Component Summary



Mental Component Score representing mental quality of life for patients with ankle osteoarthritis (OA) compared to the control group. Statistical significance is illustrated by * on the x-axis.

Table 1. Physical and Mental Component Scores for all ankle OA patients compared with controls and subdivided into the predetermined age categories.

	Ankle OA *Median (IQR; min-max)*	**Control** *Median (IQR; min-max)*	**p**
Total	(n=100)	(n=91)	
Physical Component Score	45 (40 – 50; 19 - 59)	52 (44 – 55; 13 – 62)	P = 0.003 (CI -6.7 to -1.3)
Mental Component Score	43 (39 – 47; 27 – 61)	53 (47– 56; 20 – 63)	p < 0.001 (CI -10.0 to -6.0)
Age categories (years)			
18-40	(n=21)	(n=19)	
Physical Component Score	47 (42-52; 19-56)	53 (46-56; 34-60)	p = 0.02 (CI -9.0 to -1.4)
Mental Component Score	40 (38-44; 28-50)	52 (48-56; 31-61)	p = 0.005 (CI -14.8 to -5.6)
41-60	(n=47)	(n=43)	
Physical Component Score	45 (41-51; 28-56)	51 (44-55; 13-62)	P = 0.10 (CI -7.4 to 0.73)
Mental Component Score	42 (40-45; 27-61)	54 (44-57; 20-62)	P < 0.001 (CI -11.4 to -4.97)
>60	(n=32)	(n=29)	
Physical Component Score	41 (37-49; 30-59)	50 (38-55; 20-62)	P = 0.16 (CI -8.5 to 1.8)
Mental Component Score	45 (42-48; 32-58)	53 (47-56; 27-63)	P = 0.001 (CI -7.1 to -10.4)

OA: Osteoarthritis, IQR: Interquartile range.

DISCUSSION

Our most important finding was that ankle OA patients that are willing to participate in a trial on injection therapy have a statistically significant and clinically relevant poorer outcome for both the Physical and Mental Component Scores compared with matched controls from the general population.

We found a poorer Mental Component Score (43 points) compared to the current literature on ankle OA patients (47 points).[12,13] The Mental Component Score was similar the reported scores in the literature for psychiatric (anxiety disorders, depression, and alcohol abuse/dependence) (44 points)[56] and cerebrovascular/neurologic conditions (stroke, migraine, multiple sclerosis, neuromuscular disease, Parkinson's disease, and epilepsy) (44 points).[56] Compared with knee OA

(51)[57] and hip OA (47),[57] the Mental Component Score tended to be poorer among ankle OA patients in our cohort. The average age of the patients with knee and hip OA (69 and 67 years) differed considerably from the ankle OA patients in this study (54 years). A potential explanation for the lower Mental Component Scores is that ankle OA patients may be affected more mentally by the physical limitations they experience, as they are generally younger.

For the Physical Component Score (45 points) we found a higher score than the current literature (31 points [13] and 30 points [12]) on ankle OA. This can be partially explained as being due to the selection of end-stage ankle OA patients in one of the studies, in contrast to our study where we included patients with X-rays indicating ≥ grade 2 talocrural OA on the van Dijk classification.[12] In the other study, the quality of life of all patients visiting the outpatient clinic was determined.[13] In our study, ankle OA patients wanted to take part in an injection therapy study (PRIMA trial) as they felt they were not yet ready for surgery (arthrodesis or ankle prosthesis).[54] Therefore, the difference in reported physical quality of life may possibly be explained by the influence of selection bias. Furthermore, no clinically relevant difference was seen for the Physical Component Scale of the age groups 41 to 60 and >60 years of age. We theorize that it may be due to the accumulation of other physical ailments in patients over the age of 41 years, making the relative impact ankle OA has on the physical quality of life, smaller.

We found similar scores as is reported for knee OA (43) and hip OA (41).[57] As mentioned earlier, the ankle OA patients in this study were considerably younger (54 years) than patients with knee and hip OA (69 and 67 years). A potential explanation for the higher Physical Component Scores compared with knee and hip OA, is that the relatively younger ankle OA patients are better able to compensate for the physical limitations. The significant difference in age may be explained by the difference in etiology of ankle OA and hip and knee OA.[20] Ankle OA is posttraumatic in 70% to 78% of cases, compared with 2% to 10% in hip and knee OA. Patients with posttraumatic hip and knee OA were also seen to be up to 10 years younger than patients that are not posttraumatic.[58] Biomechanically, the mortise structure of the ankle joint allows for a higher congruency than the hip and knee joint.[13,20,59] At cartilage level, that of the ankle is stiffer and less permeable to water, due to a higher content of proteoglycans and lower water content, allowing it to withstand higher loads per unit surface area.[19,20] The response of ankle cartilage chondrocytes to (catabolic) inflammatory cytokines is also reduced, giving ankle cartilage a higher repair capability, all in all making it possibly less vulnerable to primary OA.[20]

Compared with other diseases in the literature, we found a similar physical component score (45 points) for end-stage chronic kidney disease (44 points).[60] In this study based on a population in the United Kingdom, the average age was 81 years compared with an age of 54 years in this study.[60] In further comparison to other diseases, we find a similar Physical Component Score in the literature for cardiovascular (e.g., coronary heart disease and hypertension) (45),[56] endocrinological (e.g., diabetes and thyroid gland impairment) (44),[56] and cerebrovascular/neurologic conditions (43).[56]

Strengths and Limitations

A strength of this study is the large cohort of ankle OA patients and matched controls from the general population. However, there are 2 limitations. First, the ankle OA patients, were subjects who had signed up for the PRIMA trial, and were willing to take part in a blinded randomized controlled trial with 50% chance of a placebo injection. These patients had a minimal ankle OA pain of VAS ≥40 mm during daily activities. It is likely there is a selection bias in that these subjects were impacted more by their ankle OA symptoms than the average ankle OA patient. Second, although considered recent enough, the SF-36 of the matched controls dates back to 1998. In Norway, despite societal changes over a period of 2 decades, the quality of life has remained relatively stable.[61] We therefore expect this limitation to have negligible consequences.

CONCLUSION

Ankle OA patients, that were willing to participate in a trial on injection therapy, had a clinically relevant poorer mental and physical quality of life compared to matched controls from the general population. Furthermore, the physical quality of life of patients with ankle OA from younger age categories was affected more than those in older age categories. Considering the relatively young age, current limited treatment options and especially the considerable impact on the mental quality of life, the outlook of an ankle OA patient is bleak.

CHAPTER

3

Ankle Osteoarthritis and Its Association with Severe Ankle Injuries, Ankle Surgeries and Health-Related Quality of Life in Recently Retired Professional Male Football and Rugby Players

A Cross-Sectional Observational Study

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Abstract

Objectives – To determine (1) the prevalence of ankle osteoarthritis (OA) among former professional football and rugby players, (2) assess the association between ankle injuries or ankle surgeries with ankle OA, and (3) compare the mental and physical quality of life (QoL) between former professional football and rugby players with and without OA.

Methods – We conducted a questionnaire-based observational study with a cross-sectional design. Former professional football and rugby players were recruited by the Football Players Worldwide and the International Rugby Players. Information concerning ankle OA, sustained ankle injuries and ankle surgeries was gathered (medical record or most recent medical professional). Health-related QoL was assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) physical and mental health scores.

Results – Overall, 553 former professional football (n=401) and rugby (n=152) players were enrolled in the study (response rate of 56%). Ankle OA prevalence among former professional football and rugby players was 9.2% and 4.6%, respectively. Football players were more likely to suffer from ankle OA following every ankle injury and/or surgery. Football and rugby players with ankle OA had similar PROMIS physical and mental health scores to the norm for the general population.

Conclusion – Former professional football and rugby players had higher ankle OA prevalence than the general population (3.4%). Football players are more likely to suffer from ankle OA following every ankle injury and/or surgery. No clinically relevant difference was seen for physical or mental health-related QoL among football and rugby players. Preventive measures for ankle injuries are recommended.

BACKGROUND

Football and rugby union (hereafter 'rugby') are among the most popular team sports worldwide. In both sports, ankle injuries represent a significant proportion of the total injuries sustained.[62-66] Previous ankle injuries are an important risk factor for ankle osteoarthritis (OA).[9,10]

Drawer and Fuller[64,67] estimate the overall risk of injury in professional football to be 1000 times higher than in high-risk industrial occupations, with ankle injuries contributing 10%–18% of all injuries.[63] The Union of European Football Associations Champions League Injury Study reported an overall ankle injury rate of 1 injury per 1000 hours.[63] Lateral ankle sprains (51%) were the most prevalent subtype of ankle injuries.[63] In professional rugby, epidemiological studies show that ankle injuries contribute 5%–20% of all injuries.[62,64,68,69] Similar to professional football, lateral ankle sprains are the most common ankle injuries, with an injury rate of 3.8–4.5 injuries per 1000 player hours depending on the position on the field.[70]

Two retrospective cohort studies from the general population (n=390 and n=639 patients, respectively) reported that 70%–78% of ankle OA cases were associated with a previously sustained ankle injury. These previous injuries included fractures, isolated osteochondral defects of the talus and ankle ligament injuries.[9,10] Among these post-traumatic ankle OA cases, 28% were associated with a previously sustained ligamentous injury.[9] To our knowledge, there are no prospective studies on the association of ankle injuries and ankle OA.

In the general population the prevalence of ankle OA is estimated to be 3.4% in people over 50 years of age.[8] The reported prevalence of ankle OA 16–22 years after a professional football career is 12%–19%.[47,48,71] No data are available for ankle OA among former professional rugby players. In comparison with a general population control group, the prevalence of OA in any joint and the incidence of joint replacement for any joint were estimated to be four and six times higher, respectively, among former elite rugby players.[72] This has been associated with a significantly poorer mental and physical health-related quality of life (QoL).[72]

Several other studies report the association of general OA with mental health symptoms and physical health-related QoL among former elite athletes across professional team sports including football and rugby.[73,74] Therefore, the impact of OA on retired players must be considered. To date, the epidemiological evidence concerning the prevalence of ankle OA in professional football is either

outdated or limited, and in the case of rugby non-existent, while data on the association between previous ankle injury and ankle OA are scarce in both sports.

The objective of this study was threefold. First is to evaluate the prevalence of ankle OA in recently retired professional football and rugby players. Second is to determine the association between ankle injury and/or ankle surgery and ankle OA. Third is to compare the mental and physical QoL in players with and without ankle OA. Our hypotheses were that (1) recently retired professional football and rugby players have higher ankle OA prevalence than the general population (as found in the literature); (2) ankle injuries and/or ankle surgeries are associated with ankle OA; and (3) the mental and physical QoL of recently retired professional football and rugby players with OA are lower compared with players without OA.

METHODS

Design

We conducted a questionnaire-based observational study with a cross-sectional design. The study was reported according to the 'Strengthening the Reporting of Observational Studies in Epidemiology' statement.[75]

Participants

Dependent variable: ankle OA Retired professional football and rugby players were randomly recruited to reduce recruitment bias by the Football Players Worldwide (FIFPRO) and the International Rugby Players (IRP). Inclusion criteria were (1) being a retired male professional football or rugby player; (2) being younger than 50 years of age; and (3) being able to read and comprehend texts in English, French or Spanish. The definition of a retired professional football or rugby player was that he (1) has trained to improve performances, (2) has competed in the highest or second highest national league, and (3) has had training and competition as a major activity (way of living) or focus of personal interest, devoting several hours in all or most of the days for these activities, and exceeding the time allocated to other types of professional or leisure activities. If interested, players received information about the study, gave their informed consent and completed an electronic questionnaire. Once completed, the electronic questionnaires were saved automatically on a secured electronic server that only the principal investigator could access.

Sample size calculation for ankle OA prevalence indicated that 138 participants per sport were needed (power of 80%, CI of 95%, absolute precision of 5%) under the assumption of an anticipated population proportion of 10%.[76] Expecting a response rate of approximately 50%, we intended to reach at least 300 participants per sport.

Dependent variable: Ankle Osteoarthritis

The clinical diagnosis of ankle OA by a medical professional was retrospectively determined using a single question ('Have you been diagnosed with ankle osteoarthritis by a medical professional?'). Participants were given the definition of ankle OA (based on the National Institute for Health and Care Excellence criteria; adapted for age), determined as the damage of the ankle joint's cartilage that leads to activity-related joint pain with either no morning joint-related stiffness or morning stiffness that lasts no longer than 30 min.[77] For this question, participants were requested to consult either their medical record or their most recent medical professional.

Independent variable: severe ankle injury and related surgery

History of a severe ankle injury during their professional football or rugby career was examined through a single question for the sequential recording of single or multiple injury events over time. Similarly, history of an ankle-related surgery was recorded through a single question for the sequential recording of a single or multiple ankle surgeries over time. In our study, a severe ankle injury was defined as an injury that involved the ankle joint, occurred during team activities (training or match), and led to absence from either training or a match for more than 28 days.[74,75] For this question, participants were requested to consult either their medical records or their most recent medical professional.

Health-related QoL

The Patient-Reported Outcomes Measurement Information System Global Health short form (PROMIS-GH) assesses multiple domains related to health-related QoL, such as health, functioning, pain, social activities and fatigue.[76] The PROMIS-GH has been validated in several populations and languages, among which are English, French and Spanish (for detailed information, see www.nihpromis.org).[76] The global mental health and global physical health scores were calculated based on 10 items each measured on a 5-point scale (from 1 to 5) and subsequently converted.[76] These subscale scores ranged from 0 to 100, with a higher score indicating better QoL and a mean score of 50 indicating the norm for the general population.[78]

Procedures

An anonymous questionnaire (electronic and/or paper) available in English, French and Spanish was compiled (LimeSurvey Professional). It included the following descriptive variables: age, body height, body weight, duration of professional football or rugby career, level of play, duration and nature of retirement, and current employment status (employed or not employed). Additionally, this questionnaire included questions for the outcomes previously elaborated on (ankle OA, ankle injury, ankle surgery, QoL). Information about the study was sent per email to potential participants by FIFPRO and IRP. Participants interested in the study gave their informed consent and completed the electronic questionnaire. Participants were asked to complete the questionnaire within 2 weeks, with reminders being sent after 2 and 4 weeks. For privacy reasons, the responses to the questionnaires were coded and anonymised. Once completed, the electronic questionnaires were automatically saved on a secured electronic server that only the principal investigator could access. Players participated voluntarily and did not receive any reward for their participation.

Statistical analyses

Data analysis was performed using the statistical software IBM SPSS V.24.0 for Windows. Analyses were conducted separately for retired professional football and rugby players. Data were assessed (visually) for normality and presented as mean±SD, median (IQR) or frequency (proportion in %), as appropriate. Body mass index (BMI) was calculated using the provided weight and height of participants (kg/m^2). Prevalence of ankle OA, overall and within the age categories of ≤40 years and >40 years, was calculated as the proportion of the number of participants with ankle OA relative to the total number of participants in each category.[76] We chose to dichotomise age at 40 years, as our population included former professional athletes. This is opposed to Murray *et al*[8] concerning the general population (dichotomised at 50 years of age) and in line with Song *et al*[79] studying former professional American football players. We made the assumption that although no longer professionals, these former professional athletes would no longer be competing at a decent level at the age of 40. We therefore found 40 years to be a more relevant age to dichotomise than 50 years. A logistic regression analysis was performed to determine the association of the number of severe ankle injuries and/or ankle surgeries (continuous independent variable) with ankle OA (dichotomous dependent variable). Severe ankle injuries and/or ankle-related surgeries were also expressed using three predetermined categories (0, 1 and >1). This was adjusted for age and BMI, both having been identified as risk factors for OA.[80,81] Descriptive analyses of health-related QoL (global physical health and global mental health) were conducted, while comparisons between groups (retired players with

ankle OA vs retired players without ankle OA) were made using Mann-Whitney U test for independent samples.[76]

Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

Participants

From a total of 750 football and 326 rugby players contacted, respectively, 401 and 152 gave their written informed consent and completed the questionnaire (overall response rate of 56%). The characteristics of the two groups, including the predetermined subcategories for severe ankle injuries and ankle surgeries (0, 1 and >1), are illustrated in table 1.

Prevalence of ankle OA, severe injury and surgery

The prevalence of patient-reported ankle OA (including the predetermined categories of ≤40 years and >40 years) among recently retired professional football and rugby players is presented in table 2. The prevalence of ankle OA in former professional football players was 9.2% (n=37). Overall, 94% of players with ankle OA were documented to have sustained ≥1 ankle injury and 62% had undergone ≥1 ankle surgery. In the non-OA group (n=364), 54% had sustained ≥1 ankle injury and 14% had undergone ≥1 ankle surgery. Logistic regression analysis (table 3) showed that football players who had sustained a severe ankle injury were 1.3 (95% CI 1.1 to 1.6) times more likely to report ankle OA ($p<0.001$). Football players who had undergone ankle surgery were 2.1 (95% CI 1.4 to 3.1) times more likely to report ankle OA ($p<0.001$).

The prevalence of ankle OA in former professional rugby players was 4.6% (n=7). Overall, six out of seven (86%) rugby players with ankle OA reported to have sustained ≥1 ankle injury, and four out of seven (57.1%) had undergone ≥1 ankle surgery. In the non-OA group (n=145), 58.2% had sustained ≥1 ankle injury and 18.4% had undergone ≥1 ankle surgery. Logistic regression analysis (table 3) showed no significant association between either severe ankle injuries (OR=1.1, 95% CI 0.8 to 1.5) or ankle surgeries (OR=2.0, 95% CI 0.8 to 4.7) and ankle OA among former professional rugby players.

Table 1. Descriptive characteristics of recently retired professional football players and rugby players

	Football			Rugby		
	Total (n = 401)	**Ankle OA (n = 37)**	**No ankle OA (n = 364)**	**Total (n = 152)**	**Ankle OA (n = 7)**	**No ankle OA (n = 145)**
Age in years *, median (IQR; min-max / mean ± SD)	36 (32-40; 25-50)	39 (36-42; 27-49)*	36 (32-40; 25-50)*	40 ± 6	41 ± 7	40 ± 6
Height in cm, mean ± SD / median (IQR; min-max)	181 ± 7	180 ± 7	182 ± 7	186 (180-191; 166-203)	191 (173-192; 172-192)	186 (180-191; 166-203)
Weight in kg, mean ± SD / median (IQR; min-max)	82 ± 9	82 ± 13	82 ± 9	100 (91-114; 59-170)	108 (89-123; 82-130)	100 (91-113; 59-170)
BMI in kg/m^2, median (IQR; min-max))	24.8 (23.5-26.2; 20.1-32.7)	24.8 (22.9-26.6; 20.3-29)	24.7 (23.5-26.1; 20.1-32.7)	29.0 (27.1-31.4; 20.4-52.5)	32.2 (28.5-33.7; 27.4-35.3)*	28.9 (27.0-31.2; 20.4-52.5)*
Employed in % (n)	89% (350)	92% (33)	89% (317)	91% (139)	86% (6)	92% (133)
Professional career duration in years, median (IQR; min-max)	13 (10-15; 2-19)	13 (12-16; 5-18)	13 (9-15; 2-19)	10 (7-15; 2-20)	10 (8-12.5; 8-13)	10 (7-15; 2-20)
Retirement duration in years, median (IQR; min-max)	4 (2-7; 1-17)	5 (3-9; 1-12)	4 (2-7; 1-17)	8 (3-12; 0-22)	12 (2-16; 1-19)	8 (4-11; 0-22)
Level of play top league; % (n)	81% (314)	92% (34)	80% (280)	80% (106)	86% (6)	80% (100)
Forced retirement % (n)	29% (113)	27% (10)	30% (103)	36% (55)	57% (4)	35% (51)
Severe ankle injuries, median (IQR; min-max)	1 (0-2; 0-10)	2 (1-3; 0-10)	1 (0-2; 0-10)	1 (0-2; 0-20)	1 (1-2; 0-3)	1 (0-2; 0-20)
Ankle surgeries, median (IQR; min-max)	0 (0-0; 0-5)	1 (0-2; 0-5)	0 (0-0; 0-5)	0 (0-0; 0-4)	1 (0-1; 0-2)	0 (0-0; 0-4)

** Statistically significant difference between ankle OA and no ankle OA. BMI, body mass index; max, maximum; min, minimum; n = number; OA, osteoarthritis.*

Table 2. Subcategories for prevalence of reported ankle OA, severe injuries and ankle surgeries in retired football and rugby players

	Football			Rugby		
	Total (n = 401)*	**≤ 40 years (n = 271)**	**> 40 years (n = 83)**	**Total (n = 152)**	**≤ 40 years (n = 82)**	**> 40 years (n = 66)**
Prevalence ankle OA, % (95%CI)	9.2% (6.4 –12.1)	8.5% (5.2 – 11.8)	12.0% (5.0 – 19.1)	4.6% (1.2 – 8.0)	2.4% (0.9 – 5.8)	4.5% (0.5 – 9.6)
	0 ankle injuries	**1 ankle injury**	**> 1 ankle injury**	**0 ankle injuries**	**1 ankle injury**	**> 1 ankle injury**
Severe ankle injuries total, % (n)	42.5% (156)	25.3% (93)	32.2% (118)	40.5% (60)	27.7% (41)	31.8% (47)
- **With ankle OA, % (n)**	5.7% (2)	28.6% (10)	65.7% (23)	14.3% (1)	42.9% (3)	42.9% (3)
- **Without ankle OA, % (n)**	46.4% (154)	25.0% (83)	28.6% (95)	41.8% (59)	27.0% (38)	31.2% (44)
	No ankle surgeries	**1 ankle surgery**	**> 1 ankle surgery**	**No ankle surgeries**	**1 ankle surgery**	**> 1 ankle surgery**
Ankle surgeries total, % (n)	81.5% (299)	10.9% (40)	7.6% (28)	79.7% (118)	15.5% (23)	4.7% (7)
- **With ankle OA, % (n)**	38.2% (13)	29.4% (10)	32.4% (11)	42.9% (3)	42.9% (3)	14.3% (1)
- **Without ankle OA, % (n)**	85.9% (286)	9% (30)	5.1% (17)	81.6% (115)	14.2% (20)	4.3% (6)

**The sum of patients in the subcategories ≤ 40 years and > 40 years does not equal the "Total number of participants" due to missing data (regarding age).*
number, n; Osteoarthritis, OA

Table 3. Association (OR and 95% CI) of severe ankle injury and ankle surgery with ankle osteoarthritis among recently retired professional football and rugby players

	Football (n = 401)		Rugby (n = 152)	
	Unadjusted	Adjusted[¥]	Unadjusted	Adjusted[¥]
Severe ankle injury, OR (95% CI)	1.34 (1.17-1.53)	1.33 (1.14-1.55)	1.01 (0.74-1.38)	1.05 (0.75-1.47)
Ankle surgery, OR (95% CI)	2.20 (1.61-3.00)	2.09 (1.41-3.08)	1.99 (0.92-4.3)	1.96 (0.81-4.71)

[¥]*Adjusted for age and body mass index*

Mental and physical QoL

For the PROMIS physical health score, a statistically significant lower outcome was found for football (p=0.01) and rugby (p=0.009) players with OA (48 and 45 points, respectively) compared with players without OA (51 and 51 points, respectively). The PROMIS mental health score was not significantly different between players with OA and players without OA. Data are presented in table 4.

Post-hoc analysis

In the literature, forced retirement is a risk factor for postcareer mental health symptoms.[82] Following data analysis, we were concerned by the seemingly high percentage of football and rugby players who stopped due to a career-ending injury. As we were analysing the impact ankle OA had on QoL, we felt the effect of a career-ending injury on QoL to be in line with our initial objectives. Consequently we performed a post-hoc analysis to determine any associations between reported forced retirement and mental and physical PROMIS health scores. In this study, 31% of players reported to have been forced to retire, specifically 29% of football players and 36% of rugby players. The post-hoc subanalysis of all players regarding mental and physical health scores associated with voluntary retirement and in conjunction with ankle OA is presented in table 5. No post-hoc subanalysis was done for football and rugby players separately, regarding voluntary retirement in conjunction with ankle OA, due to the low number of ankle OA cases among rugby players. However mental and physical health scores in football and rugby due to forced retirement are presented separately in table 5.

Table 4. Mental and physical quality of life (0-100) of recently retired football and rugby players with ankle OA compared with players without ankle OA

	Football				Rugby			
	Total (n = 401)	With ankle OA (n = 37)	Without ankle OA (n = 364)	p	Total (n = 152)	With ankle OA (n = 7)	Without ankle OA (n = 145)	p
PROMIS mental health (median; IQR; min-max)	51; 46-56; 31-68	51; 46-53; 31-63	53; 46-56; 31-68	0.251	52; 46-56; 28-68	48; 48-53; 46-56	53; 46-56; 28-68	0.567
PROMIS Physical health* (median; IQR; min-max)	51; 46-56; 27-68	48; 42-54; 35-62*	51; 48-58; 27-68*	0.010	51; 45-54; 30-68	45; 37-48; 37-51*	51; 37-56; 30-68*	0.009

*Statistically significant difference; Max, maximum; min, minimum; OA = Osteoarthritis; PROMIS, Patient-Reported Outcome Measurement Information System.

Table 5. Post-Hoc analysis regarding mental and physical quality of life of recently retired football and rugby players who reported to have been forced to retire, and quality of life of players who reported to have been forced to retire with ankle OA compared with players without ankle OA

	PROMIS mental health (median; IQR; min-max)	p	PROMIS physical health (median; IQR; min-max)	p
Total				
Voluntarily retired* (n = 369)	53; 48-56; 31-68*	p < 0.001	54; 48-58; 30-68*	p < 0.001
Forced to retire* (n = 168)	48; 44-53; 28-68*		48; 42-51; 27-68*	
Voluntarily retiredwith OA* (n = 30)	51; 46-53; 36-63	p = 0.074	51; 45-54; 35-62*	p = 0.001
Voluntarily retired without OA* (n = 339)	53; 48-59; 31-68		54; 48-58; 30-68*	
Forced to retire with OA (n = 14)	48; 46-55; 31-63	p = 0.841	42; 40-46; 37-58	p = 0.159
Forced to retire without OA (n = 154)	48; 44-53; 28-68		48; 42-52; 27-68	
	Football*			
Voluntarily retired* (n = 272)	53; 48-56; 31-68*	p < 0.001	54; 48-58; 30-68*	p < 0.001
Forced to retire* (n = 113)	48; 44-53; 31-63*		48; 42-51; 27-62*	
	Rugby*			
Voluntarily retired* (n = 97)	53; 48-56; 31-68*	p = 0.018	54; 48-58; 35-68*	p < 0.001
Forced to retire* (n = 55)	48; 44-56; 28-68*		48; 37-54; 30-68*	

**Statistically significant difference. max, maximum; min, minimum; n, number; OA, osteoarthritis; PROMIS, Patient-Reported Outcomes Measurement Information System.*

DISCUSSION

Our most important findings were that (1) the prevalence of ankle OA among former professional football and rugby players was 9.2% (95% CI 6.4 to 12.1) and 4.6% (95% Cl 1.2 to 8.0), respectively; (2) previous severe ankle injuries and ankle surgeries are associated with ankle OA among former professional football players; and (3) ankle OA does not lead to reduced mental or physical QoL in former professional football and rugby players.

Ankle osteoarthritis in football and rugby compared with other sports and the general population

Several studies have reported symptomatic ankle OA prevalence among a variety of former elite athletes, ranging from 0% in volleyball (n=22), long distance running (n=30), elite high jump (n=30) and ballet (n=27), to 10% among former military parachutists (n=40).[83-87] In our study, the prevalence of ankle OA among former professional football (9.2%) and rugby (4.6%) players was higher than the estimated prevalence among the general population (3.4 %).[8] Murray *et al*[8] invited participants with self-reported ankle pain (11.7%) from the general population for a radiograph (radiological atlas of foot OA).[88]

Our study reports lower ankle OA prevalence compared with previous studies among former professional football players (12%–19%).[47,48,71] In these studies, data were similarly collected using cross-sectional, retrospective, self-reported questionnaires.[47,48] No previous data are available concerning ankle OA among former professional rugby players. The low ankle OA prevalence among rugby players in this study is likely due to either an under-reporting of ankle OA among rugby players or a type II error.

Association of severe ankle injuries and ankle surgeries with ankle osteoarthritis

In our study, football players were 1.3 (95% CI 1.1 to 1.6) and 2.1 (95% CI 1.4 to 3.1) times more likely to develop ankle OA for every ankle injury and ankle surgery, respectively. This is in line with previous studies that showed an association between ankle OA and ankle injuries, stating traumatic ankle injuries to be the main cause of ankle OA (70%–78%).[9,10] Consequences of ankle injuries are thought to be due to either direct damage to the articular surfaces or change in ankle joint biomechanics (eg, through chronic ankle instability due to ankle ligament damage).[89] No association was seen for severe ankle injuries or ankle surgeries and ankle OA among rugby players. Although the best estimate for the association of ankle surgeries and OA is similar to football (OR=2), the 95% CI includes 1 (0.8–4.7). This may be due to insufficient power among rugby players, as only seven reported ankle OA.

Health-related Quality of Life

Filbay *et al*[90] reported factors such as age, type of sport (contact/collision sports), OA and involuntary retirement from sport to possibly negatively impact QoL.[82,91,92] However the positive impact associated with elite sport participation, such as pride of accomplishments, social network (through sport participation), and coping and adjustment to musculoskeletal pain (due to resilience and determination), may persist and even compensate reduced physical QoL beyond retirement of the player's athletic career.[90]

Our post-hoc subanalysis revealed 29% of football players and 36% of rugby players were forced to retire. Although we reported several instances of statistically significant differences in our study for both physical and mental PROMIS health scores, all were similar to the estimated norm for the general population (50 points). Unfortunately, there is no robust minimally clinically important difference threshold for the PROMIS-10 global short form applicable to this population. Consequently, it is difficult to interpret the results. Nevertheless, although statistically significant, the PROMIS mental and physical health scores observed, for both football and rugby players, are unlikely clinically significant. Based on our data, ankle OA does not lead to reduced mental or physical QoL in former professional football and rugby players.

Strengths and limitations

We had an overall good response rate (56%) and a large group of participating football players (n=401). However, several limitations should be mentioned. First, this study had a cross-sectional design; therefore, no causal association can be determined. Second, there were only seven rugby players with OA, implying a potential serious type II error. Third, recruitment procedures were blinded to the research team, and a non-response analysis could not be performed. Fourth, research-based (retrospective) questionnaires are dependent on the accuracy and understanding of the participant. Professional athletes might generally remember the number of severe ankle injuries or surgeries resulting in a training or match absence of ≥4 weeks. However, we cannot exclude that participants were not able to precisely recall all their sustained severe ankle injuries and ankle surgeries or that they did not consult their most recent medical professional. Finally, our definition of OA did not include a clinical and radiological evaluation.

Implications for practice

The epidemiological data from this study regarding ankle OA prevalence among former professional football and rugby players, and its association with both severe ankle injuries and ankle surgeries, are an essential part of protecting athletes' health. In both professional football and rugby, a higher

prevalence of ankle OA can be expected compared with the general population. Furthermore, as the majority are post-traumatic, preventive measures and adequate rehabilitation are recommended. Awareness should be raised regarding the increased risk of developing ankle OA following each ankle injury and surgery. Additionally primary and secondary prevention programmes should be implemented. Exercise-based prevention intervention programmes, such as the FIFA 11+ in football and the movement control injury prevention programme in rugby, have found reduced ankle injury incidence and burden.[93,94] Finally, management of ankle OA is key for retired players, focusing on healthy lifestyle including physical activity, pain alleviation, function and minimising disability.[95-97] With this intention, FIFPRO has developed an 'After Career Consultation'.[98] Future studies will evaluate its relevance.

CONCLUSION

This cross-sectional study found an athlete-reported ankle OA prevalence of 9.2% and 4.6% among recently retired professional football and rugby players, respectively. Severe ankle injuries and ankle surgeries were associated with a higher prevalence of ankle OA in former professional football players. No clinically relevant differences in QoL were reported in players with OA compared with players without OA. As a higher prevalence of ankle OA can be expected in both professional football and rugby compared with the general population, and the majority are post-traumatic, primary and secondary preventive measures for ankle injuries and an optimal diagnosis and treatment plan are recommended.

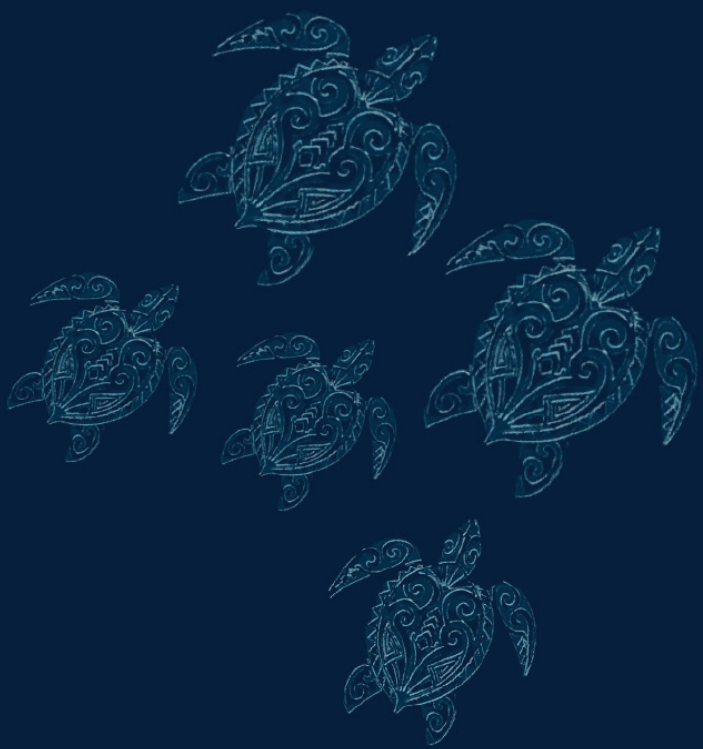
CHAPTER

4

The Completely Patient-Reported Version of the American Orthopaedic Foot and Ankle Society (AOFAS) Score

A Valid and Reliable Measurement for Ankle Osteoarthritis

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ABSTRACT

Background – The American Orthopaedic Foot and Ankle score (AOFAS) is an outcome measure for ankle and hindfoot conditions, which requires scoring from both the patients and the physician. A completely patient-reported version has been developed and used before, but its measurements properties are unknown. Our goal was to determine the measurement properties and the minimally important change (MIC) of a completely patient-reported AOFAS (PR-AOFAS) in patients with ankle osteoarthritis. Additionally, the MIC of both the PR-AOFAS and the AOFAS was estimated, which had not previously been done.

Materials and methods – The PR-AOFAS of 112 patients was evaluated for reliability, construct validity (using the AOFAS, Foot and Ankle Outcome Score, Ankle Osteoarthritis Score, Visual Analogue Scale, and Short Form-36), and responsiveness. The MIC was estimated using the optimal cut-off point of the receiver operating characteristic curve. This was a substudy of a randomized clinical trial on the efficacy of platelet-rich plasma injections for ankle osteoarthritis (OA).

Results – The PR-AOFAS had sufficient construct validity, internal consistency, test–retest reliability, and responsiveness. The smallest detectable change at group level was 2.34. The MIC was 6.5 points (95% confidence interval: 0.6–14.4).

Conclusions – The measurement properties of the Dutch PR-AOFAS were sufficient in patients with ankle osteoarthritis who are willing to participate in a trial on injection therapy. The minimally important change of the PR-AOFAS is smaller than its smallest detectable change, making it more suitable for use in groups of patients, such as a research setting.

INTRODUCTION

Patient-reported outcome measures (PROMs) enable quantification of outcomes such as pain and function and its impact on quality of life. To adequately interpret treatment effects, an outcome score must be reliable, valid, and responsive to change.[99] The American Orthopaedic Foot and Ankle Society (AOFAS) score is one of the most frequently used scores for foot and ankle conditions.[100] It combines five patient-reported items concerning pain and function with four physician-determined items concerning function and alignment, on a 0- to –100-point scale.[101]

The measurement properties of the AOFAS score were assessed in two studies (n = 133 and n = 117) with patients with end-stage ankle OA[100,101] and in two studies (n = 9 and n = 8) that included patients with ankle OA amongst other ankle and hindfoot conditions.[102,103] The available data on ankle OA found the patient-reported part of the AOFAS score to be valid and responsive.[100-107] However the minimally important change (MIC) of the AOFAS score has not been determined for ankle osteoarthritis.

Completely patient-reported outcome scores are easier for the patient, are less time-consuming, and result in more patient compliance, leading to higher response rates and thereby reduce risk of bias and increase generalizability.[100,108] In a prospective multicenter randomized controlled trial in the Netherlands, including 152 patients on the routine versus on-demand removal of syndesmotic screws, the physician-determined items were modified to patient-reported items, allowing for a completely patient-reported version of the AOFAS score.[109] However, the measurement properties of this completely patient-reported AOFAS score had not been determined.[109]

Our goal was to determine the measurement properties and the MIC of a Dutch completely patient-reported AOFAS (PR-AOFAS) score in patients with ankle osteoarthritis. Additionally, the MIC of both the PR-AOFAS and the AOFAS scores was estimated, which had not previously been done.

MATERIALS AND METHODS

Study design

This is a substudy of the Platelet-Rich plasma Injections in the Management of Ankle oa (PRIMA) trial, a randomized, double-blind, placebo-controlled, multicentre prospective study, designed to determine the efficacy of platelet-rich plasma injections in the management of ankle OA.[52,110] The PRIMA trial is approved by the Medical Ethics Review Committee Amsterdam Medical Center, the

Netherlands (ABR 2018–042, approved 23 July 2018) and is registered in the Netherlands trial register (NTR7261). This substudy was sponsored by the Marti-Keuning Eckhardt Foundation, a nonprofit patient organization.

Study population

Patients with ankle OA in six hospitals in the Netherlands (2 University Medical Centres, 2 teaching hospitals, a general hospital, and a focus clinic) were informed of the study. All participants signed an informed consent form before participating in the study. Patients were eligible for inclusion if they had a severity of ankle OA pain on a Visual Analogue Scale (VAS 0–100 mm) ≥40 mm during daily activities, radiographs (anteroposterior and lateral view) indicating ≥grade 2 talocrural OA on the van Dijk classification (joint space narrowing, with or without osteophytes),[54] and were ≥18 years of age. Patients were excluded if they had received injection therapy for ankle OA in the previous 6 months, did not want to receive one of the two therapies, had clinical signs of concomitant OA of one or more other major joints of the lower extremities that negatively affects their daily activity level, or had had a previous ankle surgery for OA or osteochondral defects in <1 year (not including surgery for an ankle fracture in the past).

Study procedures

This study was performed according to the COnsensus-based standards for the selection of health Measurement INstruments checklist as a guideline.[111] Following inclusion, as far as relevant for this study, patients completed questionnaires at baseline, 6, 12, 26 and 52 weeks.[52] The questionnaires completed included Dutch versions of the PR-AOFAS score, Foot and Ankle Outcome Score (FAOS), Ankle Osteoarthritis Score (AOS), VAS, and study short form 36 (SF-36).[52] In order to assess the test–retest reliability, at a minimum follow-up of 26 weeks under assumption of no change, an additional PR-AOFAS score was sent two weeks after a previous one with an additional question to assess change of symptoms. A Dutch version of the AOFAS score was taken during outpatient visits at baseline, 6 weeks, and 26 weeks. In order to minimise bias, all patients were seen by the same coordinating research physician of the PRIMA study.

The original patient–physician-determined American Orthopaedic Foot and Ankle society score

The AOFAS score measures pain function and alignment and was translated and validated in Dutch for ankle fractures.[106] The physician-determined items were performed by the same coordinating research physician. It consists of 9 items and 3 subscales (pain – 1 item, function – 7 items, and alignment – 1 item) of which 3 items from the function scale and the alignment scale are physician-determined. The maximum scores on all three subscales are 40, 50, and 10 points, respectively.[112]

A completely patient-reported version of the American Orthopaedic Foot and Ankle society score

For the PR-AOFAS score, the questionnaire from the RODEO trial was used.[109] Here, the physician-determined items were made more comprehendible for the patients.[109] These changes are presented in the Supplement. Where previously the physician determined sagittal and hindfoot motion and ankle–hindfoot stability and alignment, the patient was now asked in patient-friendly terms how they would rate these items. For instance, "How would you rate the mobility of your ankle compared to the other side, or compared to when you did not have symptoms." Similar to the AOFAS score, the PR-AOFAS score consists of 9 items and 3 subscales (pain – 1 item, function – 7 items, and alignment – 1 item).

The Foot and Ankle Outcome Score

The FAOS is used for functional assessment of ankle and hindfoot conditions, consists of five subscales (pain, other symptoms, activities of daily living [ADL], sport and recreation, and foot- and ankle-related quality of life) and has been shown to have sufficient reliability and validity in patients with ankle and hindfoot symptoms.[113] There are a total of 42 items, each question is assigned 0–4 points based on the answer given.[113] The scale runs from 0 (extreme symptoms) to 100 points (no symptoms).

Medical outcomes study short form 36

The SF-36 is a generic outcome measuring quality of life and has 36 items, consisting of 8 subscales (0–100 points). Of these subscales, 4 make out the Physical Component Summary (PCS) score, and 4 make out the Mental Component Summary (MCS) score (0–100 points).[53] The higher the patient scores, the higher the quality of life.

The visual analog score for pain

The VAS score (VAS 0–100 mm) is measured during activities of daily living, with 0 mm being no pain and 100 mm the worst pain imaginable.

The Ankle Osteoarthritis Score

The AOS measures pain (9 items) and disability (9 items) with a total of 18 items on a VAS (0–100 mm) and has been shown to be valid, reliable, and responsive to change in patients with ankle OA.[100] Higher scores indicate worse pain and disability.

Subjective patient satisfaction

The subjective patient satisfaction was asked according to a 4-point Likert scale (poor, fair, good and excellent) and served as an anchor to determine the responsiveness of the completely PR-AOFAS score and calculate minimal clinically important change values.

Statistical analysis

Both PR-AOFAS and AOFAS scores were assessed for reliability, construct validity, responsiveness, and interpretability (floor and ceiling effects).[114-116] Due to the absence of a retest of the AOFAS score, only internal consistency was evaluated as a reliability measure. Reliability assessment of the PR-AOFAS score comprised of internal consistency, test–retest reliability, standard error of measurement (SEM), and smallest detectable change (SDC). Additionally, the Minimal clinically Important Change (MIC) of both scales was calculated.[115,116]

Reliability

Reliability shows the degree to which the scale is free of measurement error and will be assessed through internal consistency, test–retest reliability, and measurement error. Internal consistency demonstrates the inter-relatedness among items of an outcome measure or their subscales.
A Cronbach's α between 0.70 and 0.95 demonstrates satisfactory internal consistency for both PR-AOFAS and AOFAS scores as long as the scale is unidimensional.[116,117] Test–retest reliability determines the ability to measure the same when patients with unchanged complaints take the questionnaire twice. Patients were only included in the test–retest reliability analysis for the PR-AOFAS score assessment if they had confirmed that no change had occurred. The test–retest reliability was determined using the intraclass correlation coefficient (ICC) alongside a SEM and was deemed reliable if ICC was ≥0.70.[118,119] The SEM was calculated as the square root of the within-subject variance (i.e., the sum of the between-measures variance and the residual variance).[120] The SDC (SDC = $1.96 * \sqrt{2} * SEM$) provides the magnitude of change needed to have confidence that the change is not a consequence of measurement error.[121]

Construct validity

Construct validity measures the degree to which the intended construct is measured.[114] This was assessed by determining the correlation of the PR-AOFAS and the AOFAS scores (and their subscales) with the FAOS subscales, AOS, and VAS and the PCS and MCS scores of the SF-36 at baseline using Spearman's correlation coefficient (r_s).
Correlation was categorized as high ($r > 0.5$) for similar, moderate ($0.3 \leq r \leq 0.5$) for related but dissimilar, and low ($r < 0.3$) for unrelated constructs.[111]

In total, 21 hypotheses were determined for the PR-AOFAS score and 21 for the AOFAS score. At least, moderate a priori hypothesized correlations were to be expected between the total scores and the FAOS subscales, AOS total score, the PCS score of the SF-36 and the VAS. For the pain subscale of the PR-AOFAS and AOFAS scores, high correlations were expected with the pain subscales of the FAOS, the AOS, and the VAS and moderate correlations with the PCS and the symptoms subscale of the FAOS. For the function subscale of the PR-AOFAS and AOFAS scores, high correlations were expected with the ADL and sport and recreation subscales of the FAOS, the AOS disability subscale, and the PCS. Finally, all domains of both outcomes were expected to be unrelated ($r < 0.3$) to the MCS. Confirmation of at least 75% of the aforementioned hypotheses indicates sufficient construct validity.[116]

A separate evaluation was performed to assess whether the PR-AOFAS and AOFAS assessments measure identical constructs. For this purpose, additional a priori correlation coefficients of >0.8 were to be expected between the PR-AOFAS and the AOFAS scores and their identical subscales (pain, function and alignment).

Responsiveness

Responsiveness of a PROM is defined as its ability to detect change over time.[114,122] It was determined by comparing both the PR-AOFAS and AOFAS scores at the baseline and 26 weeks. Change from the baseline at 26 weeks of the 4-point Likert-scaled subjective patient satisfaction was used as an anchor. Changes in the anchor were defined as worsened, unchanged, improved, and greatly improved.[123] Patients who improved at least 1 category were considered to have had a clinically important improvement.[123] The effect sizes (ESs) and standardized response means (SRMs) were calculated for each category of changes in the anchor.[124,125] Based on Cohen's standardized effect size, the following was hypothesized:[126]

ES and SRM <0.2 for patients who reported to be unchanged
ES and SRM ≥0.2 for patients who reported to be improved
ES and SRM ≥0.5 for patients who reported to be much improved

Responsiveness was further evaluated using the receiver operating characteristic (ROC) curve analyses. ROC curves give information on the true positive rate (sensitivity) and false-positive rate (1-specificity) for cut-off points in change score.[127] The area under an ROC curve (AUC) indicates the chance that the patient is indeed correctly improved or unimproved, a value of at least 0.7 was deemed sufficient.[111,116,127]

Interpretability

Interpretability is the meaning that can be assigned to a score or change in score.[114] In this study, interpretability was measured by determining floor and/or ceiling effects. If a large number of patients score the maximum or minimum score, the instrument can fail to detect clinical improvement or deterioration. A floor and/or ceiling effect is present if more than 15% of the study participants had the lowest or highest possible score.[115,116]

Minimal clinically important change

The Minimal Important Change (MIC) is the minimal amount of change that is perceived by the patient as "important".[115] Using the previously described anchor, the patients were categorized as either improved (or more) or unchanged (patients who were worse were excluded).[128] By use of ROC analysis, the MIC was calculated as the cut-off point that indicated the least amount of misclassification.[128] A bootstrapping procedure (with 1000 bootstraps) was performed to estimate the standard error and determine the 95% confidence interval (CI).

Agreement of the PR-AOFAS and the AOFAS scores

Agreement between the PR-AOFAS and the AOFAS scores was determined using a Bland–Altman plot with limits of agreement.[115,129] Additionally, ICCs were calculated between the PR-AOFAS, the AOFAS scores as well as between the change from baseline of the both outcome measures.

RESULTS

Inclusion

In total 112 patients were enrolled in the PRIMA study to receive either an intra-articular PRP or placebo (saline) injection and completed all baseline questionnaires and physical examinations (Table 1). In total, 63 (56%) were male and 49 (44%) female. The mean age, duration of symptoms, and body mass index was 55 years (SD 14 years), 9 years (SD 9 years), and 26.5 kg/m^2 (SD 3.8 kg/m^2), respectively. In total, 95 patients completed the second PR-AOFAS assessment (sent within 2 weeks of a previous one), of which 36 patients (38%) reported a change in complaints. Therefore, 59 patients (62%) were included in the test–retest analysis.

Reliability

The function subscale of the PR-AOFAS assessment had sufficient internal consistency (Cronbach's α 0.71, n = 112). An insufficient internal consistency was found for the total PR-AOFAS score (Cronbach's α 0.68, n = 112). The test–retest reliability was good (ICC: 0.88; 95% CI: 0.81 to 0.93; n =

59). The standard error of measurement was 6.48 and gave rise to SDCs of 17.96 and 2.34 at individual and group (n = 59) levels, respectively, on a scale that ranged from 0 to 100. The AOFAS assessment had insufficient internal consistency for both the functional subscale (Cronbach's α 0.40, n = 112) and the total score (Cronbach's α 0.47, n = 112).

Construct validity

Spearman's correlation coefficients were calculated between both PR-AOFAS and AOFAS scores, and the PCS and MCS scores of the SF-36, VAS pain, AOS and its subscales, and the FAOS scales (Table 2). Of the a priori–formulated hypotheses, 95% were confirmed for the PR-AOFAS assessment and 71% for the AOFAS assessment. For the PR-AOFAS assessment, all correlations were as expected except for the correlations between the pain subscale from the PR-AOFAS and the FAOS symptoms subscale. For the AOFAS subscales, six hypotheses had to be rejected as correlations were not as expected (Table 2).

Additionally, all hypotheses concerning the association between the two AOFAS versions were rejected as all correlation coefficients were smaller than expected.

Responsiveness

In total, 8 effect sizes and standardized response means for both PR-AOFAS and the AOFAS scores were calculated to be 100% and 75% in agreement with the predefined hypotheses, respectively (Table 3). The outcome disagreed with the hypotheses for the AOFAS in the category patients unchanged and exceeded the predefined hypothesis by 0.2. The AUC of the PR-AOFAS and the FAOS were 0.77 (95%CI: 0.68 to 0.87) and 0.66 (95%CI: 0.54.; 0.76), respectively, implying that only the PR-AOFAS assessment was considered to meet the requirements of proper responsiveness.

Table 1. Descriptives and percentages highest and lowest scores of the completely patient-reported American Orthopaedic Foot and Ankle Society, original patient–physician-determined American Orthopaedic Foot and Ankle Society, short form 36 subscales, Visual Analogue Scale pain, Ankle Osteoarthritis Score, and Foot and Ankle Outcome Score at the baseline.

n=112	Mean (SD)	Median (IQR)	Highest score, n (%)	Lowest score, n (%)
PR-AOFAS	59.4 (17.9)	64.0 (50.0 to 72.0)	0	0
PR-AOFAS Pain	19.7 (8.6)	20 (20.0 to 20.0)	1 (0.9%)	14 (12.5%)
PR-AOFAS Function	31.2 (10.3)	33.0 (26.0 to 38.0)	1 (0.9%)	0
PR-AOFAS alignment	8.1 (3.2)	10.0 (5.0 to 10.0)	78 (69.6%)	9 (8%)
AOFAS	63.6 (14.4)	67.0 (57.0 to 72.0)	0	0
AOFAS Pain	18.1 (9.0)	20.0 (20 to 20)	0	19 (17%)
AOFAS Function	36.3 (7.3)	37.0 (32.0 to 42.0)	1 (0.9%)	0
AOFAS alignment	9.2 (2.3)	10.0 (10 to 10)	97 (86.6%)	3 (2.7%)
SF-36 Physical Component Summary score	44.3 (7.6)	45.3 (38.9 to 50.2)	0	0
SF-36 Mental Component Summary score	43.4 (5.5)	43.1 (39.9 to 47.8)	0	0
VAS pain	53.0 (19.7)	52.5 (40.0 to 69.5)	0	0
AOS	48.4 (17.9)	47.1 (33.9 to 62.6)		
AOS pain	39.9 (20.8)	39.5 (24.5 to 52.5)	0	0
AOS disability	57.0 (20.0)	58.8 (41.8 to 73.4)	0	2 (1.8%)
FAOS pain	55.4 (17.7)	52.8 (41.7 to 71.5)	0	0
FAOS symptoms	46.0 (17.0)	46.4 (32.1 to 57.1)	0	0
FAOS ADL	70.7 (20.8)	75.7 (52.9 to 87.9)	2 (1.8%)	0
FAOS sport **& R**	33.5 (20.7)	30.0 (15.0 to 45.0)	0	6 (5.4%)
FAOS QoL	28.2 (16.6)	31.3 (18.8 to 37.5)	0	9 (8.0%)

PR-AOFAS: patient-reported American Orthopaedic Foot and Ankle Society; PR patient -reported; SF-36: short form 36; VAS: Visual Analogue Scale; AOS: Ankle Osteoarthritis Score; FAOS: Foot and Ankle Outcome Score; n number; SD: standard deviation; IQR: interquartile range; PCS: Physical Component Score; MCS: Mental Component Score; ADL: Activities of Daily Living; S & R: sport and recreation; QoL: quality of life.

Table 2. Construct validity using Spearman's correlation coefficients (Rs) between the patient-reported American Orthopaedic Foot and Ankle Society and American Orthopaedic Foot and Ankle Society, Physical and Mental Component Summary scores of the short form 36, Visual Analogue Scale pain, Ankle Osteoarthritis Score and the Foot and Ankle Outcome Score scales.

	PR-AOFAS Total	PR-AOFAS Pain	PR-AOFAS Function	PR-AOFAS Alignment	AOFAS Total	AOFAS Pain	AOFAS Function	AOFAS Alignment
AOFAS Total	**0.70**	0.54	0.67	0.36	-	-	-	-
AOFAS Pain	0.55	**0.63**	0.43	0.23	-	-	-	-
AOFAS Function	0.62	0.32	**0.67**	0.34	-	-	-	-
AOFAS Alignment	0.30	0.15	0.31	**0.28**	-	-	-	-
SF-36 PCS	**0.68**	**0.44**	**0.68**	0.35	**0.66**	**0.47**	**0.62**	0.28
SF-36 MCS	**-0.24**	**-0.18**	**-0.23**	**-0.11**	**-0.19**	**-0.18**	**-0.12**	**-0.20**
VAS pain	**-0.71**	**-0.57**	-0.64	-0.39	**-0.61**	**-0.52**	-0.49	-0.19
AOS	**-0.68**	-0.51	-0.65	-0.34	**-0.55**	-0.48	-0.47	-0.14
AOS pain	**-0.66**	**-0.56**	-0.60	-0.34	-0.52	**-0.51**	-0.42	-0.10
AOS disability	**-0.56**	-0.35	**-0.57**	-0.27	-0.44	-0.34	**-0.41**	-0.15
FAOS pain	**0.71**	**0.59**	0.63	0.30	**0.50**	**0.53**	0.36	0.05
FAOS symptoms	**0.39**	**0.28**	0.36	0.18	**0.14**	**0.25**	0.06	-0.09
FAOS ADL	**0.69**	0.51	**0.67**	0.33	**0.54**	0.54	**0.43**	0.07
FAOS S & R	**0.59**	0.61	**0.60**	0.60	**0.40**	0.36	**0.36**	0.05
FAOS QoL	**0.57**	0.57	0.58	0.58	**0.46**	0.42	0.38	0.17

Bold illustrates a-priori defined hypothesized correlations. Underlines confirms the a-priori defined hypotheses. Negative elations are due to the reversed scale for these measures. PR-AOFAS The completely patient-reported version of the American Orthopaedic Foot and Ankle Society (AOFAS) score; PROM Patient Reported Outcome Measure; AOFAS original patient-physician-determined AOFAS; PCS Physical Component Summary score of the Short Form-36, MCS Mental Component Summary score of the Short Form-36, VAS Visual Analogue Scale; AOS Ankle Osteoarthritis Score; FAOS Foot and Ankle Outcome Score; ADL Activities of Daily Living; S & R Sport and Recreation; QoL Quality of Life;

Table 3. Descriptives, effect sizes, and standardized response means of the completely patient-reported American Orthopaedic Foot and Ankle Society and the original patient–physician-determined American Orthopaedic Foot and Ankle Society to change.

Outcome measure	Satisfaction	n	Mean (SD) Baseline	Mean (SD) 26 weeks	Mean Difference (95% CI)	Effect size	Standardized Mean Difference
PR-AOFAS score	Worsened	8	64.5 (19.4)	55.4 (20.1)	-9.13 (-25.5; 7.3)	-0.47	-0.47
	Unchanged	38	59.4 (18.1)	62.3 (23.9)	2.84 (-2.7; 8.3)	0.16	0.17
	Improved	46	58.8 (17.6)	74.5 (15.4)	15.70 (11.5; 19.9)	0.89	1.11
	Greatly improved	4	53.3 (14.0)	78.5 (12.6)	25.25 (11.8; 38.7)	1.80	2.98
AOFAS score	Worsened	8	67.1 (11.9)	70.4 (15.1)	3.25 (-7.1; 13.6)	0.27	0,26
	Unchanged	38	62.1 (15.3)	68.9 (15.5)	6.84 (1.9; 11.7)	0.45	0.46
	Improved	46	65.2 (14.4)	78.0 (12.9)	12.74 (9.0; 16.5)	0.88	1.01
	Greatly improved	4	55.2 (15.5)	80.8 (4.8)	25.60 (9.5; 41.7)	1.65	1.97

PR-AOFAS the completely patient-reported version of the American Orthopaedic Foot and Ankle Society (AOFAS) score; AOFAS the original patient-physician-determined AOFAS; PROM Patient Reported Outcome Measure; n number; 95% CI Confidence Interval;

Interpretability

Clear ceiling effects can be seen for both the alignment subscales of the PR-AOFAS and the AOFAS (Table 1). A floor effect was observed for the AOFAS pain subscale (Table 1).

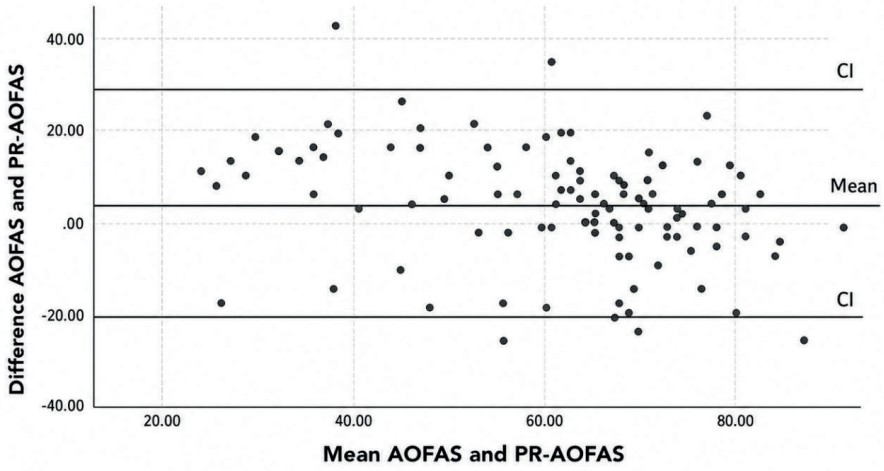
Minimal Important Change

The ROC-based calculation of the MIC was 6.5 points (95%CI: 0.6 to 14.4) for the PR-AOFAS score and 17.5 points (95%CI 2.5 to 32.5) for the AOFAS score. Accompanying sensitivity and specificity of the PR-AOFAS score were 0.42 and 0.80, respectively. The sensitivity and specificity of the AOFAS score were 0.36 and 0.89, respectively.

Agreement of the PR-AOFAS and the AOFAS scores

The ICC of the PR-AOFAS and the AOFAS scores was 0.70 (95%CI: 0.57 to 0.79) at the baseline and 0.56 (95%CI: 0.41 to 0.69) for the change from baseline. Using the Bland–Altman analysis, a systematic difference of 4.6 points (95%CI: 2.3 to 6.8) was found with limits of agreement of −18.4 and 27.6 points around this value in favour of the AOFAS score (Fig. 1).

Figure 1. Bland–Altman plot for the completely patient reported AOFAS and the original patient–physician-determined AOFAS.



AOFAS: the original patient–physician-determined American Orthopaedic Foot and Ankle Society score; PR-AOFAS the completely patient-reported American Orthopaedic Foot and Ankle Society score; PR: patient-reported; CI: confidence interval. AOFAS the original patient–physician-determined American Orthopaedic Foot and Ankle Society (AOFAS) score; PR-AOFAS the completely patient-reported version of AOFAS score; PROM Patient Reported Outcome Measure.

Discussion

Our key finding is that the Dutch version of the PR-AOFAS score has sufficient construct validity, internal consistency, test–retest reliability, and responsiveness in patients with ankle osteoarthritis who are willing to participate in a trial on injection therapy. The MIC was 6.5 points (95%CI: 0.6 to 14.4) for the PR-AOFAS score. The AOFAS score has insufficient construct validity, internal consistency, and responsiveness to change in the same population. The MIC was 17.5 points (95%CI: 2.5 to 32.5) for the AOFAS score. Although both outcome measures aim to measure identical constructs, correlation coefficients and agreement measures did not support this.

In contrast to the AOFAS score, the PR-AOFAS score has sufficient construct validity and had a higher correlation with other PROMs (Physical and Mental Component Summary scores of the SF-36, VAS pain, AOS, FAOS pain) than the AOFAS score in this study or reported in the literature.[101,102,106,107] Moderate correlations for the AOFAS score with all scales of the FAOS and the PCS score of the SF-36 was in line with other studies.[101,102,106,107]

A comparable test–retest (ICC: 0.89) capability was found for the PR-AOFAS score compared to what is previously reported (ICC: 0.89) for the patient-reported items of the AOFAS assessment (evaluating 5 of the 9 items).[101] Although the responsiveness was calculated differently in the literature, the PR-AOFAS score was found to be sufficiently and the AOFAS to be insufficiently responsive to change.[102,103,107,130] Similar to previous studies, both the PR-AOFAS and the AOFAS scores had ceiling effects at the baseline in the alignment subscale but neither scores had ceiling or floor effects in the total score.[106,107] One study found ceiling effects in the total score after 7.5 months following an ankle fracture, this is likely because a large group of patients fully recovered.[106]

A sufficient internal consistency was found for the function subscale (Cronbach's α 0.71) and insufficient internal consistency for the total score (Cronbach's α 0.68) of the PR-AOFAS score. Insufficient internal consistency was found for both the function subscale (Cronbach's α 0.40) and total score (Cronbach's α 0.47) of the AOFAS score. A Cronbach's α between 0.70 and 0.95 demonstrates satisfactory internal consistency as long as the scale is unidimensional.[116] The internal consistency of the total scores should therefore be interpreted with caution. Currently, there is limited comparison in the current literature. Pinsker et al. (2015) reported a Cronbach's α of 0.84. However, all patient-reported items were included in this analysis, including the pain scale (one item). This is incorrect as it is no longer a unidimensional measurement.[101] However, within orthopaedic surgery pain and function may be expected to be correlated, high Cronbach's α values may therefore be possible for such multidimensional scores. Furthermore, the physician-determined items of the function scale are left out. De boer et al. (2017) did measure all 7 items of the function scale in two studies and reported a Cronbach's α of 0.927 and 0.947.[106,107] However, these studies concerned patients with ankle fractures. It must also be taken into consideration that too high a Cronbach's α may be an indication that different questions are capturing the same symptoms or limitations.[116]

The minimal important change of the AOFAS score had not previously been calculated for patients with ankle osteoarthritis. In this study, the minimal clinically important change of the PR-AOFAS and the AOFAS scores was found to be smaller than its SDC (individual). As a result, this makes it less suitable for follow-up of individual patients in a clinical setting and more suitable for use in groups of patients, such as a research setting. The 95% CI from the MIC values of both outcome measures are large, indicating that this estimator should be interpreted with caution.

Although the PR-AOFAS score was expected to be similar in construct, it cannot replace the AOFAS score due to the systematic difference between the outcome measures and low level of agreement. There may be several explanations for this poor agreement. Firstly, the lower correlation could be

explained by the fact that both instruments are measuring something else. The insufficient construct validity when compared to other PROMs may be a possible explanation. However, also disability weights assigned by patients have been found to be higher than the weights based on the judgement of the physician in osteoarthritis and other musculoskeletal conditions.[5] This is further supported by the fact that the PR-AOFAS score has a higher correlation with the other PROMs as they all measure the patient's perspective. One study also found that the AOFAS had a similar responsiveness to other PROMs once the objective items were removed.[100] Secondly, the correlation of identical patient-reported items also differed. Answering the same patient-reported items could therefore have been affected by the presence of a physician or by being in a hospital or clinical setting. Finally, the ceiling effect in the alignment subscale of both the PR-AOFAS and the AOFAS scores and the floor effect in the pain subscale of the AOFAS score may result in restricted variation with a subsequent lower correlation.

Strengths of this study include the structural and elaborate evaluation of a new ankle-specific PROM with sufficient measurement properties and a moderate to high correlation with a large range of ankle-specific and generic measuring instruments, a large sample size, and the calculation of the minimal important change in a homogenous population with the same diagnosis. Limitations include a limited anchor with a 4-point Likert scale and small samples for both instruments in the worsened and greatly improved categories for the evaluation of the responsiveness. Also the content validity of neither PR-AOFAS nor the AOFAS score was assessed. Content validity includes relevance and comprehensibility of the items. Relevance and comprehensibility, usually conducted through cognitive interviews of a small sample of patients, measures the patient's understanding of the item as it is intended (i.e., does the patient understand the difference between ankle and foot mobility) and its deemed relevance to the construct. Content validity should be evaluated in future research.

CONCLUSION

The Dutch version of the PR-AOFAS score has sufficient construct validity, internal consistency, test–retest reliability, and responsiveness in patients with ankle osteoarthritis who are willing to participate in a trial on injection therapy. The minimally important change of the PR-AOFAS score is smaller than its SDC, making it suitable for use in groups of patients, such as a research setting.

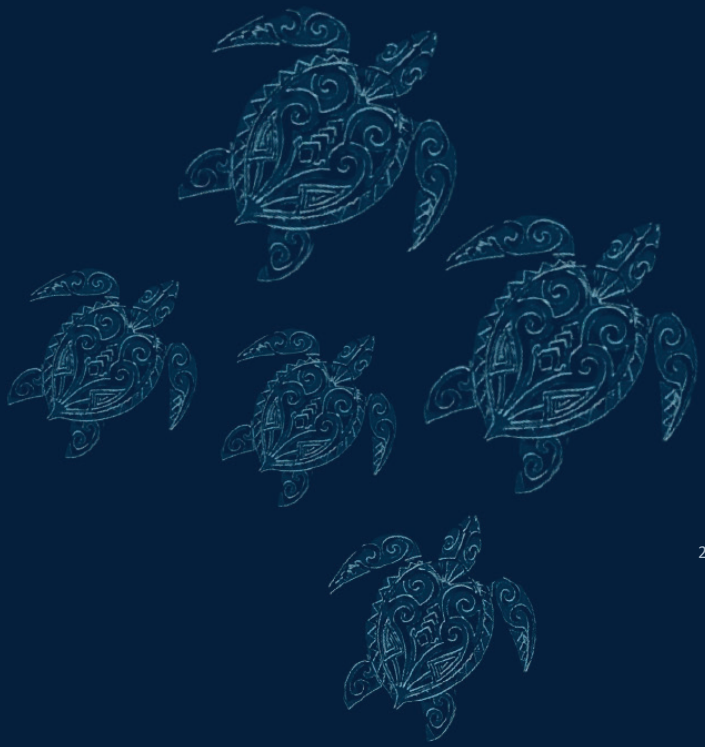
CHAPTER

5

Platelet-Rich Plasma Injection Management for Ankle Osteoarthritis Study (PRIMA)

Protocol of a Dutch Multicentre, Stratified, Block-Randomised, Double-Blind, Placebo-Controlled Trial

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Abstract

Introduction – Platelet-rich plasma (PRP) is a potentially efficacious treatment for ankle osteoarthritis (OA), but its use has not been examined in high-quality studies. Systematic reviews show that PRP injections significantly decrease pain and improve function in patients with knee OA. Ankle OA is more common than hip or knee OA in the young active population; with a prevalence of 3.4%. PRP injections in ankle OA are shown to be safe and improve quality of life over time, but no randomised controlled trial has been conducted. Our randomised controlled trial will evaluate the efficacy of PRP injections for symptom reduction and functional improvement, compared with placebo, in the treatment of ankle (talocrural) OA.

Methods and analysis – We will conduct the Platelet-Rich plasma Injection Management for Ankle OA study: a multicentre, randomised, placebo-controlled trial. One hundred patients suffering from ankle OA will be randomised into two treatment groups: PRP injection or placebo (saline) injection. Both groups will receive two injections of PRP or placebo at an interval of 6 weeks. Primary outcome is the American Orthopaedic Foot and Ankle Society score at 26 weeks. Secondary outcomes determined at several follow-up moments up to 5 years, include Ankle Osteoarthritis Score, Foot and Ankle Outcome Score, pain subscale of (0–40), Visual Analogue Scale score (0–100), Ankle Activity Score (0–10), subjective patient satisfaction Short Form Health Survey-36, Global Attainment Scaling and the EuroQol-5 dimensions-3 levels utility score. A cost-effectiveness analysis will be performed at 1 year.

Ethics and dissemination - The study is approved by the Medical Ethics Review Committee Amsterdam Medical Center, the Netherlands (ABR 2018–042, approved 23 July 2018) and registered in the Netherlands trial register (NTR7261). Results and new knowledge will be disseminated through the Dutch Arthritis Association (ReumaNederland), Dutch patient federation, conferences and published in a scientific peer-reviewed journal.

Trial registration number: NTR7261.

BACKGROUND AND RATIONALE

Platelet-rich plasma (PRP) is a potentially efficacious treatment for ankle osteoarthritis (OA), but its use has not been examined in high-quality studies. Ankle OA is more common than hip or knee OA in the young active population.[131] The incidence of symptomatic ankle OA is estimated to be 3.4% in the general adult population.[131] Patients with ankle OA have a quality of life and physical functioning comparable with hip OA, end-stage kidney disease or congestive heart failure.[13] These relatively young (predominantly female) patients have an increased risk for decreased work participation and family care. The available surgical intervention (arthrodesis) is associated with significant functional limitations. In contrast to hip and knee OA, where joint replacement is an excellent surgical alternative for severe cases, there is a clear need for effective non-surgical interventions in ankle OA. PRP is defined as plasma containing a concentration of at least 1 000 000 platelets/µL.[42] Growth factors are stored in α-granules within platelets, and are released in a selective manner on activation. Growth factors released from the α-granules of platelets are assumed to provide the regenerative benefits of PRP.

Recent reviews concluded that in animal models PRP can diminish multiple inflammatory interleukin (IL)-1-mediated effects.[43] Due to this local anti-inflammatory response, PRP might have an indirect analgesic effect. The second suggested effect might be protection of the cartilage from destructive pro-inflammatory ILs. This is mediated due to an increased messenger RNA expression of proteoglycan core protein in the articular cartilage and decreased chondrocyte apoptosis.[43] Consequently, PRP could positively influence the collagen network of the cartilage.

Recent systematic reviews on the intra-articular injection therapy in ankle OA found a lack of evidence from high-quality studies to assist in clinical decision-making.[132,133] When compared with placebo injections, hyaluronic acid or corticosteroid injections, PRP injections might significantly decrease pain and improve function in patients with knee OA.[40,134,135] Given the clinical effect on pain reduction in knee OA and a good safety profile, PRP is a promising non-surgical therapy for ankle OA.[136,137] PRP might delay the irreversible surgical options like arthrodesis. No significant adverse events have been reported in any PRP trials regarding ankle OA, knee OA, acute hamstring injuries or Achilles tendinopathy.[40,138-143] Clinical studies on PRP in ankle OA are limited to a single report of 5 cases and a prospective case series of 20 subjects, which both showed safety and significant reduction of pain at a mean of 16 months and 12 weeks follow-up.[140-144] Well-designed prospective randomised controlled trials (RCT) have not yet been performed.

METHODS AND DESIGN

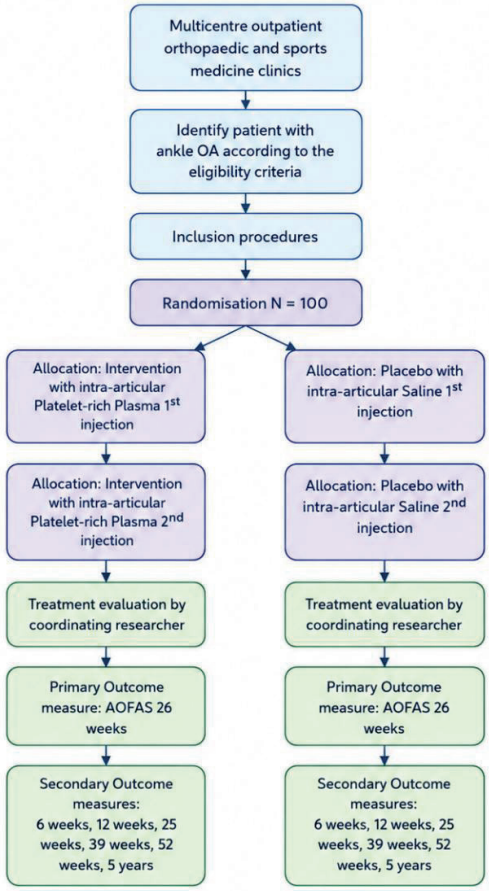
Objectives

We aim to determine the efficacy of PRP injections in the management of ankle OA by comparing two groups, both receiving two injections of either PRP or placebo solution. We hypothesise that PRP injections are efficacious for symptom reduction and functional improvement compared with placebo in the treatment of ankle (talocrural) OA.

Study design

The Platelet-Rich plasma Injection Management for Ankle OA (PRIMA) study is a multicentre, stratified, block-randomised, double-blind, placebo-controlled trial design will be conducted in order to compare two treatment groups: PRP versus placebo (saline). After the 26 weeks follow-up of the last patient in the study, the principal investigator and coordinating researcher will be unblinded only after the analysis of the primary outcome. A flow chart of the design and follow-up is shown in figure 1. The study included its first patient in August 2018 and aims to include the last patient by January 2021, consequently allowing analysis and then deblinding to commence after the last follow-up (26 weeks) of the last patient by July 2021.

Figure 1. Platelet-Rich Plasma Injection Management for Ankle OA multicentre randomised controlled trial design and follow-up procedure



Illustrating the Platelet-Rich plasma Injection Management for Ankle OA multicentre randomised controlled trial design and follow-up procedure. AOFAS, American Orthopaedic Foot and Ankle Society; OA, osteoarthritis.

Patient involvement

Active patient involvement through reviewing the proposal (reviewer level)

Active involvement of patients during the design phase was performed by two patients with ankle OA. Both reviewed the grant proposal and provided feedback.

Execution phase: patients will actively contribute

Active patient involvement will be secured by invitation of at least two patients for the annual trial monitoring and evaluation meetings (informant level).

Analysis phase: patient will review and interpret the results (reviewer level)
Using the blinded codes of the randomisation groups and after breaking the randomisation code, patients (also active in the design phase) will be given the opportunity to interpret the results from a patient perspective.

Dissemination phase: patient-oriented approach (advisor level)
Results and new knowledge will be disseminated through the Dutch Arthritis Association (ReumaNederland), the Dutch patient federation, conferences and published in a scientific peer-reviewed journal. Dissemination activities will comprise a social media strategy with active patient involvement to share results with online patient communities and an events attendance strategy enabling patient participation in seminars, conferences and workshops.

Study population

Population (base) – Patients with ankle OA in University Medical Centres, teaching hospitals, general hospitals and private specialist clinics will be informed about the study. In order to participate, patients must meet the eligibility criteria documented below.

Inclusion criteria

- Severity of ankle OA pain on a Visual Analogue Scale (VAS 0–100 mm)
- ≥40 mm during daily activities
- X-rays (anteroposterior (AP) and lateral view) indicating ≥grade 2 talocrural OA on the van Dijk classification (clarified under the 'Radiographs' section).[54]
- Age≥18 years.

Exclusion criteria

- Patient has received injection therapy for ankle OA in the previous 6 months.
- Patient does not want to receive one of the two therapies.
- Patient has clinical signs of concomitant OA of one or more other major joints of the lower extremities that negatively affects their daily activity level.
- Previous ankle surgery for OA or osteochondral defects <1 year (not including surgery for an ankle fracture in the past).

Radiographs – AP and lateral X-rays of the talocrural joints will be scored according to the van Dijk classification[54]:

- Normal joint or subchondral sclerosis.
- Osteophytes without joint space narrowing.
- Joint space narrowing with or without osteophytes.
- (Sub)total disappearance or deformation of the joint space.

Randomisation, blinding and treatment allocation

We will include patients at the centre of their first outpatient clinic appointment. For each patient the coordinating researcher will prepare a syringe with PRP and a syringe with placebo (isotonic saline: 0.9% sodium chloride). A Good Clinical Practice (GCP) approved data management system (Castor EDC, based in Amsterdam, the Netherlands) will be used to perform a computer-generated block randomisation scheme with patients stratified to centre with a variable block size of 2, 4 or 6. This procedure will ensure treatment allocation concealment. The coordinating researcher, treating physician and patient all remain blinded to the allocated intervention. An independent researcher from the coordinating location will have access to the randomisation result and the allocated intervention. This will be relayed to a GCP-certified research assistant at the centre. The research assistant then selects one of the two syringes based on the allocated intervention and blinds the syringe with a covering sheath, ensuring concealment of the content of the syringe. The patients, treating physicians and coordinating researcher will all be blinded to the allocation of the intervention and to the contents of the syringe. The success of blinding will be assessed by asking patients which injection they think they have received just after the injection procedure, this will then be registered accordingly.

After the 26 weeks follow-up of the last patient in the study, the principal investigator and coordinating researcher will be unblinded only after the analysis of the primary outcome. The patients will remain blinded to the therapy until the 52 weeks follow-up (online supplementary appendix 1) of the last patient in the study.

Intervention

In this study, patients will be randomised into two treatment groups: PRP injection or placebo saline injection. For each patient, the coordinating researcher will prepare a PRP and a placebo injection (isotonic saline: 0.9% sodium chloride). The PRP syringe will be prepared according to the instructions

of the manufacturer.[138] Prior to commencement of the study, the coordinating researcher was trained by a representative of Arthrex, as well as two experienced members of the PRIMA trial research group (GR and RJdV) with a vast scientific experience regarding PRP preparation and injection.[138,139] The PRP will be prepared using a widely used and commercially available system (Arthrex double syringe PRP system, Arthrex Medizinische Instrumente GmbH, Garching, Germany).

One syringe of 15 mL autologous blood will be collected twice from the cubital vein: at inclusion and at a time interval of 6 weeks. After blood collection the syringe will undergo 5 min of centrifugation and the injection will be given within 30 min following venepuncture to prevent formation of blood clots. No additional substances (calcium, thrombin or citrate) will be added to the PRP solution. For each procedure, 2 mL of PRP or placebo will be prepared and injected into the affected ankle joint under ultrasonographic guidance using a sterile technique. All patients will receive a second injection at 6 weeks, regardless of the effect of the first injection. To guarantee blinding for the allocated treatment of the patient, treatment assessor and treating physician, blood will be drawn and both PRP and placebo will be prepared according to exactly the same procedure for each patient (both at inclusion and at a time interval of 6 weeks after the first injection). However, in the control group, patients will be injected with 2 mL of physiological saline instead of PRP. An unblinded research assistant will blind one of the two identical syringes based on the allocated intervention using a specially manufactured covering sheath in order to conceal randomisation. Following the intra-articular injection, the syringe covered by the sheath (containing either the remnants of the PRP or saline) is handed to the unblinded research assistant, who will dispose of the syringe, therefore keeping the treating physician and coordinating researcher blinded. After the intervention, patients are advised to avoid heavy or repetitive stress to the ankle joint for a period of 48 hours. Furthermore, patients receive a leaflet containing usual-care healthy lifestyle advice beneficial for ankle OA. This includes losing weight and exercise (avoiding heavy or repetitive ankle loading exercises) such as walking, cycling or swimming.

Use of co-intervention

Patients are instructed to avoid the use of co-interventions and non-steroidal anti-inflammatory drugs if possible, 24 hours prior to the intervention and if possible up to a year after the first injection. Throughout the study, key treatment (including usual care: exercise therapy and healthy lifestyle advice) and co-interventions used by patients will be registered, such as non-steroidal anti-inflammatory drugs, other analgesic drugs, intra-articular injections or inlays.

Study procedures

In the event the patient meets the criteria for inclusion and exclusion, the patient will be informed in more detail about the study procedure. At that time, the patient can ask questions about the study and decide whether they will participate and sign the informed consent form. Subsequently, the patient will proceed to inclusion and the randomisation procedure.

Inclusion

Patients are recruited for inclusion by their treating physicians at location. Following inclusion PRP will be prepared according to the PRP system instructions of the manufacturer. During the first two consultations, a total of two intra-articular injections will be documented with a time interval of 6 weeks. The patient will have no additional costs to usual care as a result of taking part in this study.

Physical examination will be performed on three occasions up to 26 weeks from baseline. Patient-reported outcome measures (PROMs) will be used to evaluate the treatment effect up to 5 years. A cost-effectivity analysis will be performed at 1 year using the PROductivity and DISease Questionnaire (PRODISQ). The time-frame of the follow-up questionnaires is further illustrated in table 1. Questionnaires will be managed and distributed digitally using a GCP-approved data management system (Castor EDC).

Table 1. Time-frame of the follow-up questionnaires	
Follow-up	
Baseline	• 1st intervention injections • Physical Examination • AOFAS • PROMs • PRODISQ cost-effectivity
6 weeks	• 2nd intervention injection • Physical Examination • AOFAS • PROMs
12 weeks	• AOFAS • PROMs • PRODISQ cost-effectivity
26 weeks	• AOFAS • PROMs • PRODISQ cost-effectivity
39 weeks	• PRODISQ cost-effectivity
52 weeks	• AOFAS • PROMs • PRODISQ cost-effectivity
5 years	• AOFAS • PROMs

In addition to the AOFAS score, the following PROMs will be taken: FAOS, AOS, VAS, AAS, SF-36, GAS, EQ-5D-3L. These PROMs will be elaborated on further on. Furthermore, PRODISQ will be used to perform a cost-effectivity analysis. These questionnaires can be found in online supplementary appendix 1.
AAS, Ankle Activity Score; AOFAS, American Orthopaedic Foot and Ankle Society; AOS, Ankle Osteoarthritis Score; EQ-5D-3L, EuroQol-5 dimensions-3 levels; FAOS, Foot and Ankle Outcome Score; GAS, Global Attainment Scaling; PRODISQ, PROductivity and DISease Questionnaire; PROM, patient-reported outcome measures; SF-36, subjective patient satisfaction Short Form Health Survey-36; VAS, Visual Analogue Scale.

Replacement of individual patients after withdrawal

In the sample size calculation, we compensated for an expected loss of 10% of patients to follow-up. No patients will be replaced after withdrawal.

Safety

All adverse events reported spontaneously by the patient or observed by the investigator or his staff will be recorded. A variety of conditions have been treated with PRP ranging from muscle and tendon injuries to intra-articular injections of the knee and ankle. To date, no serious adverse events have been documented in the literature, concerning PRP intra-articular injections of the ankle. In accordance with the Central Committee on Research Involving Human Subjects guidelines, this study was classified as low risk for adverse events. Therefore, the local Medical Ethical Commission will be

notified of any serious adverse events. In the event this happens, the advice of the Medical Ethical Commission will be followed accordingly.

Outcome measures

Primary study parameter/end point – The primary objective of this study will be to quantify pain or functional improvement using the American Orthopaedic Foot and Ankle Society (AOFAS) score at 26 weeks follow-up. Studies evaluating the efficacy of PRP in knee OA maintained a follow-up between 3 and 12 months. We therefore opted to take 26 weeks for our primary outcome measure.136 The AOFAS is a validated scale for ankle OA (0–100) measuring three subdomains (pain, function and alignment), which together total nine items.[104,106,112,145,146] The subdomain of pain is measured by one item where a maximal score of 40 indicates no pain. Function consists of 7 items where full function is indicated by the maximal score of 50 points. Similar to the pain subdomain, alignment has a potential maximum score of 10 points using one item, indicating good alignment.[106,112] The AOFAS questionnaire, having undergone forward and backward translation to Dutch by de Boer et al, has an excellent internal consistency (Cronbach's α=0.947) and an excellent test–retest reliability (Intraclaas Correlation Coefficient 0.93).[106]

Secondary study parameters/end points

Secondary outcome measures are a number of other PROMs. Specific time points of the secondary outcome measures can be found in table 1.

1. Ankle Osteoarthritis Score (AOS) is a Visual Analogue Scale (VAS) from 0 to 100 mm with 18 questions; 9 relating to pain and 9 relating to disability.
2. Foot and Ankle Outcome Score (FAOS): each question is assigned 0–4 points based on the answer given. The scale runs from 0 (extreme symptoms) to 100 points (no symptoms).
3. In order to evaluate pain, the pain subscale of AOFAS (0–40 points) will be analysed. On this scale, the lower the score the more pain the patient has. Additionally, a VAS score (VAS 0–100 mm) is measured during activities of daily living, with 0 mm being no pain and 100 mm the worst pain imaginable.
4. Total AOFAS score at the other time points than the primary one (at 6, 12 and 52 weeks as well as 5 years).
5. Ankle Activity Score (0–10 points) is scored according to chart based on the performable activity level
6. Subjective patient satisfaction (four categories): poor, fair, good, excellent.

7. Short Form Health Survey-36 is a health-related quality of life score (0–100 points). The higher the patient scores, the higher the disability.
8. The Global Attainment Scaling is a method of scoring based on achievement related to predetermined goals in agreement with the patient. Points are subtracted for not achieving the predefined goals or vice versa. Scores range from 100 (high functioning) to 0 (severely impaired)
9. EuroQol-5 dimensions-3 levels (EQ-5D-3L) utility score allows a patient's health to be defined by a 5-digit number.
10. PRODISQ will be used to determine indirect costs and direct costs cost-effectivity. PRODISQ is taken at baseline and every 3 months thereafter up until 1 year. This will be done in conjunction with the EQ-5D-3L.

Loss to follow-up

The coordinating researcher will attempt to limit loss to follow-up as much as possible by contacting every patient and being present at every patient visit. All digital questionnaires will be constantly monitored to ensure they are being filled in and otherwise followed up by the coordinating researcher. In the event of patient withdrawal, an analysis of demographic and prognostic characteristics will be done on these cases and the remaining patients. As previously described by Järvinen *et al*, we will document the patient eligible for and compliant with each follow-up.[146]

Missing items

Missing items of a score will be handled according to the instructions of the specific scales. In the event of no instructions, we will calculate the percentage of missing items on a scale. Due to the potential impact on trial conclusions, multiple imputation (if >10% missing items on a scale) will be applied.

Sample size

Based on previous and ongoing studies, the study protocol of the RCT is designed to detect a difference of 12 points (0–100) on the AOFAS score. There is no official agreement on the minimal clinical important difference for the AOFAS score regarding ankle OA. However in relatable musculoskeletal literature, 10%–15% of the used scale was reported.[139,147,148] Our predefined minimal clinical important difference of 12% is located within this range.[139,147,148] Based on a previous placebo-controlled RCT on injection therapy (hyaluronic acid) in ankle OA by De Groot *et al*, an SD of 16.3 can be expected.[133] Taking into account a two-sided level of significance of 5%, a power of 90% and a

dropout rate of 10%, approximately 50 (45 plus 10% drop out) patients per group will be needed (n=100 in total).

Data management

After giving permission for participating in this study, patients will receive a link to fill in digital surveys. All data gained outside Castor EDC will be stored on the AMC secured hard drive. All data will be coded and stored in the Castor EDC online database, which meets the AMC safety criteria and GCP guidelines. The primary investigator and project leader will safeguard the coded data through password secured access. All patient's data will be archived for at least 15 years and handled with in accordance with the Dutch Personal Data Protection Act (Wbp). Data protection is provided through the safety protocol of Castor EDC with automated backups and Secure Sockets Layer (SSL) security.

Statistical analysis

A standard operating procedure will be available to logically recode and clean the data. The data will be interpreted according to a blinded data interpretation scheme described by Järvinen *et al*.[146] A statistical expert (SB) is present among the authors. The authors will interpret the statistical results until a consensus is reached. Once the authors are in agreement, the two groups will be unblinded and no changes will be made to the interpretation of the results.

Baseline characteristics

Baseline characteristics will be analysed between groups using descriptive statistics.

Primary outcome measure

Analysis will be performed using an intention-to-treat approach. To test for the effect of treatment on the between-group difference in primary outcome, we will use a repeated measurement general linear model. Changes from baseline to all follow-up time points will be included in the model. Adjustments will be made for those baseline variables that influenced the primary outcome with $p<0.10$.

Secondary outcome measures

To test for the effect of treatment on between-group differences in secondary outcomes, we will use the repeated measurement general linear model. Changes from baseline to all follow-up time points will be included in the model.

Economic analysis

In the event of a positive significant outcome, an economic analysis is needed to support a possible change of practice. An economic analysis (costs) will be performed in order to determine cost-effectiveness.

We will assess the differences in mean quality-adjusted life years (QALYs), costs and net benefits between the PRP injection group and the placebo group using linear models. We express the cost-effectiveness by using cost-effectiveness acceptability curves from both a healthcare perspective and a societal perspective. With multiple bootstrap replicates of the average difference in costs and effects in the incremental cost-effectiveness plane, we will express the uncertainty of our cost-effectiveness analysis.

The cost-effectivity analysis will be performed with a 1 year time horizon. We use the three-level EQ-5D questionnaire (Euroqol, Rotterdam, the Netherlands) to calculate QALYs as the area under the curve of the utility scores measured over 12 months, according to the Dutch pricing system. The analysis will be based on indirect costs and direct costs and will be determined using PRODISQ. PRODISQ is taken at baseline and every 3 months thereafter up until 1 year.

Monitoring committee

The PRIMA trial will be monitored by the clinical research unit (CRU) of the coordination study centre. The CRU aims to improve the quality of clinical research and ultimately, patient care. Before the PRIMA trial commenced, a monitoring plan was set-up. This monitoring plan facilitates compliance with the Human Research Act (WMO), GCP (ICH-GCP) guidelines (5.18.1) and/ or ISO14155, which require monitors to verify that:

1. the rights and well-being of human subjects are protected;
2. recorded study data are accurate, complete and verifiable with the source documents;
3. the conduct of the study is compliant with the currently approved protocol and with applicable laws regulatory requirements, for example, WMO, ICH-GCP, ISO14155.

Throughout the study, monitoring will be performed at initiation of the trial, at each participating centre once approximately three patients have been enrolled, after approximately 10–15 enrolled patients have completed the 26-week follow-up, after 70 patients have been enrolled and after database lock.

Ethics and dissemination

In the events of amendments or other changes, co-researchers will be notified. If relevant, patients participating will also be notified. Intellectual data will be the property of the PRIMA study group. Participant data that underline the results reported in this article following de-identification will be shared anonymously on request following publication. Data will be shared, wherever legally and ethically possible and in line with ICMJE guidelines, with researchers who provide a methodologically sound proposal. Data will be stored in a repository (Figshare) under management of the medical library of the AMC. Any proposal should contain: title, background, rationale, objective, methods (eligibility criteria, variables and timeframe of interest, statistical plan), information regarding publication including authorship.

The results of this project study and new knowledge will be disseminated through the Dutch Arthritis Association (ReumaNederland), presentations, news publications, blogs, websites, social media and professional organisations (rheumatology, orthopaedics, primary care medicine, sports medicine, public health) and the Dutch patient federation (Patiëntenfederatie Nederland). The patients will also be informed about the results of the study. The study will be conducted according to the principles of the Declaration of Helsinki, GCP and the Medical Research Involving Human Subjects Act (WMO). The board of each participating hospital reviewed and approved the local feasibility. Monitoring and auditing will be carried out throughout the study. In the event of serious adverse events, these will be documented and reported to the monitor and the Medical Ethics board. Eligible patients will be informed of the study and will sign an informed consent form before participating (acquired by researchers associated with the study). Provisions for post-trial care as compensation for those who suffer harm from trial participation is documented in the patient information.

DISCUSSION

This is the first study evaluating the efficacy and cost-effectiveness of PRP injections in the treatment of ankle OA with a multicentre, stratified, block-randomised, double-blind, placebo-controlled design. The primary outcome is the AOFAS score at 26 weeks. Our study will also evaluate the long-term efficacy of PRP for up to 5 years.

PRP has been shown to alleviate symptoms of patients suffering from knee OA.[137] In the absence of effective evidence-based non-surgical interventions for ankle OA, PRP would fulfil a clear clinical need. Previous trials concerned with the efficacy of PRP for multiple indications are usually of low

quality and adhere to a follow-up of 26 weeks or shorter. Furthermore, a cost-effectiveness analysis has never been performed in previous trials on PRP in the treatment of OA.

A positive study outcome would have a significant impact leading to change in clinical practice, where PRP could be offered as a non-surgical intervention. A negative outcome will prevent the widespread use of a non-efficacious treatment.

This study has potential limitations. First of all, due to financial constraints (semi-quantitative), MRI-defined cartilage degenerative changes will not be used as a secondary outcome score. Furthermore, the composition of PRP is not analysed. This decision is based on the fact that PRP preparation and composition has frequently been analysed and is typically not performed in clinical practice prior to injection.[149] The PRP we use (Hettich Rotofix32 A centrifuge and Arthrex syringes) is one out of a multitude of commercially available PRP products. All these products differ in their production method and content, and different treatment regimens regarding dose, timing and number of injections are used in clinical practice. The generalisability to other PRP products and treatment regimens remains unknown.

CONCLUSION

This will be the first RCT to assess the efficacy and cost-effectiveness of PRP in ankle OA.

CHAPTER

6

Effect of Platelet-Rich Plasma Injections vs Placebo on Ankle Symptoms and Function in Patients With Ankle Osteoarthritis

A Randomized Clinical Trial

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ABSTRACT

Importance – Approximately 3.4% of adults have ankle (tibiotalar) osteoarthritis and, among younger patients, ankle osteoarthritis is more common than knee and hip osteoarthritis. Few effective nonsurgical interventions exist, but platelet-rich plasma (PRP) injections are widely used, with some evidence of efficacy in knee osteoarthritis.

Objective – To determine the effect of PRP injections on symptoms and function in patients with ankle osteoarthritis.

Design, Setting, and Participants – A multicenter, block-randomized, double-blinded, placebo-controlled clinical trial performed at 6 sites in the Netherlands that included 100 patients with pain greater than 40 on a visual analog scale (range, 0-100) and tibiotalar joint space narrowing. Enrollment began on August 24, 2018, and follow-up was completed on December 3, 2020.

Interventions – Patients were randomly assigned (1:1) to receive 2 ultrasonography-guided intra-articular injections of either PRP (n = 48) or placebo (saline; n = 52).

Main Outcomes and Measures – The primary outcome was the validated American Orthopaedic Foot and Ankle Society score (range, 0-100; higher scores indicate less pain and better function; minimal clinically important difference, 12 points) over 26 weeks.

Results – Among 100 randomized patients (mean age, 56 years; 45 [45%] women), no patients were lost to follow-up for the primary outcome. Compared with baseline values, the mean American Orthopaedic Foot and Ankle Society score improved by 10 points in the PRP group (from 63 to 73 points [95% CI, 6-14]; P < .001) and 11 points in the placebo group (from 64 to 75 points [95% CI, 7-15]; P < .001). The adjusted between-group difference over 26 weeks was −1 ([95% CI, –6 to 3]; P = .56). One serious adverse event was reported in the placebo group, which was unrelated to the intervention; there were 13 other adverse events in the PRP group and 8 in the placebo group.

Conclusions and Relevance – Among patients with ankle osteoarthritis, intra-articular PRP injections, compared with placebo injections, did not significantly improve ankle symptoms and function over 26 weeks. The results of this study do not support the use of PRP injections for ankle osteoarthritis.

Trial Registration – Netherlands Trial Register: NTR7261

INTRODUCTION

Osteoarthritis affects an estimated 250 million people worldwide and is associated with pain and disability, especially in the lower extremities.[3] In 2018, ankle (tibiotalar) osteoarthritis was estimated in a UK-based study to affect approximately 3.4% of adults.[8] Younger active patients with ankle osteoarthritis have reduced quality of life, comparable to people with hip osteoarthritis, kidney failure, and congestive heart failure.[12,13] However, effective nonsurgical interventions are not available for ankle osteoarthritis.[132,150]

Platelet-rich plasma (PRP) injections are used increasingly to manage osteoarthritis.[39,44,132,151] PRP is derived from autologous blood using a centrifugation system to facilitate growth factor release from the α-granules found in platelets.[152,153] These growth factors modulate the intra-articular environment, potentially facilitating an anti-inflammatory, anabolic, and analgesic effect.[152,154] The global commercial market for PRP is projected to more than double, from an estimated $190 million in 2019 to $400 million in 2024 and an estimated $1.2 billion by 2028.[44,151]
PRP injections for knee osteoarthritis have been investigated in 21 randomized clinical trials.[39] Meta-analyses report some benefits for PRP injections in knee osteoarthritis.[39]

Investigation of PRP for ankle osteoarthritis is limited to 4 small case series, and all have reported statistically significant improvements in symptoms and function.[52,132] Randomized clinical trials comparing PRP with placebo in patients with ankle osteoarthritis have not been performed. The Platelet-Rich Plasma Injections for the Management of Ankle Osteoarthritis (PRIMA) randomized clinical trial assessed the efficacy of PRP injections in ankle (tibiotalar) osteoarthritis.

METHODS

Study Design

This study was a multicenter, stratified, block-randomized, double-blind, placebo-controlled trial performed in 6 centers (2 university medical centers, 2 teaching hospitals, 1 general hospital, and 1 private specialist clinic) in the Netherlands. A detailed description of the study design has been published.[52] The initial and revised protocol and statistical analysis plan are shown in Supplement 1.[52] The study protocol and all amendments were approved by the local medical ethics review committee of Amsterdam UMC (Amsterdam, The Netherlands). Written informed consent was obtained from all participants. The study was monitored by the clinical research unit of the

Amsterdam UMC (Amsterdam, The Netherlands). The study protocol was amended and approved by the local medical ethics review committee on May 5, 2020, after the start of enrollment but before any results were available. Due to the COVID-19 pandemic, some patients were unable to receive their second study injection. Therefore, based on recent literature recommendations for studies affected by the COVID-19 pandemic, the participation of these patients in this study was discontinued and new patients were enrolled (COVID-19 lockdown–related protocol amendment).[155] Due to this COVID-19 amendment, only the patients who were able to receive 2 injections were included and were analyzed according to their randomization group.

Study Participants

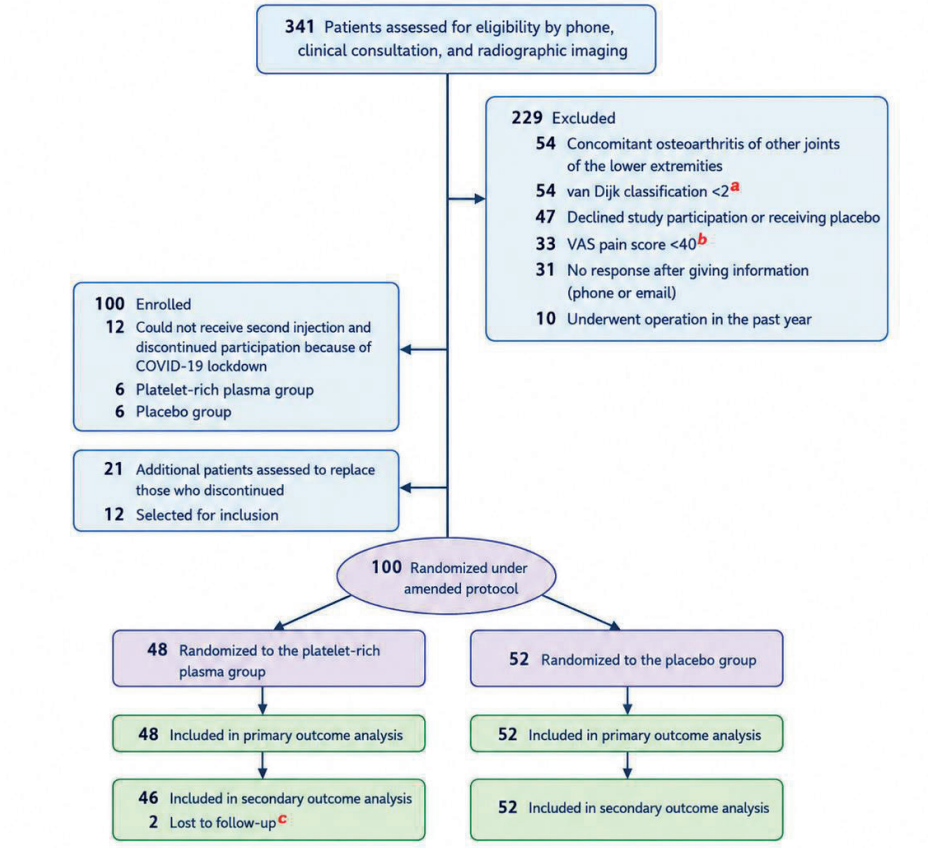
Patients with ankle osteoarthritis were informed of the study at orthopedic and sports medicine outpatient clinics at the 6 centers. Patients were eligible if they were 18 years or older, had a score of at least 40 for ankle osteoarthritis pain severity on a visual analog scale (VAS; range, 0-100; higher scores indicate more severe pain) during daily activities, and had radiographic imaging (anteroposterior and lateral view) indicating at least grade 2 tibiotalar osteoarthritis on the van Dijk classification.[54] Patients were excluded if they received injection therapy for ankle osteoarthritis in the past 6 months, declined either therapy, had signs of concomitant osteoarthritis of 1 or more other major joints of the lower extremities that impaired their daily activity level, or underwent a previous ankle operation for osteoarthritis or osteochondral defects less than 1 year before randomization (not including surgery for an ankle fracture in the past). Further details on baseline measurements, including radiological variables, are provided in eTables 1 and 2 in Supplement 2 and the published protocol.[52]

Randomization and Blinding

Patients were randomized to receive PRP vs placebo (saline) via intra-articular injections (Figure 1). A Good Clinical Practice–approved data management system (Castor EDC) was used to perform computer-generated block randomization stratified by center using variable block sizes of 2, 4, and 6 in a 1:1 ratio. Physicians referred potentially eligible patients. The coordinating research physician determined eligibility based on inclusion and exclusion criteria, obtained written informed consent, and enrolled patients in the study. The coordinating research physician initiated randomization in the data management system but remained blinded to the allocated intervention. To ensure blinding of the intervention and concealment of randomization, the coordinating research physician prepared a syringe with PRP and a syringe with placebo (isotonic saline: 0.9% sodium chloride). Only the independent research assistants had access to the randomization result in the data management

system. These research assistants covered study syringes with a specially manufactured thick plastic covering sheath to conceal the appearance of the study intervention and temperature of the syringe. After the intra-articular injection, the syringe covered by the sheath (containing either the remnants of the PRP or saline) was handed back to the independent research assistant, who disposed of the syringe in effort to maintain blinding of the patient, treating physician, and coordinating researcher. The success of blinding was assessed by asking patients just after the injections what treatment they thought they had received.

Figure 1. Patient Flow in a Study of the Effect of Platelet-Rich Plasma Injections vs Placebo on Ankle Symptoms and Function in Patients With Ankle Osteoarthritis.



[a] *van Dijk classification: 0 indicates normal joint or subchondral sclerosis; 1, osteophytes without joint space narrowing; 2, joint space narrowing with or without osteophytes; 3, (sub)total disappearance or deformation of the joint space.*

[b] *Visual analog scale (VAS) score ranges from 0 to 100, higher scores indicate more severe pain.*

[c] *Prior to each consult the questionnaires were checked for completeness. A reminder was then sent by email in the event of incompleteness. Two patients did not complete the secondary outcome questionnaires at 26 weeks because they felt it was too time consuming.*

Procedures

Patients received 2 intra-articular injections 6 weeks apart. An optimal PRP formulation has not been identified. Therefore, PRP (leukocyte poor) was prepared using a widely used and commercially available system (Arthrex double syringe PRP system, Arthrex Medizinische Instrumente GmbH) used previously in other studies.[138,156,157] One syringe of 15 mL of autologous blood was collected from the cubital vein at inclusion and 6 weeks later. After blood collection, the syringe was centrifuged for 5

minutes and the injection was administered within 30 minutes after venipuncture to prevent blood clot formation. No additional substances (calcium, thrombin, or citrate) were added to the PRP solution. For each procedure, 2 mL of PRP or placebo was injected into the affected ankle joint under ultrasonography guidance using sterile technique. The anteromedial needle placement was located medially from the tendon of the tibialis anterior, lateral to the medial malleolus, and at the level of the ankle joint line. The anterolateral needle placement was located just lateral to the peroneus tertius tendon, medial to the lateral malleolus, and at the level of the ankle joint line. Local anesthetic was not used. After the injection, patients were advised to avoid heavy or repetitive stress to the ankle joint for 48 hours. Patients were instructed to avoid co-interventions and nonsteroidal anti-inflammatory drugs (NSAIDs) 24 hours prior to the intervention and, if possible, up to 1 year after the first injection. Both PRP and NSAIDs potentially affect the inflammatory cascade and may interact with and reduce the efficacy of PRP.[152] Throughout the study, co-interventions, such as NSAIDs or intra-articular injections, used by patients were registered. All participants received lifestyle and exercise counseling for osteoarthritis at enrollment, consistent with standard care for patients not undergoing surgical treatment (Supplement 2).

Outcomes

The primary outcome was the American Orthopaedic Foot and Ankle Society (AOFAS) score over 26 weeks of follow-up.[52] The AOFAS is a validated scale for ankle osteoarthritis (range, 0-100 points; higher scores indicate less pain and better function) that measures 3 subdomains (pain [40 points; 1 item], function [50 points; 7 items], and alignment [10 points; 1 item]) totaling 9 items.[100,106] The AOFAS is translated and validated in Dutch. The AOFAS was administered at baseline, 6-week follow-up, and 26-week follow-up by the coordinating research physician, who traveled to all sites for all patients. Secondary outcome measures were assessed at baseline and at 6-, 12-, and 26-week follow-up. Secondary outcomes were total AOFAS score at 6 weeks (other time points than the primary outcome)[106]; the AOFAS pain subscale score (range, 0-40 points; lower scores indicate more pain; minimal clinically important difference [MCID] unknown for ankle osteoarthritis)[106]; the Foot and Ankle Outcome Score (5 scales: pain [MCID, 15], symptoms [MCID, 7], quality of life [MCID, 18], activity of daily living [MCID, 23], and sport and recreation [MCID, 21]; all scales range from 0 to 100 points; higher scores indicate fewer symptoms)[158]; the Ankle Osteoarthritis Scale, measuring pain and disability (range, 0-100 points; higher scores indicate more symptoms; MCID, 28 points)[100,158,159]; pain during activities of daily living, measured on a visual analog scale (range, 0-100; higher scores indicate more pain; MCID unknown for ankle osteoarthritis)[160]; the Ankle Activity Score (scored according to a chart based on the performable activity level; range, 0-10 points; higher scores indicate higher ankle

stress activities; MCID unknown for ankle osteoarthritis)[161]; self-reported patient satisfaction (4 categories: excellent, good, fair, poor); the 36-Item Short Form Health Survey (measuring health-related quality of life; range, 0-100 points; higher scores indicate better quality of life; MCID unknown for ankle osteoarthritis)[100]; the Global Attainment Scaling (based on achievement related to predetermined goals in agreement with the patient; higher scores indicate more achievement; score of −2 to 3 indicate decline from baseline; MCID unknown for ankle osteoarthritis)[162]; and the 3-Level EuroQol 5-Dimension tool (measuring the generic quality of life across 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression expressed using a summary index of 0-1, with 0 indicating death and 1 indicating full health, and a health visual analog scale ranging from 0 to 100, with 0 indicating the worst health imaginable and 100 indicating the best; MCID unknown for ankle osteoarthritis).[163] All adverse events reported spontaneously by the patient or observed by the investigator or their staff were recorded.

Sample Size

The study was designed to have statistical power to detect a MCID of 12 points on the primary outcome of AOFAS score (range, 0-100) over 26 weeks.[139,147,148] There is no official agreement on the MCID for the AOFAS score regarding ankle osteoarthritis. In knee and hip osteoarthritis with comparable disease specific patient-reported outcome measures, a 10% to 15% change of the used scale was reported as minimal clinically important difference.[139,147,148] Our predefined MCID of 12% is located within this range.[139,147,148]

With a 2-sided significance level of 5%, 90% power, a dropout rate of 10%, and an expected SD of 16.3, a total of 50 patients per group were needed (100 in total).[52]

Statistical Analysis

To test for the effect of treatment on the between-group difference in the primary outcome, we used a general linear model for repeated measures. Changes from baseline to all follow-up time points were included in the model. Adjustments were made for those baseline variables that were associated with the primary outcome, with $P < .10$, using a multivariable analysis (general linear model repeated measures) with stepwise backward elimination. To test for the effect of treatment on between-group differences in the secondary outcomes, we used a general linear model for repeated measures. Changes from baseline to all follow-up time points were included in the model.

Patients were analyzed according to their randomization group. The efficacy results that include patients whose participation was discontinued due to the COVID-19 lockdown were analyzed in a sensitivity analysis.

For missing data, single imputation by last observation carried forward was planned if missing data occurred within 10 weeks of the last observation. Multiple imputation was planned if there were more than 10% missing items on a scale. Little's missing completely at random test was used to allow an assumption that the missing data were missing at random. A sensitivity analysis was planned if more than 5% of data were missing.
The data were interpreted according to a blinded data interpretation plan.[146] The principal investigator, coordinating research physician, and co-investigators interpreted the blinded statistical results until a consensus was reached (Supplement 2). Patients (none of whom were randomized into the trial) attended this meeting and were given opportunity to interpret the results from a patient perspective. Once study investigators and patients agreed on result interpretation, an independent investigator assessed interpretation of the blinded results.[146] Following the written interpretation of the independent investigator, data were unblinded and no changes were made to the interpretation (Supplement 2). Statistical analyses were performed using IBM SPSS, version 26, for Windows. A 2-sided $P \leq .05$ was considered statistically significant. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

Post Hoc Analysis

To test the robustness of study findings, we performed a post hoc mixed-effects model analysis for the primary and secondary outcomes adjusting for the enrolling centers (as random effects) to account for biases introduced by greater similarities of patients within sites than among sites.

RESULTS

Enrolment began August 24, 2018, and the last patient completed the 26-week follow-up on December 3, 2020. In total, 320 patients were assessed for eligibility, of whom 100 (31%) were enrolled in the trial. The initial protocol included randomization of 100 patients (49 in the PRP group and 51 in the placebo group). Due to the COVID-19 lockdown, 12 participants could not receive their planned second injection and were excluded from the trial, and were replaced by 12 new randomized

participants. A total of 21 additional patients were evaluated to identify the 12 (57%) who were randomized in the trial to replace the 12 participants who discontinued during the COVID-19 lockdown. Of the 100 included participants, 48 were randomized to receive PRP and 52 were randomized to receive placebo (Figure 1). There were no missing data for the primary outcome. Two patients did not complete the secondary outcome questionnaires at 26 weeks. Baseline characteristics are presented in Table 1. The study population had a mean (SD) age of 55.6 (13.8) years, 45 participants were women (45%), and the population had a mean (SD) body mass index of 26.7 (3.8).

Primary Outcome

The mean (SD) baseline AOFAS scores were 63 (13) in the PRP group and 64 (16) in the placebo group. Between baseline and 26-week follow-up, the mean AOFAS score improved by 10 points (95% CI, 6-14) in the PRP group compared with 11 points (95% CI, 7-15) in the placebo group (Table 2; Figure 2 and Figure 3). The following 2 baseline variables were associated with the primary outcome, with *P* <.10: duration of symptoms of ankle osteoarthritis (in years) and radiological talar tilt (in degrees) (eTable 16 in Supplement 2). The adjusted between-group difference of PRP vs placebo for AOFAS improvement over 26 weeks was −1 point ([95% CI, –6 to 3]; *P* = .56). The unadjusted between-group difference of the primary outcome is presented in Supplement 2. The sensitivity analysis of all 112 randomized patients showed an adjusted between-group difference of PRP vs placebo for AOFAS improvement at 26 weeks of −2 points ([95% CI, –8 to 3]; *P* = .40) (Supplement 1 and eTable 3 in Supplement 2). In a post hoc sensitivity analysis, there was no statistically significant between-group difference of PRP vs placebo for AOFAS change over 26 weeks (–2 points [95% CI, –5 to 1]; *P* = .16) (eTable 4 in Supplement 2).

Secondary Outcomes

No statistically significant between-group differences were found for any secondary outcomes at 6, 12, or 26 weeks (Figure 4 and eTable 4-13 in Supplement 2). No statistically significant between-group differences were found in the post hoc sensitivity analysis for any secondary outcomes at 6, 12, or 26 weeks (eTables 4-13 and eFigures 1-3 in Supplement 2).

Adverse Events

One serious adverse event was reported and deemed unrelated to the injection intervention. It consisted of a transient ischemic attack in the placebo-group three weeks after the first injection. No other patients reported any symptoms of infection or intra-articular hematoma caused by the injection of PRP or saline. There were 13 other adverse events in the PRP group and 8 in the placebo group (eTable 15 in Supplement 2).

Success of Blinding

After the first (baseline) injection 33 patients (69%) in the PRP group and 36 (69%) in the placebo group thought they had received the PRP injection. After the second injection at 6 weeks, 29 (60%) of the PRP group and 36 (69%) of the placebo group thought they had received the PRP injection.

Table 1. Baseline Characteristics of the study population

	No. (%)	
	PRP-group (n =48)	Placebo-group (n =52)
Male, gender, N (%)	26 (54%)	29 (56%)
Female gender, N (%)	22 (46%)	23 (44%)
Age in years, Mean (SD)	54.8 (13.3)	56.4 (14.4)
Weight in kg, Mean (SD)	86.5 (15.3)	82.6 (14.4)
Height in meters, Mean (SD)	1.77 (0.09)	1.78 (0.10)
BMI in kg/m^2, Mean (SD)	27.5 (4.2)	26.0 (3.3)
Laterality, Left (%)	25 (52%)	27 (52%)
Duration of symptoms of ankle OA in years, Median (IQR)	5 (2 to 8)	8 (3 to 14)
Frequency of sports, N (%)		
< 1 time per week	19 (40%)	25 (48%)
1-2 times per week	21 (44)	16 (31%)
3-4 times per week	6 (13%)	6 (12%)
>5 times per week	2 (4%)	5 (10%)
Recreational exercise (not competitive)	48 (100%)	52 (100%)
Previously sustained ankle trauma	47 (98%)	52 (100%)
Anterior drawer test present, N (%)	14 (29%)	10 (19%)
Ankle ROM in degrees, Median (IQR)	55° (46° to 62°)	55° (41° to 65°)
Weighted Radiographs, N (%)	39 (81%)	38 (73%)
Radiological ankle OA grade according to van Dijk[17] classification, N (%)[a]:		
Grade 2 Joint space narrowing with or without osteophytes	29 (60%)	40 (77%)
Grade 3 (Sub)total disappearance or deformation of the joint space	19 (40%)	12 (23%)
Radiological ankle OA grade according to Kellgren Lawrence, N (%)[b]:		
Grade 3 Moderate diminution of joint space	29 (60%)	40 (77%)
Grade 4 Joint space greatly impaired, subchondral sclerosis	19 (40%)	12 (23%)
Radiological ankle OA grade according to Takakura, N (%)[c]:		
Stage 1 Signs of subchondral sclerosis or osteophyte formation	24 (50%)	31 (60%)
Stage 2 Tibiotalar tilt with varus alignment, no subchondral bone contact	6 (13%)	10 (19%)
Stage 3 Tibiotalar tilt with varus alignment, subchondral bone contact	9 (19%)	6 (12%)
Stage 4 Global tibiotalar joint space narrowing with complete contact	9 (19%)	5 (10%)
Radiological medial distal tibial angle, in degrees, Median (IQR)[d]	90.0° (87.5° to 92.0)	90.6° (87.5° to 91.6)
Radiological talar tilt, in degrees, Median (IQR)[e]	-0.25° (-3.4° to 2.0°)	-0.15° (-1.9° to 1.7°)
Baseline AOFAS, Mean (SD)[f]	63 (13)	64 (16)

Abbreviations: PRP: Platelet-rich plasma; n: number; SD: Standard Deviation; BMI: Body Mass Index; OA: Osteoarthritis Ankle; IQR: Interquartile range; ROM: Ankle Range of motion, this is plantar flexion + dorsal flexion; AOFAS: American Orthopaedic Foot and Ankle Society;

[a] *Van Dijk classification: 0 Normal joint or subchondral sclerosis; 1 Osteophytes without joint space narrowing; 2 Joint space narrowing with or without osteophytes; 3 (Sub)total disappearance or deformation of the joint space*
[b] *Takakura classification: 0 No tibiotalar tilt, no signs of arthritis; 1 No tibiotalar tilt, signs of subchondral sclerosis or osteophyte formation; 2 Tibiotalar tilt with varus alignment, no subchondral bone contact; 3 Tibiotalar tilt with varus alignment, subchondral bone contact; 4 Global tibiotalar joint space narrowing with complete contact*
[c] *Kellgrenn-Lawrence classification: 1 Minute osteophyte of doubtful significance; 2 Definite osteophyte, joint space unimpaired; 3 Moderate diminution of joint space; 4 Joint space greatly impaired, subchondral sclerosis*
[d] *The medial distal tibial angle: the angle between the centre of the tibia shaft and the tibia plafond; <90° is a valgus angle, >90° is a varus angle.*
[e] *Radiological talar tilt = (tibio-talar angle) – (medial distal tibial angle). The tibio-talar angle: the angle between the centre of the tibia shaft and the talar dome. All negative values illustrate a varus alignment, positive values illustrate a valgus alignment.*
[f] *AOFAS: American Orthopaedic Foot and Ankle Society score; range 0-100 points; higher scores indicate less pain and better function; No clinical cut-off scores are available, but as an indication, end-stage ankle OA patients undergoing an ankle arthrodesis or arthroplasty were reported to have a mean AOFAS score of 36 - 43.*

Table 2. Primary and secondary outcomes over 26 Weeks

	PRP-group (N=48)	Placebo-group (N=52)	Mean Difference (95% CI) over 26 weeks[a]
Primary outcome over 26 weeks			
AOFAS, Mean (SD) [n][b]	73 (14) [48]	75 (14) [52]	-1 (-6 to 3)
Secondary outcome over 26 weeks[c]			
AOFAS-pain subscale, Median (IQR) [n][d]	30 (20 to 30)	30 (20 to 30)	0 (-2 to 2)
Foot and Ankle Outcome Score[e]			
Pain, Median (IQR) [n]	67 (52 to 78) [46]	71 (50 to 88)	-2 (-8 to 4)
Symptoms, Mean (SD) [n]	54 (18) [46]	55 (21)	-2 (-8 to 4)
Activity of Daily Living, Median (IQR) [n]	82 (69 to 93) [46]	84 (71 to 97)	-1 (-7 to 6)
Quality of Life, Median (IQR) [n]	31 (25 to 50) [46]	38 (25 to 55)	-1 (-7 to 6)
Sport and Recreation, Median (IQR) [n]	40 (20 to 51) [46]	40 (25 to 60)	-1 (-9 to 8)
AOS, Median (IQR) [n][f]	26 (12 to 36) [46]	23 (8 to 41)	1 (-6 to 8)
VAS, Median (IQR) [n][g]	40 (24 to 50) [46]	44 (19 to 65)	3 (-5 to 10)
AAS, Median (IQR) [n][h]	4.0 (2.8 to 5.0) [46]	4.0 (1.3 to 5.0)	0.1 (-0.7 to 0.9)
SF-36, Mean (SD) [n][i]			
Mental Component Summary score NL	42 (6) [46]	43 (6)	0 (-2 to 2)
Physical Component Summary score NL	47 (7) [46]	47 (8)	-1 (-3 to 2)
GAS, Median (IQR) [n][j]	-1 (-2 to 0) [46]	-1 (-2 to 0)	0.0 (-0.3 to 0.3)
EQ-5D-3L, Median (IQR) [n][k]			
EQ-5D-3L summary index	0.8 (0.7 to 0.8) [46]	0.8 (0.8 to 0.8)	0 (-0.1 to 0.0)
EQ-5D-3L Health Visual Analogue Scale	80 (68 to 89) [46]	80 (71 to 86)	-3 (-9 to 2)

Abbreviations: PRP: Platelet Rich Plasma; CI: Confidence Interval; SD: Standard Deviation; n: number; IQR: Interquartile Range; NL: Adjusted for the Dutch population.

[a] *General linear repeated measures model including all time-points up to 26 weeks.*

[b] *AOFAS: American Orthopaedic Foot and Ankle Society score; range 0-100 points; higher scores indicate less pain and better function; Adjusted for duration of clinical symptoms of ankle osteoarthritis and radiological talar tilt. See footnote of table 1 for what this score may look like clinically.*

[c] *Secondary outcomes are unadjusted.*

[d] *AOFAS pain subscale; range 0-40 points; with higher scores indicating more pain. Unfortunately no clinical cut-off or indication is available.*

[e] *FAOS: Foot and Ankle Outcome Score; consists of 5 scales (pain, symptoms, quality of life, activity of daily living and sport and recreation); range 0-100 points; higher scores indicate less pain and better function and quality of life. No clinical cut-off scores are available, but as an indication, end-stage ankle OA patients undergoing an ankle arthrodesis or arthroplasty were reported to have a pre-operative mean score of 26 (pain), 32 (symptoms), 37 (quality of life), 17 (activity of daily living) and 13 points (sport and recreation).*

[f] *AOS: Ankle Osteoarthritis Score measures pain and disability; range 0-100 points; higher scores indicate more symptoms. No clinical cut-off scores are available, but as an indication, end-stage ankle OA patients undergoing an ankle arthrodesis or arthroplasty were reported to have a pre-operative mean score of 52 – 58 points.*

[g] *VAS: pain during activity of daily living on a Visual Analogue Scale; range 0-100 mm; higher scores indicate more pain. No clinical cut-off scores are available, but as an indication, end-stage ankle OA patients undergoing an ankle arthrodesis or arthroplasty were reported to have a pre-operative mean score of 51 – 60 points.*

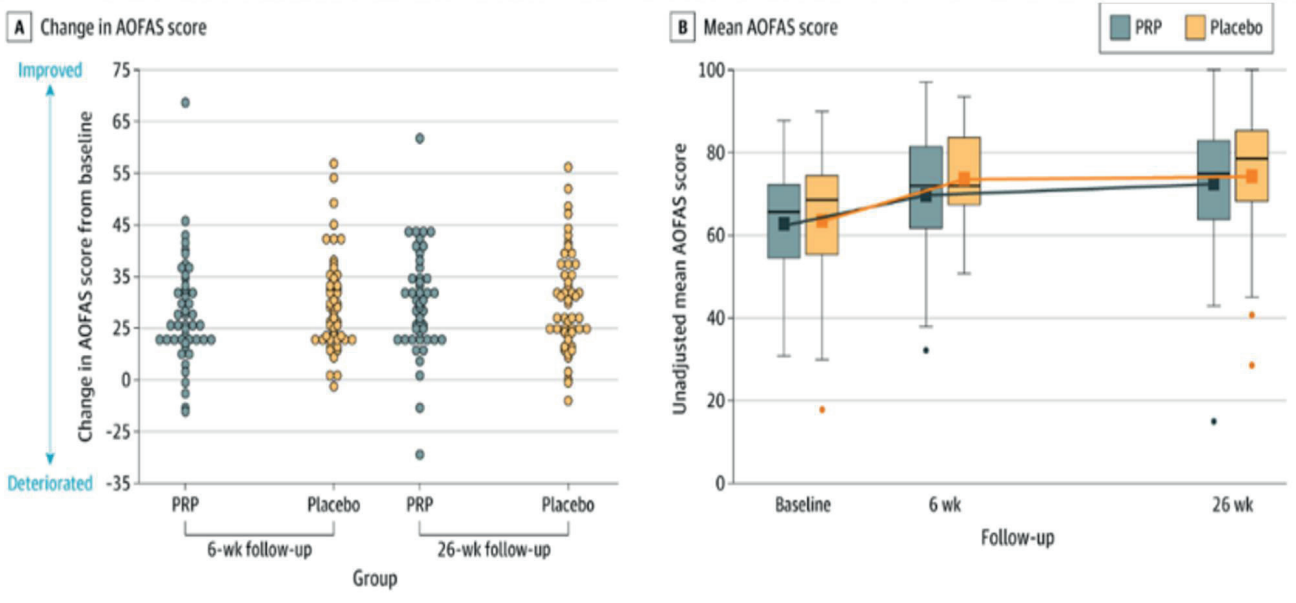
[h] *AAS: Ankle Activity Score; measures performable activity level; range 0-10 points; higher scores indicate higher ankle-stress activities. Unfortunately no clinical cut-off or indication is available.*

[i] *SF-36: Short Form-36 Health Survey, measures health-related quality of life measured using 8 subscales which can be summarized into a Mental and a Physical Component Summary score; range 0-100 points; higher scores indicate higher quality of life. No clinical cut-off scores are available, but as an indication, surgically treated end-stage ankle OA patients were reported to have a pre-operative mean scores of 30 - 36 (PCS) and 54 – 56 (MCS) points. The norm for the general population is 50 points.*

[j] *GAS: Global Attainment Scaling, based on achievement related to predetermined goals in agreement with the patient; range -2 to 3; lower scores indicating decline from baseline, higher scores indicating achieving more than the predefined goals. Unfortunately no clinical cut-off or indication is available.*

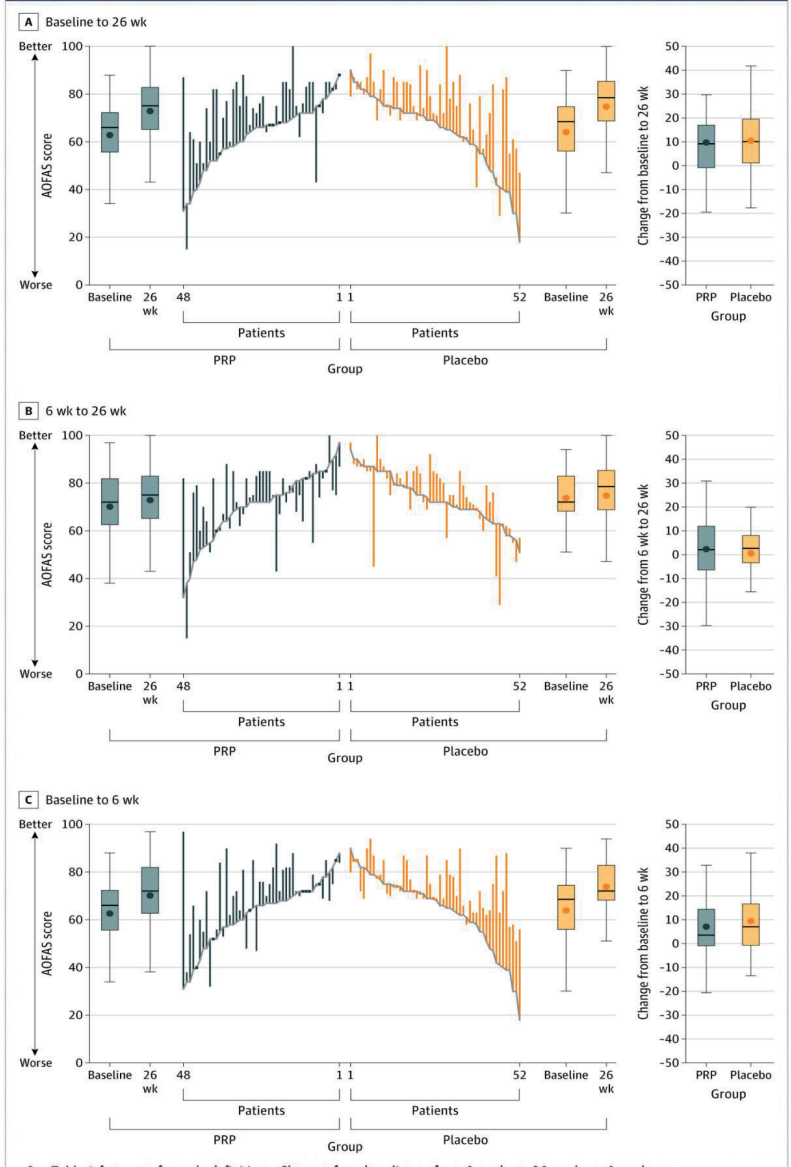
[k] *EQ-5D-3L: EuroQol-5 dimensions-3 levels, measuring the generic quality of life across 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) presented using a summary index (0-1, indicating death and full health, respectively) and a health VAS (0-100 indicating worst health imaginable to best health imaginable). Unfortunately no clinical cut-off or indication is available for the EQ-5D-3L summary index. For the EQ-5D-3L VAS, 64 points has been reported for surgically treated end-stage ankle OA patients.*

Figure 2. Change in AOFAS score and mean AOFAS score over follow-up

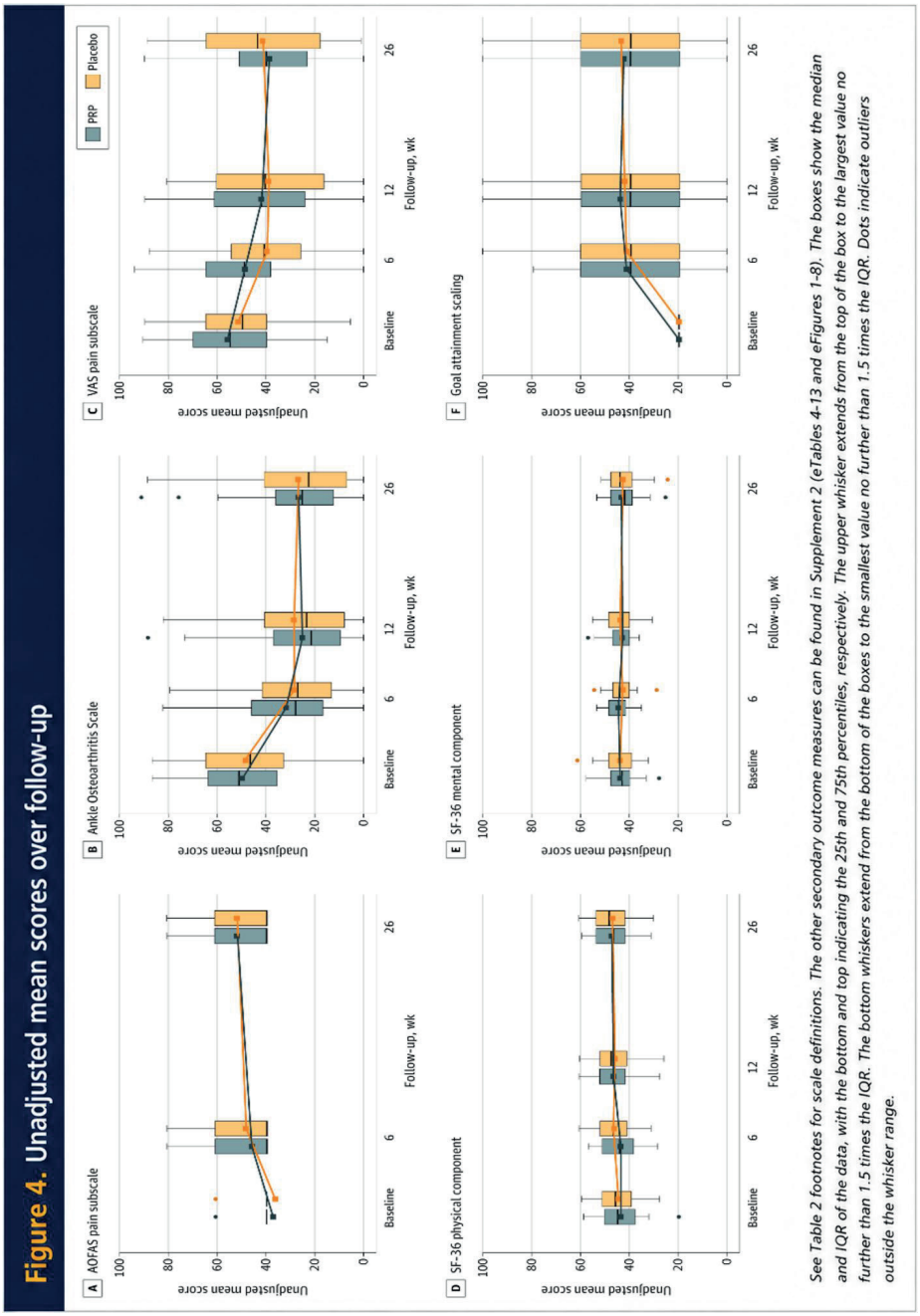


See Table 1 footnotes for scale definitions. *The mean difference* between the PRP and the placebo group over 26 weeks was −1 (95% *CI*, −6 to 3). *The boxes show the* median and IQR, with the bottom and top indicating the 25th and 75th percentiles, respectively. The upper whisker extends from the top of the box to the *largest value nc further than 1.5* times the *IQR. The bottom whiskers extend from the bottom of the boxes to the smallest value no further than 1.5 times the IQR. Dots indicate outliers outside the whisker range.*

Figure 3. Change in AOFAS score over time and comparison between groups



See Table 1 footnotes for scale definitions. Changes from baseline or from 6 weeks to 26 weeks or 6 weeks are represented by the vertical lines. Upward and downward lines indicate improvement and deterioration, respectively. The horizontal lines in the boxplots from bottom to top show the 25th, 50th (median), and 75th percentiles. The dot in the boxplot indicates the mean. The whiskers indicate the highest and lowest values.



See Table 2 footnotes for scale definitions. The other secondary outcome measures can be found in Supplement 2 (eTables 4-13 and eFigures 1-8). The boxes show the median and IQR of the data, with the bottom and top indicating the 25th and 75th percentiles, respectively. The upper whisker extends from the top of the box to the largest value no further than 1.5 times the IQR. The bottom whiskers extend from the bottom of the boxes to the smallest value no further than 1.5 times the IQR. Dots indicate outliers outside the whisker range.

DISCUSSION

In this double-blind, randomized, multicentered, placebo-controlled clinical trial involving patients with ankle (tibiotalar) osteoarthritis, intra-articular PRP injections, compared with saline placebo injection, did not significantly improve the primary outcome that assessed pain, function, and alignment over 26 weeks or any other secondary outcome measures. The likelihood of clinically relevant benefit is small, because the minimum clinically important difference was outside the 95% CI of the primary outcome.

Previous evidence for PRP injections in ankle osteoarthritis was limited to 4 small case series with methodological flaws.[132,154] Two retrospective case series of 5 and 20 patients reported an improvement of 21% and 67% on the VAS. Two prospective case series, of 20 and 44 patients, reported an improvement of 29% and 59% on the VAS at 6 months.[132,154]

In knee osteoarthritis, 14 of the 21 randomized clinical trials of PRP showed methodological limitations, including moderate to high risk of bias and small sample sizes.[39] Four of these trials were placebo-controlled, and all reported beneficial results for PRP.[156,164-166] The pooled results in a recent meta-analysis of the total Western Ontario and McMaster Universities Osteoarthritis Index (range, 0-100) of 125 patients show a weighted mean difference for the placebo group of 21 points (95% CI, 15-27), suggesting a clinically relevant benefit.[39] Results reported here for ankle osteoarthritis were not consistent with these potentially beneficial effects in knee osteoarthritis.
The improvement within the placebo (saline) group observed in this study was consistent with other placebo studies.[167,168] Clinical efficacy of saline is unlikely considering the low injection volume (2 mL) and previous sham-controlled studies in knee osteoarthritis that showed no difference between saline joint irrigation (1-10 L) and sham intervention.[169,170]

Strengths of this study included the placebo-controlled double-blind study design, absence of any loss to follow-up for the primary outcome, and performance of all primary outcome measurements by coordinating single research physician. The nationwide recruitment in 6 centers (2 university medical centers, 2 teaching hospitals, 1 general hospital and 1 private specialist clinic) enhances the generalizability of the results.

Limitations

This study has several limitations. First, the generalizability of results to other platelet-rich blood products may be limited. Alternative platelet-rich blood interventions differ in dose, timing, and number of injections and in composition of platelets and leukocytes. However, the product administered in this trial was also used as in several other osteoarthritis trials and the concentration of the platelet rich plasma was comparable to that used in these prior trials.[144,156,171] Second, analysis of the composition of PRP in this study was not conducted.[52] However, the composition of this specific system has been analyzed previously,[172] including in a previous randomized clinical trial.[138] PRP analysis is typically not performed in clinical practice prior to injection. Third, magnetic resonance imaging, sensitive for detecting potential structural cartilage changes and degree of inflammation in joints was not a secondary outcome due to financial constraints. Fourth, there was no control for differences in physical therapy between the two groups.

CONCLUSIONS

Among patients with ankle osteoarthritis, intra-articular platelet-rich plasma injections, compared with placebo injections, did not significantly improve ankle symptoms and function over 26 weeks. The results of this study do not support the use of PRP injections for ankle osteoarthritis.

CHAPTER

7

Platelet-Rich Plasma Injections for the Treatment of Ankle Osteoarthritis

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Abstract

Background – Ankle osteoarthritis is debilitating and usually affects relatively young people, often as a result of previous ankle traumas, frequently occurring in sports. Platelet-rich plasma (PRP) injections for ankle osteoarthritis have shown no evidence of benefit over the course of 26 weeks. Previous studies on PRP for knee osteoarthritis showed that clinically significant improvements with PRP occurred between 6 to 12 months in the absence of initial benefit. No studies have evaluated the effect of PRP from 6 to 12 months in ankle osteoarthritis.

Purpose – To assess the efficacy of PRP injections in ankle osteoarthritis over the course of 52 weeks.

Study Design – Randomized controlled trial; Level of evidence, 1.

Methods – In this 52-week follow-up trial, 100 patients with ankle osteoarthritis were randomized to a PRP group or placebo (saline) group. Patients received 2 intra-articular talocrural injections: at inclusion and after 6 weeks. Patient-reported outcome measures were used to assess pain, function, quality of life, and indirect costs over 52 weeks.

Results – Two patients (2%) were lost to follow-up. The adjusted between-group difference for the patient-reported American Orthopaedic Foot & Ankle Society score over 52 weeks was −2 points (95% CI, −5 to 2; P = .31) in favor of the placebo group. No significant between-group differences were observed for any of the secondary outcome measures.

Conclusion – For patients with ankle osteoarthritis, PRP injections did not improve ankle symptoms and function over 52 weeks compared with placebo injections.

Registration – NTR7261 (Netherlands Trial Register).

Ankle osteoarthritis severely affects quality of life and is secondary to a previously sustained ankle injury in 70% to 78% of cases. Patients who have ankle osteoarthritis are younger than patients with knee or hip osteoarthritis, who mostly have primary osteoarthritis.[9,10,12,13,173] Treatment options are limited; the current standard for end-stage ankle osteoarthritis is arthrodesis, which can result in significant functional limitations.[174]

Regenerative medicine, such as platelet-rich plasma (PRP), is increasingly popular for the treatment of osteoarthritis. The high concentration of platelets in PRP is hypothesized to modulate the intra-articular environment due to the release of growth factors, subsequently mediating a potential anti-inflammatory, anabolic, and analgesic effect.[43,152] The global market for PRP is rapidly growing and is estimated to be 1.2 billion Euros by 2028.[142]

A systematic review assessing the efficacy of PRP for knee osteoarthritis reported significant improvements in pain, function, and stiffness in favor of PRP at 12 months.[39] A randomized, double-blind, placebo-controlled trial on the effectiveness of blood products for knee osteoarthritis showed a beneficial effect between 6 and 12 months, despite no between-group differences at earlier follow-ups.[175] In our previous randomized controlled trial of patients with ankle osteoarthritis, no between-group difference was found between the PRP and the placebo group over 26 weeks.[110] No randomized controlled trials have assessed the efficacy of PRP in the treatment of ankle osteoarthritis over a long-term period beyond 26 weeks of follow-up.

The primary aim of this study was to conduct a 1-year follow-up of a randomized controlled trial on the efficacy of PRP on function and pain in the treatment of ankle osteoarthritis. Secondary outcome measures included multiple patient-reported outcome measures assessing pain, function, quality of life, and indirect costs.

METHODS

Trial Design

This was a 1-year follow-up study of a multicenter, stratified, block-randomized, double-blind, placebo-controlled trial performed in 6 centers (2 university medical centers, 2 teaching hospitals, 1 general hospital, and 1 private specialist clinic) in the Netherlands. The study protocol has been previously published.[52] The study was registered at Trialregister.nl (NTR7261) and was approved by

the local medical ethics review committee of the Academic Medical Center (ABR 2018-042; July 23, 2018; Amsterdam, the Netherlands).

The protocol was amended and approved by the local medical ethics review committee on May 5, 2020, after the beginning of enrollment but before any results were available. Due to the first lockdown of the COVID-19 pandemic as part of the institutional and national COVID-19–related clinical research (safety) regulations, 12 patients were unable to receive their second injections. Based on the recommendations for studies affected by the COVID-19 pandemic, the participation of these 12 patients in the Platelet-Rich plasma Injection Management for Ankle study was discontinued, and 12 new patients were included (COVID-19 lockdown–related protocol amendment).[155] Because of this COVID-19 amendment, the intention-to-treat analysis was modified to an analysis of the 100 patients who received 2 injections. The study was monitored by the Clinical Research Unit of the Amsterdam UMC.

Patients

Patients with ankle osteoarthritis were informed of the study at orthopaedic and sports medicine outpatient clinics of the 6 centers. Patients were considered eligible if they had ankle pain severity on a visual analog scale (VAS) ≥40 mm (0-100 mm) during daily activities and had radiographs (anteroposterior and lateral view) indicating grade ≥2 talocrural osteoarthritis on the van Dijk classification.[54] Patients were excluded if they had received injection therapy for ankle osteoarthritis in the previous 6 months, declined either therapy, had signs of concomitant osteoarthritis of ≥1 other major joint of the lower extremities that impaired their daily activity level, or had undergone a previous ankle operation for osteoarthritis or osteochondral defects <1 year before randomization (not including surgery for an ankle fracture in the past). Written informed consent was obtained from all patients.

Randomization and Blinding

We randomized 100 patients to 2 treatment groups: intra-articular injection of PRP or placebo (saline). A good clinical practice–approved data management system (Castor EDC) was used to perform a computer-generated block randomization scheme with patients stratified to center with a variable block size of 2, 4, and 6 in a 1:1 ratio. Possibly eligible patients were indicated by the treating physicians. The coordinating research physician (L.D.A.P.) assessed fulfillment of eligibility criteria, obtained written informed consent, and enrolled patients in the study. The coordinating research physician (L.D.A.P.) initiated randomization in Castor EDC but remained blinded to the allocated intervention. To ensure blinding of the intervention and concealment of allocation, the coordinating

research physician (L.D.A.P.) prepared a syringe with PRP and a syringe with placebo (isotonic saline: 0.9% sodium chloride). Only the independent research assistants had access to the randomization result in Castor EDC, and they blinded the syringe with the allocated intervention using a specially manufactured covering sheath, ensuring concealment of the content of the syringe. After the intra-articular injection, the syringe covered by the sheath (containing the remnants of either PRP or saline) was handed back to the independent research assistant, who disposed of the syringe, therefore ensuring blinding of the patient, treating physician, and coordinating researcher (L.D.A.P.). The patients and treating physicians remained blinded to the allocation of the intervention and to the content of the syringe until 12 months after the first injection of the last patient. Although the coordinating researcher and other project members were unblinded at group level for the 26-week interpretation, only the coordinating researcher (L.D.A.P.) was unblinded at the individual level and had access to the individual patient-allocated intervention. This ensured that all study team members, except the coordinating researcher (L.D.A.P.), remained blinded at group level for the 52-week follow-up.

For the 52-week results, the unblinded coordinating researcher (L.D.A.P.) refrained from analyzing the data. A study team member (still blinded at individual level) performed the analysis at group level (G.R.).

Interventions

On inclusion, patients were given advice on the benefits of exercise and weight loss. Specifically, patients were advised to perform activities such as walking, cycling, and swimming with steady weightbearing on the ankle (no sudden impact) for ≥30 minutes each day. Patients received 2 intra-articular talocrural injections: at inclusion and after 6 weeks. The PRP was prepared using a widely used and commercially available system (Arthrex double-syringe PRP system; Arthrex Medizinische Instrumente GmbH). One syringe of 15 mL of autologous blood was collected twice from the cubital vein: at inclusion and after 6 weeks. After blood collection, the syringe underwent 5 minutes of centrifugation, and the injection was given within 30 minutes after venipuncture to prevent blood clot formation. No additional substances (calcium, thrombin, or citrate) were added to the PRP solution. For each procedure, 2 mL of PRP or placebo was injected into the affected ankle joint under ultrasound guidance using a sterile technique. After the intervention, patients were advised to avoid heavy or repetitive stress to the ankle joint for 48 hours. Patients were instructed to avoid the use of co-interventions. Specifically, patients were advised to avoid using nonsteroidal anti-inflammatory drugs (NSAIDs) 24 hours before the intervention and if possible up to a year after the first injection, given the effect of NSAIDs on platelet function. Both PRP and NSAIDs potentially affect the inflammatory cascade, with a possible interaction and reduced PRP efficacy as a result.[152]

Outcomes

The primary outcome over 26 weeks was published on October 26, 2021.[46] Questionnaires were sent at baseline and 6, 12, 26, 39, and 52 weeks and were managed and distributed digitally using the Castor EDC system.

Outcome Measures

The primary outcome measure was the patient-reported portion of the American Orthopaedic Foot & Ankle Society (AOFAS) score over 52 weeks.[106,109] By using a completely patient-reported AOFAS score, we could measure pain and function at 52 weeks without the need for an extra patient visit normally required for the physician-determined part of the original patient-reported and physician-determined AOFAS score. The patient-reported version of the AOFAS was administered at baseline and 6, 12, 26, and 52 weeks and was evaluated for measurement properties on the time points it overlapped with the original patient-reported and physician-determined AOFAS score and other secondary outcome measures. The patient-reported AOFAS had sufficient construct validity, internal consistency (Cronbach's α, 0.7; n = 112), test-retest reliability, and responsiveness.[176]

The following secondary outcomes were assessed. The Foot and Ankle Outcome Score entails 5 scales: Pain (minimal clinically important difference [MCID], 15 points), Symptoms (MCID, 7 points), Quality of Life (MCID, 18 points), Activities of Daily Living (MCID, 23 points), and Sport and Recreation (MCID, 21 points). All scales range from 0 to 100 points, where higher scores indicate fewer symptoms.[158,177] The Ankle Osteoarthritis Score measures pain and disability on a scale of 0 to 100 points, where higher scores indicate more symptoms (MCID, 28 points).[100] Pain during activities of daily living was measured on a VAS of 0 to 100 mm, where higher scores indicate more pain (MCID unknown for ankle osteoarthritis). The Ankle Activity Score is determined according to a chart based on the performable activity level and is scored from 0 to 10 points, where higher scores indicate higher ankle-stress activities (MCID unknown for ankle osteoarthritis).[161] Subjective patient satisfaction was indicated by 4 categories (excellent, good, fair, and poor). The 36-Item Short Form Health Survey measures health-related quality of life on a scale from 0 to 100 points, where higher scores indicate higher quality of life (MCID unknown for ankle osteoarthritis).[53,100] The Global Attainment Scaling is based on achievement related to predetermined goals in agreement with the patient and is scored from −2 to 3, where lower scores indicate decline from baseline and higher scores indicate achieving more than the predefined goals (MCID unknown for ankle osteoarthritis).[162] The EuroQol–5 dimensions–3 levels measures the generic quality of life across 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It is expressed using a summary index of 0 to 1, indicating death and full health, respectively, along with a

health VAS of 0 to 100, indicating worst health imaginable to best health imaginable, respectively (MCID unknown for ankle osteoarthritis).[163]

Indirect costs were assessed over 52 weeks using questionnaires and consisted of absenteeism, presenteeism, and productivity loss of unpaid work.[178] Patients were asked about their costs in the previous 28 days, as this was considered a reliable recall period.[179] Because the questionnaire was sent every 3 months, the results were extrapolated over the 3 months by multiplying by 3 as per instructions of the questionnaire protocol.[178] Absenteeism indicates the loss of production attributable to absence from paid work due to mental or physical health. It was calculated by multiplying the extrapolation factor (3) by the standard production value (€34.75)[180] by the length of the participant's working day (in hours) and the total number of days the participant was absent from work. Presenteeism indicates reduced production or efficiency of paid work attributable to mental or physical health. It was calculated by multiplying the extrapolation factor (3) by the standard production value (€34.75)[180] by the length of the participant's working day (in hours) by the number of days participants were suboptimal at work and by their average daily efficiency loss. Productivity loss of unpaid work included (partial) inability to perform household chores or charity work. This was determined by multiplying the extrapolation factor (3) by the standard production value of unpaid work (€14)[180] by the number of days and average number of hours that productivity loss of unpaid work occurred. We present costs (in Euros and US dollars) as mean with standard deviation in order to include the weight of the outliers on both sides. A median value is also provided to allow better understanding of the data.

No data concerning adverse events were collected at 52 weeks. All adverse events up to 26 weeks are presented in the Appendix Table A13 (available in the online version of this article).

Statistical Methods

To test for the effect of treatment on the between-group difference, we used a mixed-model analysis and corrected for enrolling center as a random effect. Changes from baseline to all follow-up time points were included in the model, thereby allowing us to analyze change over a 52-week period. The patient-reported AOFAS score was adjusted for those baseline variables that influenced it with $P < .10$. Efficacy analyses were conducted in the modified intention-to-treat population in line with the COVID-19 lockdown–related protocol amendment. The analyses included all randomly assigned patients who received PRP or placebo injections. Results and analyses are presented as defined by the version of the Statistical Analysis Plan (Appendix, available online) that was in place when the database was locked. The handling of missing data is specified in our predetermined Statistical

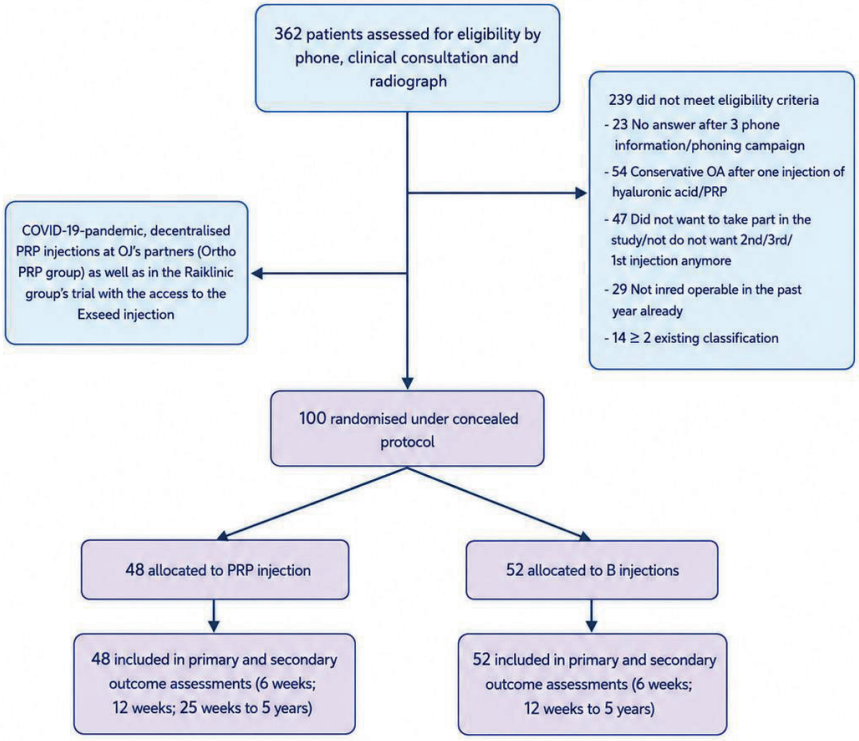
Analysis Plan. After the 52-week follow-up of the last patient in the study, the data were once again cleaned and recoded.

The data were interpreted according to a blinded interpretation plan.[110] The study group members, except for the coordinating researcher, interpreted the blinded statistical results until a consensus was reached. Patients (also active in the design phase, not in the study) interpreted the results from a patient perspective. When the study group members and patients were in agreement, an independent investigator scrutinized the interpretation of the blinded results. The 2 groups were then unblinded, and no changes were made to the interpretation of the results. Thus, study group members were unblinded only after the blinded analysis and interpretation of the 52-week outcome. When designing the study, we estimated that 90 patients were needed to detect a clinically relevant between-group difference for the primary outcome (the AOFAS score over 26 weeks) and anticipated a loss to follow-up of 10%.[52]

RESULTS

Between August 2018 and July 2020, we randomly assigned 100 patients to 1 of 2 groups: the PRP group (n = 48) and the placebo group (n = 52) (Figure 1). All randomized patients received the allocated interventions. The mean age and body mass index were 55.6 ± 13.8 years and 26.7 ± 3.8, respectively. In total, 55 (55%) of the patients were male. Table 1 shows the baseline characteristics.

Figure 1. Participant recruitment, randomization, and follow-up to week 52 (secondary endpoint)



Participant recruitment, randomization, and follow-up to week 52 (secondary endpoint). 1, van Dijk classification using ankle radiograph; OA, normal joint or subchondral sclerosis; 1, osteophytes without joint space narrowing; 2, joint space narrowing with or without osteophytes; 3, (sub)total disappearance or deformation of the joint space. 2 Before each consultation, the questionnaires were checked for completeness. A reminder was sent via email in the event of incompleteness. One patient did not complete the secondary outcome questionnaires at 52 weeks because he thought it was too time-consuming. One patient died from an unrelated disease before 52 weeks. OA, osteoarthritis; PRP, platelet-rich plasma; VAS, visual analogue scale.

Table 1. Baseline Characteristics of the study population

	PRP-group (n =48)	Placebo-group (n =52)
Sex, male, N (%)	26 (54%)	29 (56%)
Age in years, Mean (SD)	54.8 (13.3)	56.4 (14.4)
Weight in kg, Mean (SD)	86.5 (15.3)	82.6 (14.4)
Height in meters, Mean (SD)	1.77 (0.09)	1.78 (0.10)
BMI in kg/m^2, Mean (SD)	27.5 (4.2)	26.0 (3.3)
Laterality, Left (%)	25 (52%)	27 (52%)
Duration of symptoms in years, Median (IQR)	5 (2 to 8)	8 (3 to 14)
Frequency of sports, N (%)		
< 1 time per week	19 (40%)	25 (48%)
1-2 times per week	21 (44%)	16 (31%)
3-4 times per week	6 (13%)	6 (12%)
>5 times per week	2 (4%)	5 (10%)
Level of exercise		
Recreational	48 (100%)	52 (100%)
Competitive/ Professional	0 (0%)	0 (0%)
Previously sustained ankle trauma	47 (98%)	52 (100%)
Anterior drawer test present, N (%)	14 (29%)	10 (19%)
Ankle ROM in degrees, Median (IQR)	55° (46° to 62°)	55° (41° to 65°)
Weighted Radiographs, N (%)[a]	39 (81%)	38 (73%)
Radiological ankle OA grade according to van Dijk[7] classification, N (%)[b]		
Grade 2	29 (60%)	40 (77%)
Grade 3	19 (40%)	12 (23%)
Radiological ankle OA grade according to Kellgren Lawrence, N (%)[c]		
Grade 3	29 (60%)	40 (77%)
Grade 4	19 (40%)	12 (23%)
Radiological ankle OA grade according to Takakura, N (%)[d]		
Stage 1	24 (50%)	31 (60%)
Stage 2	6 (13%)	10 (19%)
Stage 3	9 (19%)	6 (12%)
Stage 4	9 (19%)	5 (10%)
Radiological medial distal tibial angle, in degrees, Median (IQR)[e]	90.0° (87.5° to 92.0)	90.6° (87.5° to 91.6)
Radiological talar tilt, in degrees, Median (IQR)[f]	-0.25° (-3.4° to 2.0°)	-0.15° (-1.9° to 1.7°)
Baseline AOFAS, Mean (SD)[g]	63 (13)	64 (16)

Abbreviations: PRP: Platelet-rich plasma; n: number; SD: Standard Deviation; BMI: Body Mass Index; OA: Osteoarthritis Ankle; IQR: Interquartile range; ROM: Ankle Range of motion, this is plantar flexion + dorsal flexion; AOFAS: American Orthopaedic Foot and Ankle Society**;**

[a] *Weighted radiographs are radiographs taken while the patient is bearing weight on the ankle.*
[b] *Van Dijk classification on ankle x-ray: 0 Normal joint or subchondral sclerosis; 1 Osteophytes without joint space narrowing; 2 Joint space narrowing with or without osteophytes; 3 (Sub)total disappearance or deformation of the joint space*
[c] *Takakura classification: 0 No talocrural tilt, no signs of arthritis; 1 No talocrural tilt, signs of subchondral sclerosis or osteophyte formation; 2 talocrural tilt with varus alignment, no subchondral bone contact; 3 talocrural tilt with varus alignment, subchondral bone contact; 4 Global talocrural joint space narrowing with complete contact*
[d] *Kellgrenn-Lawrence classification: 1 Minute osteophyte of doubtful significance; 2 Definite osteophyte, joint space unimpaired; 3 Moderate diminution of joint space; 4 Joint space greatly impaired, subchondral sclerosis*
[e] *The medial distal tibial angle: the angle between the centre of the tibia shaft and the tibia plafond; <90° is a valgus angle, >90° is a varus angle.*
[f] *Radiological talar tilt = (tibio-talar angle) – (medial distal tibial angle). The tibio-talar angle: the angle between the centre of the tibia shaft and the talar dome. All negative values illustrate a varus alignment, positive values illustrate a valgus alignment.*
[g] *AOFAS: American Orthopaedic Foot and Ankle Society score; range 0-100 points; higher scores indicate less pain and better function;*

Clinical Outcome

For analysis of the patient-reported AOFAS score over 52 weeks, 2 patients were lost to follow-up. One patient died due to a preexisting malignant cancer that had metastasized, and the other patient did not want to complete any more questionnaires. The unadjusted between-group difference for the patient-reported AOFAS score over 52 weeks was 4 points (95% CI, −7 to −1; *P* = .02) in favor of the placebo group. The primary outcome over 52 weeks was adjusted for radiological talar tilt in degrees, duration of symptoms of ankle osteoarthritis in years, ankle range of motion in degrees, body weight in kilograms, and height in meters. The adjusted between-group difference for patient-reported AOFAS scores over 52 weeks was −2 points (95% CI, −5 to 2; *P* = .31) in favor of the placebo group (Table 2 and Figure 2). The individual changes in AOFAS scores from baseline to 52 weeks are presented in Figure 3.

Table 2. Clinical outcomes over 52 Weeks (secondary end-point)

	PRP-group (N=48) Mean (SD)	placebo-group (N=52) Mean (SD)	Mean Difference (95% CI) over 52 weeks[a]
Primary outcome			
Completely patient reported AOFAS score	69 (19)	67 (22)	-2 (-5 to 2)
Secondary outcomes			
Foot and Ankle Outcome Score[b]			
Pain	68 (17)	67 (22)	1 (-2 to 5)
Symptoms	53 (17)	53 (20)	2 (-1 to 5)
Activity of Daily Living	80 (16)	77 (21)	0 (-4 to 3)
Quality of Life	39 (18)	38 (24)	0 (-3 to 3)
Sport and Recreation	42 (26)	38 (28)	-1 (-5 to 3)
AOS[c]	27 (20)	28 (24)	-1 (-4 to 3)
VAS[d]	39 (23)	38 (26)	-3 (-7 to 1)
AAS[e]	4.0 (2.2)	3.6 (2.0)	-0.1 (-0.5 to 0.3)
SF-36[f]			
Mental Component Summary score	44 (5)	42 (6)	0 (-1 to 1)
Physical Component Summary score	45 (8)	47 (9)	1 (0 to 2)
GAS[g]	-0.9 (1.3)	-0.8 (1.3)	0 (-0.2 to 0.2)
EQ-5D-3L[h]			
EQ-5D-3L summary index	0.8 (0.2)	0.8 (0.2)	0 (0.0 to 0.0)
EQ-5D-3L Health Visual Analogue Scale	74 (20)	77 (16)	4 (0 to 7)

Abbreviations: PRP: Platelet Rich Plasma; CI: Confidence Interval; SD: Standard Deviation; n: number; IQR: Interquartile Range; NL: Adjusted for the Dutch population.

[a] Mixed model including all time-points up to 52 weeks adjusted for enrolling centre as random-effect.

[b] FAOS: Foot and Ankle Outcome Score; consists of 5 scales (pain, symptoms, quality of life, activity of daily living and sport and recreation); range 0-100 points; higher scores indicate less pain and better function and quality of life.

[c] AOS: Ankle Osteoarthritis Score measures pain and disability; range 0-100 points; higher scores indicate more symptoms.

[d] VAS: pain during activity of daily living on a Visual Analogue Scale; range 0-100 mm; higher scores indicate more pain.

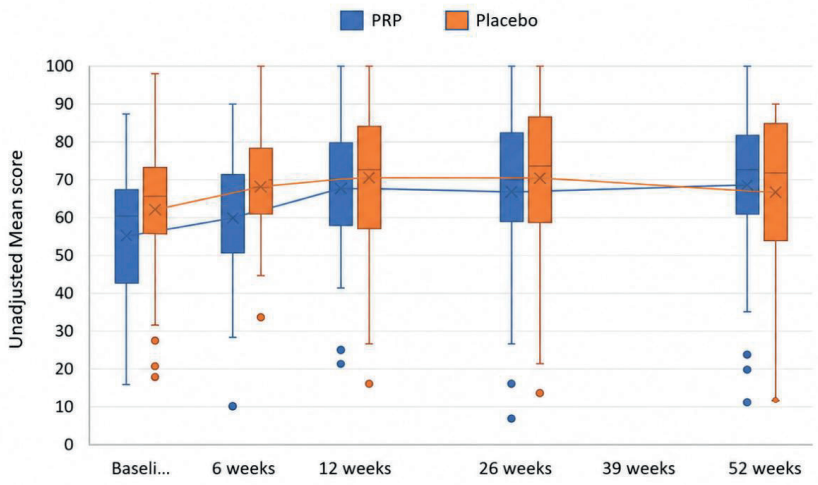
[e] AAS: Ankle Activity Score; measures performable activity level; range 0-10 points; higher scores indicate higher ankle-stress activities.

[f] SF-36: Short Form-36 Health Survey, measures health-related quality of life measured using 8 subscales which can be summarised into a Mental and a Physical Component Summary score; range 0-100 points; higher scores indicate higher quality of life.

[g] GAS: Global Attainment Scaling, based on achievement related to predetermined goals in agreement with the patient; range -2 to 3; lower scores indicating decline from baseline, higher scores indicating achieving more than the predefined goals.

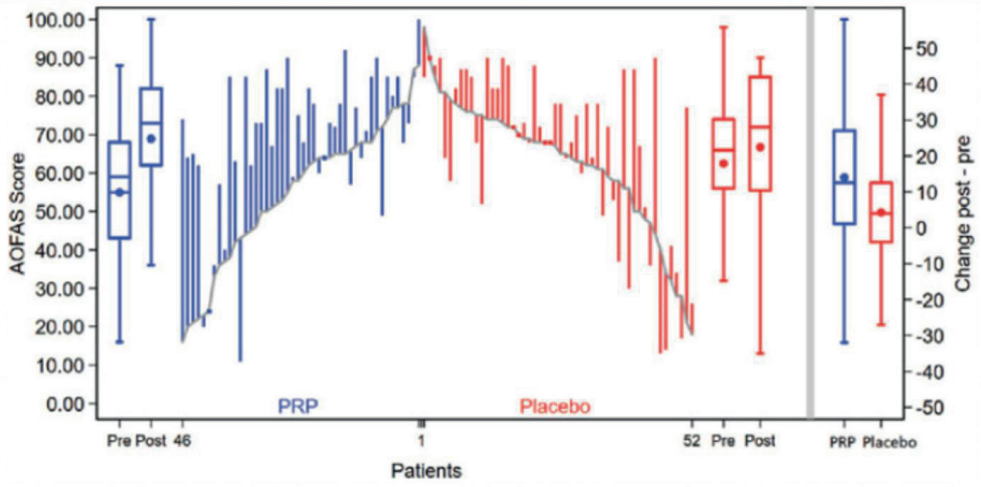
[h] EQ-5D-3L: EuroQol-5 dimensions-3 levels, measuring the generic quality of life across 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) presented using a summary index (0-1, indicating death and full health, respectively) and a health VAS (0-100 indicating worst health imaginable to best health imaginable).

Figure 2. Mean Foot and Ankle Outcome Score over 52 weeks



Mean scores for the unadjusted, patient-reported version of the American Orthopaedic Foot & Ankle Society score in patients treated with platelet-rich plasma (PRP) and placebo (range, 0-100 points; higher scores indicate less pain and better function). See Table 2 notes for scale definitions. The horizontal lines in the boxplots from bottom to top show the 25th, 50th (median), and 75th percentiles. The X in the boxplot indicates the mean. The whiskers indicate the 25th percentile –1.5 × IQR and the 75th percentile +1.5 × IQR. Baseli, baseline; IQR, interquartile range.

Figure 3. Change in unadjusted AOFAS score by group



Change in unadjusted American Orthopaedic Foot & Ankle Society (AOFAS) score (range, 0–100 points; higher scores indicate less pain and better function) for each participant by group at baseline and 52 weeks. The baseline patient-reported AOFAS scores for individual participants are connected with a line. See Table 2 notes for scale definitions. Changes from baseline are represented by the vertical lines for platelet-rich plasma (PRP) and placebo. Upward and downward lines indicate improvement and deterioration, respectively. The boxplots (from left to right) show the summary at pre- and postinjection for PRP, at pre- and postinjection for placebo, and the changes by group. The horizontal lines in the boxplots from bottom to top show the 25th, 50th (median), and 75th percentiles. The dot in the boxplot indicates the mean. The whiskers indicate the 25th percentile −1.5 × IQR and the 75th percentile +1.5 × IQR. IQR, interquartile range; Post, postinjection; Pre, preinjection.

No statistically significant between-group difference was found for improvement in any of the secondary outcome measures at 52 weeks. The results of the secondary outcome measures can be found in Table 2 and Figure 4 and in Appendix Tables A3 to A11 and Appendix Figures A1 to A4 (available online).

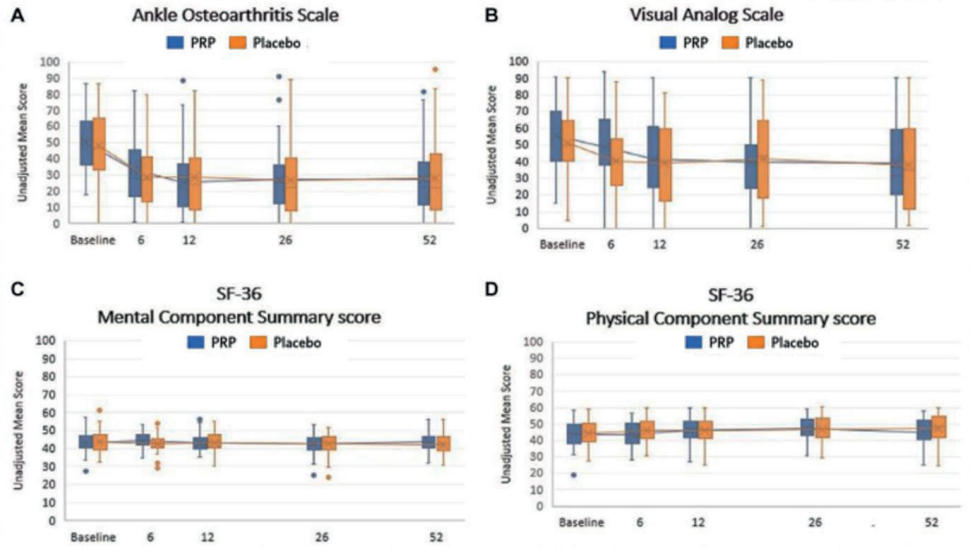
Because clinical efficacy was not found, no between-group cost-effectiveness analysis was performed (as defined in the trial protocol). The indirect costs were determined for all patients who participated in the study. The mean annual indirect cost for a patient with ankle osteoarthritis was €2908 ±€6679 ($3414.54 ± $7842.42) (Table 3). Direct costs were not considered representative for the direct costs of an average patient with ankle osteoarthritis in practice, because patients were instructed not to undergo any interventions or co-interventions in the 52 weeks after the first injection.

Table 3. Indirect costs of patients with ankle osteoarthritis based on absenteeism, presenteeism and loss of unpaid work

	Absenteeism mean (SD)	Presentism mean (SD)	Productivity loss of unpaidwork mean (SD)	Annual indirect costs mean (SD)
PRP-group (n=46)	€1575 (€3925)	€1023 (€3142)	€785 (€2154)	**€3384 (€7382)**
placebo-group (n=52)	€987 (€3893)	€800 (€2104)	€683 (€2041)	**€2469 (€5997)**
All ankle OA patients	€1269 (€3900)	€907 (2642)	€732 (€2086)	**€2908 (€6679)**
	Absenteeism median (IQR; min-max)	**Presentism median (IQR; min-max)**	**Loss of unpaid work median (IQR; min-max)**	**Annual indirect costs median (IQR; min-max)**
PRP-group (n=46)	€0 (€0 - €0; €0 - €18302)	€0 (€0 - €209; €0 – €16847)	€0 (€0 - €0; €0 - €8400)	**€0 (€0 - €2565; €0 - €35921)**
placebo-group (n=52)	€0 (€0 - €0; €0 - €23352)	€0 (€0 - €584; €0 – €11718)	€0 (€0 - €0; €0 – €10248)	**€0 (€0 - €2139; €0 - €31386)**
All ankle OA patients	€0 (€0 – €0; €0 – €23352)	€0 (€0 – €480; €0 - €16847)	€0 (€0 – €0; €0 – €10248)	**€0 (€0 – €2465; €0 – €35921)**

Absenteeism: Amount of days absent from paid work due to mental or physical health; Presenteeism: Reduced productivity at work due to reduced mental or physical health; Productivity loss of unpaid work: (partially) not being able to carry out unpaid work such as household chores or charity work due to reduced mental or physical health; Annual indirect costs: The sum of Absenteeism, Presenteeism and productivity loss of unpaid work; SD Standard deviation; OA: Osteoarthritis; IQR Interquartile Range.

Figure 4. Unadjusted secondary outcomes over 52-week follow-up



Unadjusted secondary outcomes over the 52-week follow-up period (secondary endpoint). (A) Ankle Osteoarthritis Scale, (B) visual analog scale, (C) 36-item Short Form Health Survey (SF-36) Mental Component Summary, and (D) SF-36 Physical Component Summary, at baseline and 6, 12, 26, and 52 weeks. The horizontal lines in the boxplots from bottom to top show the 25th, 50th (median), and 75th percentiles. The X in the boxplot indicates the mean. The whiskers indicate the 25th percentile −1.5 × IQR and the 75th percentile +1.5 × IQR. IQR, interquartile range; PRP, platelet-rich plasma.

DISCUSSION

In this study, which is the first double-blind, randomized, placebo-controlled clinical trial assessing the long-term effect of PRP in patients with ankle (talocrural) osteoarthritis, we found that intra-articular PRP injections, compared with saline placebo injections, did not significantly improve any of the outcome measures. The likelihood of a clinically relevant benefit is very small because the MCID was outside the 95% CI of patient-reported AOFAS score over 52 weeks.

This is a follow-up of a previous study in which no significant between-group differences were found over 26 weeks between the PRP and the placebo group.[110] Again, over the course of 52 weeks, no between-group differences could be found for any of the outcome measures. The patient-reported AOFAS score over 52 weeks was adjusted for radiological talar tilt, duration of symptoms of ankle osteoarthritis, ankle range of motion, body weight, and height. None of the other covariates presenting at baseline were found to influence the outcome with $P < .10$. According to a literature review of PRP treatment for knee osteoarthritis, benefit increased over time, being not significant at earlier follow-ups but clinically significant after 6 to 12 months.[152] However, the studies reviewed had

considerable methodological limitations (such as small sample sizes, few placebo-controlled studies, and other risk-of-bias concerns) and therefore low level of evidence, which necessitates caution when interpreting these results. A recent high-quality, double-blind, randomized, placebo-controlled trial (N = 288) did not find any significant between-group difference.[181]

Indirect Cost for Ankle Osteoarthritis

Because clinical efficacy was not found, no between-group cost-effectiveness analysis was performed (as defined in the trial protocol). This is the first study to determine the mean annual indirect cost for a patient with ankle osteoarthritis, which was €2908 ±€6679 ($3415 ± $7842). Because direct costs (medical consumption) were not included, the values reported here are only a portion of the total estimated costs for a patient with ankle osteoarthritis. The estimated indirect costs for knee osteoarthritis ranged from €830 to €7379 ($979-$8705) per person per year.[182-184] These costs are within a similar range of the indirect costs for ankle osteoarthritis. For osteoarthritis in general, the indirect costs have been estimated to be almost twice the amount of direct costs.[7] An estimation of total annual economic burden of a patient with ankle osteoarthritis could therefore be projected at almost €4500 ($5300).

Strengths and Limitations

The strengths of this study include the placebo-controlled, double-blind study design, a 2% loss to follow-up, and performance of all measurements by 1 coordinating research physician. The nationwide recruitment in 6 centers (2 university medical centers, 2 teaching hospitals, 1 general hospital, and 1 private specialist clinic) enhances the generalizability of the results. Furthermore, this is the first estimation of the economic burden (indirect costs) of ankle osteoarthritis. This study has several limitations. First, the generalizability of the findings to other platelet-rich blood products may be limited. Alternative platelet-rich blood interventions differ in regimen (dose, timing, and number of injections) and in composition of platelets and leucocytes. However, the product administered in this trial was used in several other osteoarthritis trials, and the concentration of the PRP was comparable with that used in these previous trials.[144,171,185] Second, we did not analyze the composition of PRP in this study.[52] The composition of this specific system has been analyzed previously,[172,186] including in a previous randomized clinical trial.[138] In clinical practice, PRP analysis typically is not performed before injection. Third, we did not control for physical therapy or other co-interventions between the 2 groups. Because we randomized participants, it is unlikely that there was a large between-group difference in adherence to the prescribed home-based exercise program.

CONCLUSION

Intra-articular PRP injections, compared with placebo injections, did not significantly improve ankle symptoms and function over the course of 52 weeks in patients with ankle osteoarthritis. The results of this study do not support the use of PRP injections for posttraumatic ankle osteoarthritis, which is common in athletes.

CHAPTER

8

What Is the Efficacy of Intra-articular Injections in the Treatment of Ankle Osteoarthritis?

A Systematic Review

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ABSTRACT

Background – Ankle osteoarthritis (OA) is painful and can impact a patient's physical and mental quality of life. Although intra-articular injections are commonly used to alleviate symptoms, there is conflicting evidence concerning their efficacy. Therefore, an updated systematic review would be informative.

Question/purpose – In this systematic review, we asked: Are there clinically important benefits or harms associated with the use of intra-articular injections in the treatment of ankle OA?

Methods – We used PubMed, Embase, and the Cochrane Library to search for randomized controlled trials on intra-articular injections for the treatment of ankle OA in June 2021, and updated the search in January 2022; eligible dates were from the date of inception of each database through January 2022. Reference lists of eligible studies and previous reviews were manually screened. Two reviewers independently assessed studies for eligibility. We included seven studies. Three compared hyaluronic acid (HA) with saline, one compared HA with exercise, one compared four different regimens of HA, one compared platelet-rich plasma (PRP) with saline, and one compared botulinum toxin Type A (BoNT-A) with HA. A total of 340 patients were included: 141 in the HA arms, 48 in the PRP arm, 38 in the BoNT-A arm, and 113 in the saline arms. Across all studies, the mean age was 52 ± 21 years, and 35% were women (119 of 340 patients). Methodologic quality was assessed using the Cochrane Risk of Bias 2.0 tool. Of the included studies, the risk of bias was low in two studies, presented some concerns in one study, and was high in four studies. According to the Grading of Recommendations Assessment, Development, and Evaluation methodology, the level of evidence was very low for HA, moderate for PRP, and very low for BoNT-A. The level of heterogeneity was high, and we opted to perform a systematic review rather than a meta-analysis. A clinically relevant difference was based on whether the between-group difference surpassed the cutoff point determined as the minimum clinically important difference.

Results – No clinically relevant differences were found among HA, PRP, and BoNT-A and their control groups at 3, 6, or 12 months. No studies reported any serious adverse events in any treatment group.

Conclusion – Given the lack of observed efficacy in this systematic review, these treatments should not be used in practice until or unless future high-quality studies find evidence of efficacy.

INTRODUCTION

The estimated incidence of ankle osteoarthritis (OA) is 3.4%, 70% to 78% of which is posttraumatic.[2,9,10] In professional former football and rugby players, ankle OA has been associated with previous ankle injuries, and the estimated incidence of ankle OA is higher (9.2% and 4.6%, respectively) in these athletes than in the general population.[46] The quality of life of patients with ankle OA may be impacted substantially, and the level of diminished quality of life from ankle arthritis has been shown to be comparable to that reported for hip OA, end-stage kidney disease, and congestive heart failure.[12,13,173] Early attempts at ankle arthroplasty had poor results, but the design of contemporary third-generation implants has led to considerably improved outcomes such as preserved motion, restoration of normal gait, and improved survivorship.[187] However, complications after ankle arthroplasty remain more common than after knee or hip arthroplasty, and because of this, ankle arthrodesis remains the preferred treatment for most patients.[174,188] Because patients with ankle OA tend to be younger and more active than patients with knee and hip OA, their longer projected lifespan is impacted more severely by a reduced quality of life or substantial functional limitations after ankle arthrodesis. Owing to these concerns, nonsurgical approaches are a mainstay of the treatment of patients with ankle OA, and intra-articular injections are commonly used to alleviate ankle OA symptoms.

Previous systematic reviews on the efficacy of intra-articular injections for ankle OA have had methodologic issues, including pooling the results of studies with a high risk of bias and inferior methods for synthesizing evidence.[132,189] Furthermore, since the publication of those previous reviews, one new trial has been published on intra-articular interventions for ankle OA.[110] There is therefore a need for an updated synthesis of the best available evidence.
With this in mind, we performed a systematic review in which we asked: Are there clinically important benefits or harms associated with the use of intra-articular injections in the treatment of ankle arthritis?

PATIENTS AND METHODS

The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews with registration number CRD42021254200. This study used the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement as a guideline.

Eligibility Criteria

Randomized controlled trials (RCTs) evaluating intra-articular injection therapy for ankle OA were eligible for this review. We excluded articles written in languages other than English, Dutch, or German and studies not conducted in humans.

Information Sources and Search Strategy

We searched the databases of Medline (PubMed), Embase (Ovid), and the Cochrane Library from the date of inception of each database through January 2022. The main keywords in our searches were ankle joint, osteoarthritis, and intra-articular injections. We tracked citations by manually screening the reference lists of eligible studies and previous reviews as well as conference proceedings. The search revealed 398 studies. After duplicates were removed, 348 records remained. Eight relevant studies remained after title and abstract screening. After a full-text review, seven studies[110,133,190-194] met the inclusion criteria. No additional studies were found through citation tracking or conference proceedings (Fig. 1), and we did not consider articles on preprint servers.

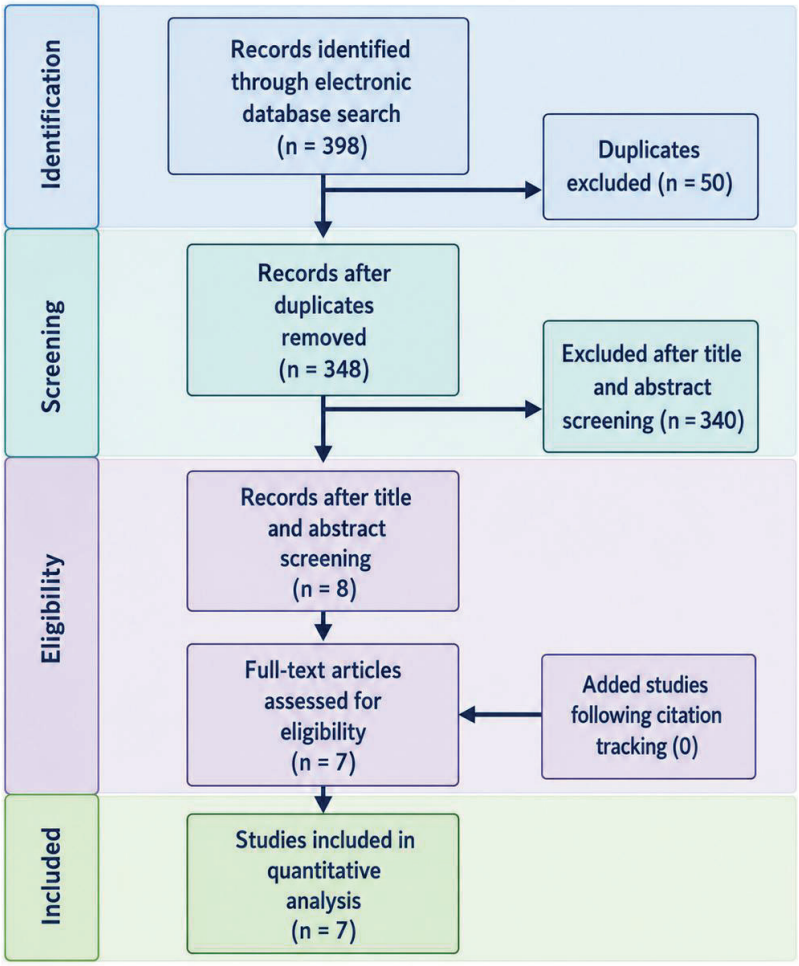
Selection Process

Two reviewers (LDAP and MJM) independently assessed studies for eligibility. These two reviewers screened titles and abstracts and obtained relevant articles. Those same reviewers independently read the full text of all relevant articles. Eligible articles were included. A third reviewer (GR) resolved any difference in opinion where no consensus could be reached.

Study Characteristics

Seven studies were included, (Table 1). Hyaluronic acid (HA), platelet-rich plasma (PRP), botulinum toxin Type A (BoNT-A), and saline were reported as the intra-articular interventions in the included RCTs. The studies included three comparing HA with saline,[133,190,192] one comparing HA with exercise,[191] one comparing four different regimens of HA[194], one comparing PRP with saline[110] and one comparing BoNT-A with HA.[193] In total, 15 patient groups were identified with nine arms assessing HA, one arm assessing PRP, four arms assessing saline, and one arm assessing BoNT-A. Across all studies, the mean age was 52 ± 21 years, and 35% were women (119 of 340 patients). A total of 340 patients with ankle OA were included: 141 in the HA arms, 48 in the PRP arm, 38 in the BoNT-A arm, and 113 in the saline arms. Of the six studies with HA as an intervention (three studies versus saline,[133,190,192] one versus other HA regimens,[194] one versus a progressive ankle exercise program,[191] and one versus BoNT-A,[193] two studies had a follow-up of 3 months,[133,190] three studies had a follow-up of 6 months,[190,192,194] and one study had a follow-up of 12 months.[191]

Figure 1. Search flow diagram



This flow diagram shows the results of the search.

Table 1. Characteristics and outcomes of included studies

Study	Intervention	Product (manufacturer)	Injection regimen (guidance)	Age in years mean ± SD (or range)	gender, (% men)	Symptom duration in years, mean (or range)	Follow-up length in weeks	Number of patients lost to follow-up	Manufacturer funding (yes/no)	Main results
HA versus saline										
DeGroot et al.[133] (2012) (n = 64)	HA (n = 39)	Supartz® (Seikagaku) Low molecular weight: 620 to 1170 kDa	One injection under 2.5-mL fluoroscopic guidance	54.1 ± 14.5	61.5%		12	4	No	No between-group differences:3 months AOS p = 0.14[a]; effect size = 0.4 AOFAS p = 0.90[a]; effect size = 0.4 VAS p = 0.31[a]; effect size = 0.3
	Saline (n = 37)			61.9 ± 14.1	55.5%			4		
Cohen et al.[190] (2008) (n = 28)	HA (n = 15)	Hyalgan® (Fidia Farmaceutici S.p.A.) Low molecular weight 500-730 kDa	5 injections of 1-mL (weekly) fluoroscopic guidance	56.2 ± 14.1	93%		26	1	Yes	No clinically relevant between-group differences: 3 months AOS p = 0.04[a]; effect size = 1.0 WOMAC p = 0.03[a]; effect size = 1.0 6 months AOS p = 0.14[a]; effect size = 0.7 WOMAC p = 0.12[a]; effect size = 0.7
	Saline (n = 13)			43.4 ± 14.9	85%			1		
Salk et al.[192] (2006) (n = 17)	HA (n = 9)	Hyalgan® Low molecular weight 500 to 730 kDa	5 injections of 1 mL (weekly) No guidance	57.8 ± 1.8	56%		26	1	Yes	No between-group differences: 6 months AOS p = 0.32[a]: effect size [b] WOMAC p > 0.05[a]; effect size [b]
	Saline (n = 8)			60.0 ± 13.9	63%			2		
HA versus HA										
Witteveen et al.[194] (2010) (n = 26)	HA (n = 7)	Orthovisc® (Anika Therapeutics) Moderate molecular weight: 1000-2900 kDa	One injection of 1 mL No guidance	31 (26 to 28)	57%		27	2	No	
	HA (n = 7)		One injection of 2 mL No guidance	47 (33 to 63)	43%			4		
	HA (n = 6)		One injection of 3 mL No guidance	51 (39 to 71)	83%			1		
	HA (n = 6)		Three injections of 1 mL (weekly) No guidance	40 (21 to 63)	100%			2		

HA versus progressive exercise program										
Karatosun et al.[191] (2008) (n=30)	HA (n = 15)	Adant® (Meiji Seika Pharma Co) Low molecular weight: 600 to 1200 kDa	Three injections of 2.5 mg (weekly) No guidance	52.1 ± 11.3	60%		52	0	Unclear	No between-group differences: 12 months AOFAS p > 0.05[a]; effect size [b] VAS p > 0.05[a]; effect size [b]
	PE (n = 15)		Home-based PE program + four in-hospital training sessions	25.1 ± 12.1	80%			0		
PRP versus saline										
Paget et al. [110] (2021) (n = 100)	PRP (n = 48)	ACP Double Syringe System® (Arthrex)	Two injections of 2 mL (6-week interval) US guidance	54.8 ± 13.3	54%	5 (2 to 8)	26	0	No	No between-group differences: 3 months AOS -3 (-12 to 6) p = 0.47; effect size [b] VAS 1 (-8 to 11) p = 0.82; effect size [b] 6 months AOS 0 (-8 to 9) p = 0.90; effect size [b] AOFAS -1 (-6 to 3) p = 0.56; effect size [b] VAS -2 (-12 to 8) p = 0.71; effect size [b]
	Saline (n = 52)			56.4 ± 14.4	56%	8 (3 to 14)		0		
Botulinum toxin Type A versus HA with rehabilitation exercise										
Sun et al.[193] (2014) (n = 75)	BoNT-A (n = 38)	100-unit of BoNT-A (Allergan, Inc) in 2 mL saline Hyalgan® (Fidia Farmaceutici S.p.A.) Low molecular weight 500 to 730 kDa	One injection of 2 mL No guidance	49.5 ± 10.9	62.5%	5.6 ± 3.7	26	3	No	
	HA + EX (n = 37)			50.6 ± 10.3	61.2%	5.3 ± 4.0		2		

A negative value shows superiority in favor of the first-named intervention.

[a]Apart from the p value, no further data were available; the effect size had the following cutoff points: < 0.2 = small effect; 0.2 to < 0.5 = medium effect; and > 0.8 = large effect.

[b]It was not possible to calculate effect size.

SD = Standard Deviation; n = number; HA = Hyaluronic Acid; kDa = KiloDaltons; PE = progressive exercise program; ACP = autologous conditioned plasma; PRP = Platelet-rich Plasma; BoNT-A = Botulinum toxin Type A; EX = Exercise; MCID = Minimal Clinically Important Difference; AOS (Ankle Osteoarthritis Scale: 0 to 100) with an MCID= 28 points; AOFAS (The American Orthopaedic Foot & Ankle Society score: 0 to 100) with an estimated MCID of 12 points; VAS (Visuale Analogue Scale: 0-100) with an estimated MCID of 20 points; WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index: 0-100) with an estimated MCID of 20 points.

In these studies, low–molecular weight and medium–molecular weight HA was used. Ultrasound-guided injections were performed in three studies.[110,133,190] Injection schedules varied from single injections to five injections with varying dosages. The trial follow-up durations ranged from 3 to 12 months. The most frequently used scores were the VAS pain score and the Ankle Osteoarthritis Scale, followed by the American Orthopaedic Foot and Ankle score and WOMAC (Table 1).

Data Collection Process

One reviewer (MJM) extracted data using a standardized template. Information extracted from each trial included the characteristics of trial participants (including age, gender, years since diagnosis, history of trauma, and radiologic grade) and the trial's inclusion and exclusion criteria; type of interventions, controls, and regimen (dose, frequency, injection interval); type of outcome measure and value; safety data (including the incidence of adverse events and serious adverse events and discontinuations because of adverse events); and funding.

Outcomes

We determined that outcome was the between-group difference in any patient-reported outcome measure score for ankle pain or function such as (but not limited to) the American Orthopaedic Foot and Ankle Society score (range 0 to 100 points, with higher scores indicating less pain and better function), Ankle Osteoarthritis Scale (range 0 to 100 points, with higher scores indicating more symptoms), VAS (range 0 to 10 mm, with higher scores indicating more pain), and Foot and Ankle Outcome Score (all scales range from 0 to 100 points, with higher scores indicating less symptoms) at 3, 6, and 12 months as well as any radiologically determined cartilage response (such as increase in radiologic cartilage thickness), side effects, or safety outcomes reported. The clinically relevant difference was based on the between-group mean difference relative to the (estimated) minimum clinically important difference (MCID) of the patient-reported outcome measure used to measure ankle OA. The MCID has not yet been determined for multiple patient-reported outcome measures, but was estimated to be 20 points for the VAS,[147] 12 points for the American Orthopaedic Foot and Ankle Society score,[110] and 20 points for the WOMAC score.[147] The reported MCID for the Ankle Osteoarthritis Scale was 28 points,[195] and for the subscales of the Foot and Ankle Outcome Score (five scales: pain, symptoms, quality of life, activity of daily living, and sport and recreation), it was 15, 7, 18, 23, and 21, respectively.[113,177] Effect sizes were calculated (if there were sufficient data) as follows: (mean pretreatment – mean posttreatment) / pooled standard deviation. Effect size was defined as small (0.2 to < 0.5), medium (0.5 to < 0.8), or large (≥ 0.8).[196]

Risk of Bias

Two reviewers (LDAP and MJM) independently assessed the risk of bias in the included studies using the Cochrane Risk of Bias tool 2.0.[197] If there was a difference in opinion, the two reviewers reached a consensus. Otherwise, the independent opinion of a third reviewer (GR) was used to decide. When one of the primary risk-of-bias assessors was involved as a coauthor of one of the included studies, the noncoauthor risk-of-bias assessor (MJM) evaluated the articles to avoid a conflict of interest over these studies. His assessment was seconded by an independent reviewer (JD, not a study author). The risk of bias of the included RCTs was assessed as low in two studies, presented some concerns in one study, and was high in four studies (Fig. 2).

Figure 2. Cochrane Risk of Bias Assessment of Included RCTs

Study	Intervention	Randomization process	Deviations from the intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall risk of bias
Cohen et al. [5]	HA versus SAL	●	●	●	●	●	●
DeGroot et al. [6]	HA versus SAL	●	●	●	●	●	●
Salk et al. [22]	HA versus SAL	●	●	●	●	●	●
Witteveen et al. [34]	HA versus HA	●	●	●	●	●	●
Karatsoun et al. [13]	HA versus PE	●	●	●	●	●	●
Paget et al. [18]	PRP versus SAL	●	●	●	●	●	●
Sun et al. [27]	BoNT-A versus HA + Ex	●	●	●	●	●	●

This figure demonstrates the Cochrane Risk of Bias assessment of the included RCTs. BoNT-A = botulinum toxin-A; HA = hyaluronic acid; PRP = platelet-rich plasma; PE = progressive exercise; SAL = saline; EX = rehabilitation exercises. A color image accompanies the online version of this article.

The level of evidence of each outcome was graded as high, moderate, low, or very low according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.[198]Because all included studies were RCTs, they started at a high level of evidence. The level of evidence for an outcome was downgraded one or two levels (depending on how serious the quality of evidence was impacted) for each of the five criteria. Very low was the lowest level of evidence,

regardless of whether the level could have been downgraded more. This means that for an intervention to have a very low level of evidence (the lowest level of evidence), it must be downgraded at least three levels. Should an intervention be downgraded five levels, it will still be graded as having a very low level of evidence and would seem (according to the GRADE criteria) to have an equally low level of evidence as an intervention that has been downgraded three levels.
The five criteria were risk of bias; inconsistency in the results of published data; indirectness, that is, how well the available data answer the review's question (for example, when a comparison group is not an ideal control group); imprecision, in which we assessed whether there was enough information (for instance, the rule of thumb is that the total number of participants for an outcome should be more than 400); and publication bias. As with the risk of bias assessment, if one of the GRADE assessors was a coauthor of one of the included studies, it was assessed by assessors not involved in that study (MJM or JD). Any discrepancy was resolved by a third assessor (GR).
The level of evidence for HA was very low (Table 2). The level of evidence was downgraded a total of five levels, two levels for a high risk of bias among most studies, one level for inconsistency in results, one level for indirectness because the small number of studies used different regimens and HA products, and one level for imprecision because there were fewer than 400 participants in total. No publication bias was detected. The level of evidence could not be downgraded lower than a very low level of evidence. The level of evidence for PRP was moderate. Because there is only one RCT on the efficacy of PRP,[110] it was downgraded one level for imprecision because the total number participants was fewer than 400 (Table 2).

Table 2. GRADE evaluation of the included interventions

Intervention	Risk of bias	Inconsistency of results of published data	Indirectness[a]	Imprecision[b]	Publication bias	Total level of evidence
Hyaluronic acid	-2	-1	-1	-1	0	Very low
Platelet-rich plasma	0	0	0	-1	0	Moderate
Botulinum toxin-a	-2	0	0	-1	0	Very low

Each intervention starts off at high level of evidence and is potentially downgraded 1 or 2 levels from high to moderate, low and very low, with very low being the lowest level possible.

[a]How well the available data answers the reviews question (for example, when a comparison group is not an ideal control group).

[b]Is there enough information (for instance, the rule of thumb is that the total number of participants for an outcome should be more than 400).

The level of evidence for BoNT-A was very low. The level of evidence was downgraded a total of three levels, two levels because of serious risk of bias concerns in the one study available and one level for imprecision because the total number of participants was fewer than 400 (Table 2).

Statistical Analysis

We planned to perform a meta-analysis if at least two studies had the same or similar interventions and comparators and the studies had a low risk of bias.[199] In the event the included studies were not suited for a meta-analysis, we planned to perform a best-evidence synthesis. There was only one study concerning PRP and BoNT-A. Five studies compared HA and saline.[133,150,190-192] However, these studies had different follow-up timepoints and outcome measures. Only three[133,190,192] could be compared at 3 months; only one had a low risk of bias, and two[190,192] could be compared at 6 months, none of which had a low risk of bias. To avoid compounding errors related to the risk of bias, we did not perform a meta-analysis.

RESULTS

Benefits of Injectable Products for Ankle OA

No clinically relevant differences were found in any of the studies assessing the efficacy of HA (Table 1).[133,190-192,194] Paget et al.[110] evaluated the efficacy of two PRP injections versus saline injections and found no between-group differences for any of the reported patient-reported outcome measures at any timepoint (Table 1). Sun et al.[193] evaluated the efficacy of BoNT-A and found no between-group differences for any of the patient-reported outcome measures at any timepoint (Table 1). No clinically relevant differences were found in any of the patient-reported outcome measures at any timepoint (Table 3).

Table 3. Interventions and outcomes of RCTs

Intervention	Number of studies	Outcome	Effect 12 weeks	Effect 26 weeks	Effect 52 weeks	Level of evidence
Hyaluronic acid	5	AOFAS	x	NR	x	Very low
		AOS	x	x	NR	
		VAS	x	x	x	
		WOMAC	x	x	NR	
Platelet-rich plasma	1	AOFAS	x	x	x	Moderate
		AOS	x	x	x	
		VAS	x	x	x	
Botulinum toxin type-A	1	AOFAS	x	x	NR	Very low
		AOS	x	x	NR	
		VAS	x	x	NR	

Symbol "x" no clinically important differences between intervention and control; NR = not reported

Harms

No severe or systemic adverse events were reported during the postinjection follow-up period in any treatment group. The most frequently reported adverse events were mild pain and local swelling at the injection site, the proportions of which ranged between 6% and 29% in three studies (no between-group differences).[192-194] Witteveen et al.[194] reported pain and swelling in 27% of patients (seven of 27 patients) across all arms. All reported adverse events resolved without medical intervention.

DISCUSSION

Ankle OA substantially impairs a patient's mental and physical quality of life. Intra-articular injections are commonly used to alleviate symptoms, but evidence of their efficacy is conflicting. We therefore performed an updated systematic review of the best-available evidence. No clinically relevant differences were found among HA, PRP, and BoNT-A and their control groups in the treatment of ankle OA. After using the GRADE tool, the level of evidence was very low for HA, moderate for PRP, and very low for BoNT-A. No studies reported any serious adverse events in any treatment group. There is currently insufficient evidence to justify the use of any type of intra-articular injection in ankle OA treatment.

Limitations

The available evidence is limited by a lack of high-quality, placebo-controlled trials, and most studies had small patient groups. Only two RCTs that assessed PRP and HA were classified as having a low risk of bias, with both reporting no statistical differences between the intervention and placebo (saline) groups. The low number of patients, low methodologic quality, and lack of a placebo control group may have resulted in an overestimation of the apparent benefits of treatment. Given the lack of clinically important benefits found in our systematic review, this limitation seems especially important, because it is even less likely that these treatments are worthwhile. The heterogeneity of the included studies regarding important matters such as follow-up period, outcomes used, and intervention regimens limit a meaningful interpretation of the available evidence. The low number of studies and participants, as well as heterogeneity, limits the possibility of performing a subgroup analysis on the efficacy of interventions during different stages of the disease or a meta-analysis. Additionally, studies about intra-articular corticosteroid injections, which are frequently used in practice, or emerging regenerative interventions such as stem cells are extremely limited.

Consequently, results are extrapolated from studies concerning knee OA, which is a different joint both biomechanically and biologically. Only one study assessed the efficacy of methylprednisolone in 12 patients (24 ankles with OA) and found an improvement in the Foot and Ankle Outcome Score with 6 months of follow-up.[200] However, the lack of randomization, blinding, a control group, and small sample mean that the quality of evidence of that study was poor. In knee OA, corticosteroid injections are considered controversial because of contradictory short-term and long-term results and because their use may worsen cartilage degeneration.[201-203] Although mesenchymal stem cell therapy has been used in the knee, a recent meta-analysis found that six of nine included trials on the topic had a high risk of bias,[204] which means that the results likely appear better in trials than they would in real-world practice. So far, to our knowledge, the only study on the topic in patients with ankle arthritis included only six patients;[205] more research is needed before conclusions can be drawn regarding the utility, if any, of this approach. Additionally, because no analysis was done based on gender, we cannot assume these findings apply equally to men and women. In four studies, the men-to-women ratio was between 50% to 65% in favor of men; in the three other studies, men represented up to 80% to 93% of the intervention arms (Table 1). However, because there is little overall evidence of efficacy, these treatments should not be used in men or women.

Benefits and Harms of Injectable Products for Ankle OA

Hyaluronic Acid – There is no evidence to support the use of HA as a treatment for ankle OA. Previous reviews reported promising results for HA. However, of the five studies we evaluated in this systematic review, only one study had a low risk of bias and only one study found a statistical benefit, but none found clinically relevant effect-size differences for the Ankle Osteoarthritis Scale and WOMAC scores at 12 weeks,[132,189] because none of the between-group differences were greater than the relevant MCIDs. No new RCTs have been published on the efficacy of intra-articular HA injections since the publication of the previous reviews on injection therapy for ankle OA.[132,189] In a previous review, two studies with saline as a control group were pooled at 26 weeks, reporting a mean difference of 18 points on the Ankle Osteoarthritis Scale (range 0 to 100) at 26 weeks.[189] However, we have a methodologic concern about this analysis, because these two studies with risk of bias concerns should not have been pooled.[190,192] Pooling heterogeneous studies that are at moderate or high risk of bias compounds errors and may produce misleading conclusions that may be interpreted as having more credibility.[199] Two studies with saline as a control group were pooled at 12 weeks and reported a mean difference of 1 point on the Ankle Osteoarthritis Scale. The study that favored HA had a high risk of bias,[190] in contrast to the study that favored saline, which had a low risk of bias. In general, studies that are at high risk of bias will tend to overestimate the benefits of the treatment being studied. Overall, despite common use, there is no robust evidence that HA works in the

treatment of ankle OA. Pooling and compounding errors resulted in a mean difference of only 18 points on the Ankle Osteoarthritis Scale, which is lower than the reported MCID of 28 points,[195] suggesting that any benefit with the use of those products is so small that it might not be considered important by patients, if they even perceive the difference. HA therefore should not be used in practice until or unless high-quality studies find evidence of efficacy.[206]

PRP – No between-group difference in ankle symptoms and function beyond 26 weeks was seen in the first and only RCT on the efficacy of PRP in the treatment of ankle OA of which we are aware.[110] PRP is a high concentrate of platelets achieved through centrifugation of the patient's blood after venipuncture.[43,207] The platelets are thought to release growth factors and cytokines that modulate the intra-articular environment, facilitating an anabolic effect and reducing inflammation.[43,207] However, the no-difference finding suggests that PRP should not be used in practice for this indication.

BoNT-A – BoNT-A is thought to inhibit neurotransmitters such as acetylcholine, thereby reducing peripheral sensitization and indirectly reducing central sensitization.[208] In ankle OA, only one nonblinded RCT was available; at 26 weeks, this treatment was not shown to be as effective as HA injections,[193] which our systematic review found was not effective, so until or unless high-quality randomized trials demonstrate otherwise, we recommend against the use of this product as well.

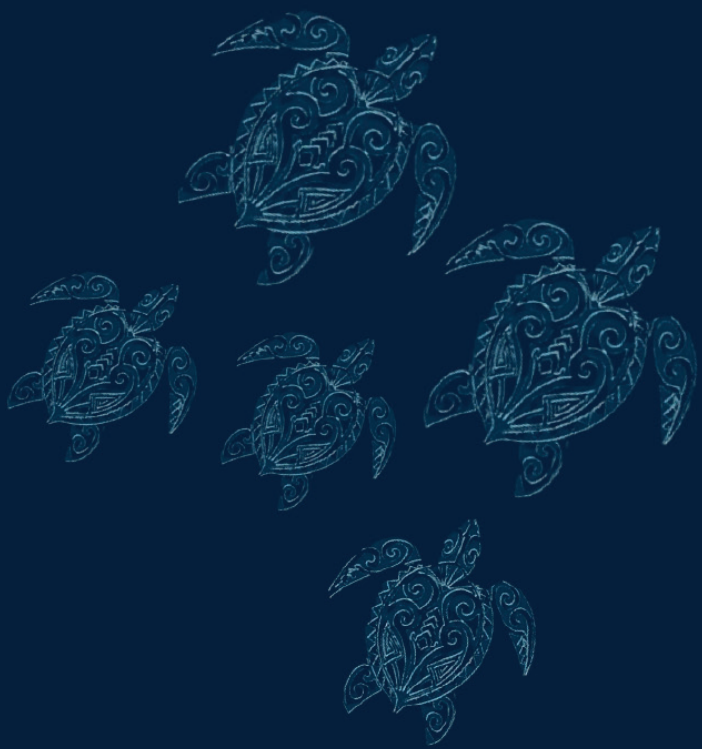
CONCLUSION

This systematic review found insufficient evidence to justify the use of intra-articular injections of HA, PRP, or BoNT-A for the treatment of patients with ankle OA. Because of this, we recommend against their use in practice until or unless future high-quality studies find evidence of efficacy. Future studies should be randomized, blinded, well-powered, and placebo controlled.

CHAPTER

9

Discussion



In this thesis we aimed to supplement the existing scientific knowledge on ankle OA by assessing the quality of life, the association with sustained ankle traumas in former professional athletes, a possible novel innovative treatment and an overview of current injectable treatment options. In this chapter we reflect on the key findings and methodology. We also look at the challenges and necessities for future research and clinical practice.

The Ankle Trauma and Ankle Osteoarthritis Odyssey

The quality of life in relatively younger patients (18 to 40 years of age) with ankle OA is impacted more both physically and specifically mentally than older age groups. In **chapter 2**, the impact of ankle OA on mental and physical quality of life was prospectively investigated by match-controlling 91 patients that took part in the PRIMA trial (efficacy of PRP in the treatment of ankle osteoarthritis) for age and gender from the normal Dutch population.[52,173] In line with previously published literature, we found that ankle OA significantly impacted both the physical and mental quality of life.[173] The reason for the reduced mental and physical quality of life is most likely multifactorial. It can be imagined that the discomfort associated with ankle OA can limit their daily activities, their ability to engage in physical activity or even worse, limit or even diminish their physical independence.

The impacted quality of life found to be more pronounced in relatively younger patients is presumably due to the higher physical demands and expectations, the relatively larger loss of physical function compared to themselves or contemporaries, possible disrupted career aspirations and the longer projected life span compared to older patients.[173] Social factors may also play a key role in determining the individual quality of life with reduced social interaction and participation in social events leading to loneliness.

In **chapter 3,** we looked into the association of ankle injuries and ankle surgeries and the development of ankle OA in a high risk population, namely former professional football and rugby players. This was a cross-sectional questionnaire based study where former professional players were included through FIFPRO and World Rugby. On average both populations sustain a significant amount of ankle injuries and also ankle surgeries as a result.[209] The repetitive high-impact nature of these sports lay a significant burden on the ankle joint. In football, ankle injuries form 10%-18% and in rugby ankle injuries form 5%–20% of all sustained injuries.[63,64,68,69,210] No previous data is available for the prevalence of ankle OA among rugby players. However rugby players were seen to have six times as much OA and joint replacements.[211] We similarly found that football players had a higher prevalence of ankle OA (9%) compared to the general population.[47-49] Football players were 1.3 times more likely to develop ankle OA for every ankle injury sustained and were 2.1 times more likely to

develop ankle OA for every ankle surgery they underwent.[209] Although similar results were seen among rugby players, insufficient rugby players were included to reach sufficient power. Therefore the results of the rugby player cohort should be interpreted with caution.

Relevance for Clinical Practice

The post-traumatic nature of ankle OA is troubling due to the significant impact it has on both mental and physical quality of life especially in relatively younger patients (18 to 40 year olds).[173]
In general, the prevalence and association of ankle injuries and ankle surgeries with ankle OA, highlight the need for implementation of prevention strategies and appropriate post-injury management to mitigate long-term consequences.[209]

Relevance for Research

There are currently no effective treatments for end-stage ankle OA besides ankle arthrodesis. Future research should focus on early detection and early interventions that may mitigate or stop the progression of the mechanical and biological cascade triggered by an ankle trauma.

Unleashing Clinimetrics on Patient Reported Outcome Measures (PROM) for Ankle OA

There were no validated PROMs for ankle OA. In the PRIMA trial (double- blind, randomized placebo-controlled trial investigating the efficacy of PRP in the treatment of ankle osteoarthritis) the American Orthopaedic Foot and Ankle Society (AOFAS) score was the primary outcome measure. The AOFAS was the most frequently used measurement for ankle OA during the design of the trial. To support any potential findings we included an additional eight secondary outcome measures, of which three were specific ankle PROMs (Ankle Osteoarthritis Score (AOS), Foot and Ankle Outcome Score (FAOS) and the Ankle Activity Score (AAS)). The AOFAS was the most frequently used measurement for ankle OA.[13] However, the AOFAS had been under considerable scrutiny due to the ceiling and floor effect and it had never been validated for ankle OA.[212] Additionally, part of the AOFAS had to be filled in by a clinician, meaning patients would have to come to the clinic for each follow-up. However no minimally important change (MIC) had been determined for the AOFAS. In **chapter 4** we looked at the measurement properties of the AOFAS as well as a completely patient-reported version of the AOFAS (PR-AOFAS). The creation of a completely patient reported version of the AOFAS would allow for more efficient and feasible high quality studies due to frequent and longer follow-ups. This included construct validity, internal consistency, test–retest reliability, and responsiveness. The measurement properties of the PR-AOFAS were seen to be sufficient, unlike the AOFAS which was seen to have insufficient construct validity, internal consistency, and responsiveness to change in the same population.

Relevance for Clinical Practice

Based on our main findings, as the MIC was smaller than the Smallest Detectable Change (SDC - individual), both the AOFAS and PR-AOFAS are not suitable for follow-up of individual patients in a clinical setting. Both are more suitable for use in groups of patients, such as a research setting. However, suitability for its use references to the MIC being smaller than the SDC, not measurement properties of the PROM being sufficient.

Relevance for Research

It is important that research does not blindly follow statistical significance, but looks to clinically relevant differences, judging efficacy by its change compared to the MIC of the measurement used. Proper clinimetrical validation of PROMs for both populations and the disease in question are important when looking to perform high quality studies. Different cultures and populations have different priorities (e.g. function over pain) or deem certain questions or measurements of a PROM more or less important. Relevance and comprehensibility of PROMs for populations, through content validity, should be investigated in order to determine whether the patient's understanding of an item is as it is intended.

Searching for effective Injectable Treatments for Ankle OA: To PRP or not to PRP

The impact ankle OA has on the patient has been elaborately described. An effective treatment is therefore imperative. In the knee literature some articles have reported promising results concerning the efficacy of PRP for the treatment of knee OA.[165] In **chapter 5 to chapter 7** we describe the protocol, 26 week and 52 week results of a multicentre double-blind randomized placebo-controlled trial: the Platelet-Rich Plasma Injections for the Management of Ankle Osteoarthritis (PRIMA) trial.[52,110,213] In this trial we included 100 patients and assessed the efficacy of PRP compared to a control group (placebo: saline). We found no between-group differences for any of the primary or secondary outcome measures (concerning, pain, function, quality of life or individualised goal assessment) over 26 or 52 weeks.[110,213]

Placebo effects differ depending on the invasiveness of the intervention. The more invasive the intervention, the higher the placebo effect.[167,214] Although there was a significant within-group difference compared to baseline, this difference was in line with an expected placebo effect following injections, even the effect lasting up to six months has been reported in placebo studies.[137,167] A potential physiological solution for the improvement from baseline within both groups is the so-called flush effect. Flushing a joint with a fluid would dilute the local environment of inflammatory

factors. However this seems highly unlikely. Not only is it questionable whether 2ml could achieve a flush effect, previous sham studies done in knees found no between-group difference following intra-articular flushing with 10 litres of saline.[169,170] Another study compared placebo injections to sham injections (dry needle) and also found no between-group differences, suggesting that the change from baseline is due to context and not a physiological effect.[215] To date there are six other randomised controlled trials including hyaluronic acid and botulinum toxin A, assessing efficacy at 12, 26 and 52 weeks (**chapter 8**).[110,133,190-194] Unfortunately no clinically significant differences were seen for any of the interventions for the treatment of ankle OA.

Relevance for Clinical Practice

Despite initial promising results, PRP showed no superior improvement in pain and function, compared to placebo, in the treatment of ankle OA. In fact none of the available injectable treatments reported in the literature and researched in a randomized controlled setting showed clinically relevant improvements. This thesis does therefore not support the use of PRP, Hyaluronic acid or Botulinum Toxin A to be used for the treatment of ankle OA in clinical practice until high quality studies have shown otherwise.

Relevance for Research

Methodology is extremely important for the interpretation of the quality of results. For instance, PRP has initially shown promising results for a number of diseases and injuries. However, many of these studies were small groups, single armed and had no blinding for the interpretation of the results. In the PRIMA trial we observed a within-group improvement from baseline at both 26 and 52 weeks. It is understandable that a clinician following expert opinion is charmed by the healing effects. A certain bias in wanting an intervention to help for a disease lacking treatment options is also quite understandable. However, following assessment in large high quality randomized controlled trials, no efficacy was found for the use of PRP in the treatment of a number of these diseases and injuries, such as Achilles tendinopathy, acute hamstring injuries or knee OA.[39,138,139,181,216] Future research should focus on large high quality randomized placebo-controlled trials with a double blind interpretation scheme such as Jarvinen et al.[146]

Future perspectives

The latest recommendations from the European Alliance of associations for Rheumatology (EULAR) and the Osteoarthritis Research Society International (OARSI) consider the core treatment for osteoarthritis to include weight loss, muscle strengthening, joint mobility, proprioception and aerobic exercises. Especially as the link between the severity of symptoms associated with osteoarthritis and

a sedentary lifestyle has been well established.[217] However further treatment options are lacking, apart from arthrodesis for end-stage ankle OA. Health systems are starting to strain or have already cracked under the pressure of a considerable lobsided balance of supply and demand of treatment and pathology, to a point where healthcare can nearly no longer be considered a right. In order to be able to maintain standards of health care, future research and clinical efforts should focus more on prevention and early detection of the disease that may mitigate or stop the progression of the cascade of ankle OA. As the majority of patients with ankle OA has a posttraumatic entity, future research should focus on determining cartilage related risk factors for disease progression, thereby targeting patients at risk. The Orthopaedic and Sports Medicine department of Amsterdam UMC is currently on such an endeavour, where the needle scope is being used to assess visual signs of cartilage damage that had been missed by MRI. By better understanding the different phases of ankle OA, tailored treatment modalities can be better implemented.

Additionally, future research should entail the validation of an existing or the creation of a new ankle OA PROM where the measurement properties are sufficient. Lastly, as with many novel treatments, evidence is often based on small single armed retrospective experimentations. However, often continued systematic reviews are written sometimes incorporating no new randomized controlled trials each update. Especially when a number of small methodologically poor studies still follow despite large randomized controlled trials disproving efficacy, such as the use of PRP in the treatment of Achilles tendinopathy.[139] Journals can play a pivotal role in this simply by demanding methodologically sound protocols to be published before commencement of trials and by disregarding studies of poor methodological quality, especially after recent randomized controlled trials have disproved efficacy. In order to attain objective measurement of clinically relevant outcomes, assessment using blinded interpretation methods such as Jarvinen et al,[146] should become common if not obligatory practice. Additionally, many non-profit and government grants are being used to disprove expensive treatments. By the time high methodologically sound trials are set-up, new unfounded treatments are replacing the former. Responsibility of high quality randomized controlled trials proving efficacy should become an ethical obligation of the producer, even if only in partnership with non-profit or government organizations.

CONCLUSION

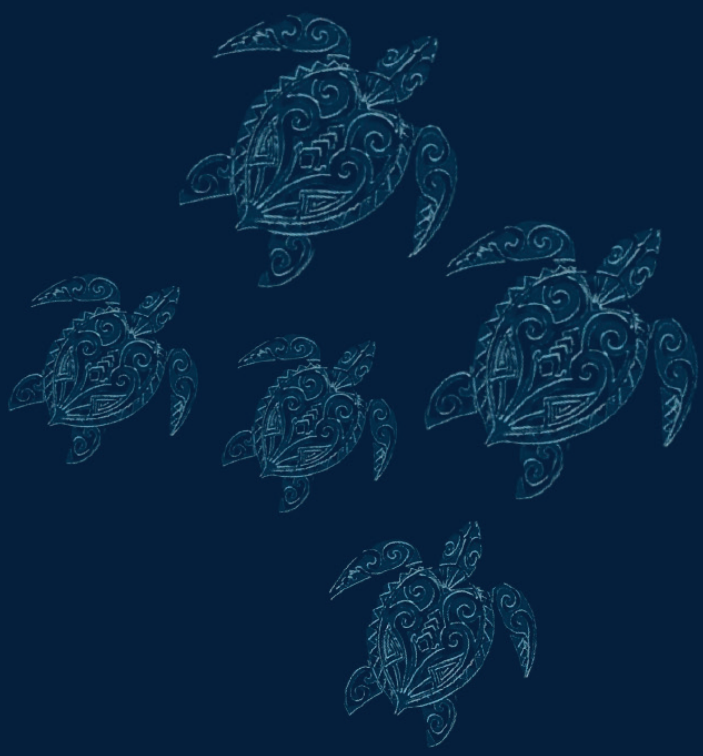
In this thesis we found that the quality of life of patients with ankle OA is impacted both mentally and physically, and that specifically relatively younger patients are impacted even more. We found a

higher prevalence of ankle OA among former professional football players, and that they were more likely to suffer from ankle OA following each ankle injury or ankle surgery. In a randomised placebo-controlled trial for patients with ankle OA, PRP injections did not improve ankle symptoms and function over 26 or 52 weeks compared with placebo injections. Finally, in a systematic review, no clinically relevant differences were found for any injectable treatment (PRP, Hyaluronic acid, Botulinum toxin) for ankle OA based on randomized controlled trials. These treatments should not be used in practice until or unless future high-quality evidence of efficacy is found.

CHAPTER

10

Summary



ENGLISH SUMMARY

Ankle osteoarthritis (OA) is a debilitating condition, with a majority having a previously sustained ankle trauma. Currently there are limited treatment options for ankle OA with arthrodesis being the golden standard for end-stage ankle osteoarthritis and the impact on quality of life is reportedly significant. In **chapter 1** an introduction to this thesis is given where we discuss the epidemiology, pathogenesis, financial and social impact of Ankle OA. We then go into the anatomy, biomechanics and biology of the ankle. A background is then given on treatment options for ankle OA as well as the methods for measuring the treatment effects of the randomized controlled trial presented in this thesis.

In **chapter 2** we aimed to determine the physical and mental quality of life of patients with ankle OA. We performed a case-control study where we matched 100 patients with ankle OA with 91 age- and gender- matched controls and measured quality of life using the physical and mental component summary scores of the Short Form-36. A clinically relevant difference was found for both the Physical (P=0.003; 95% CI −6.7 to −1.3) and Mental Component Summary scores (P < 0.001; 95% CI −10 to −6). Patients with ankle OA had a median of 45 points (matched controls 52 points) and 43 points (matched controls 53 points) for the Physical and Mental Component summary scores, respectively. In **chapter 3** we aimed to determine the prevalence of ankle OA among former professional football and rugby players and to assess the association between ankle injuries or ankle surgeries with ankle OA. We conducted a cross-sectional questionnaire-based observational study including former professional football (n=401) and rugby players (n=152). We found that former professional football (9.2%) and rugby (4.6%) players had a higher prevalence of ankle OA compared to what had been reported for the general population (3.4%). Also football players were more likely to suffer from ankle OA following every ankle injury and/or surgery.

We aimed to determine the measurement properties and minimally important change (MIC) of a completely patient-reported version of the AOFAS (PR-AOFAS) in patients with ankle OA in **chapter 4**. In total the PR-AOFAS of 112 patients, included for the PRIMA trial, was evaluated for reliability, construct validity and responsiveness. The measurement properties were assessed using the AOFAS, Foot and Ankle Outcome Score, Ankle Osteoarthritis Score, Visual Analogue Scale, and Short Form-36. The MIC was estimated using the optimal cut-off point of the receiver operating characteristic curve. The measurement properties of the PR-AOFAS was seen to be sufficient (construct validity, internal consistency, test-retest reliability, and responsiveness), unlike the AOFAS which was seen to have insufficient construct validity, internal consistency, and responsiveness to change in the same

population. As the MIC was smaller than its smallest detectable change, the PR-AOFAS is more suitable for use in groups of patients such as would be used in a research setting.

Chapter 5 contains the protocol of a double-blind placebo controlled randomized trial (PRIMA trial) where we assessed the efficacy of platelet-rich plasma (PRP) in the treatment of ankle OA. In total 100 patients with ankle OA were included over 6 centres and randomised into two treatment groups. One group received PRP injections and the control group received a placebo (saline) injection. Both groups received two injections of either PRP or placebo at an interval of 6 weeks. The primary outcome was the American Orthopaedic Foot and Ankle Society (AOFAS) score at 26 weeks. Secondary outcome measures were taken at baseline, 6, 12, 26 and 52 weeks and included the Ankle Osteoarthritis Score, Foot and Ankle Outcome Score (FAOS), pain subscale of (0–40), Visual Analogue Scale score (VAS; 0–100), Ankle Activity Score (AAS; 0–10), subjective patient satisfaction Short Form Health Survey-36 (SF-36), Global Attainment Scaling (GAS) and the EuroQol-5 dimensions-3 levels utility score (EQ5d3l). A cost-effectiveness analysis would be performed at 1 year in the event efficacy for PRP was found. Patients, physicians and assessors were blinded. Results were unblinded only after the blinded analysis and interpretation of the data. In **chapter 6** we present the 26 week results of the PRIMA trial. Following randomisation, 48 patients were in the PRP group and 52 patients were in the placebo (saline) group. There was no loss to follow-up. Compared to baseline a 10 point improvement was seen in the PRP group compared to an 11 point improvement in the placebo group for the primary outcome (AOFAS score) over 26 weeks. Following adjustment for potential confounders no statistical difference was found for the primary outcome or any of the secondary outcome measures. We therefore concluded that PRP injections did not significantly improve ankle symptoms and function over 26 weeks compared to placebo injections. In **chapter 7** we present the 52 week results of the PRIMA study. Studies concerning the efficacy of PRP in the treatment of knee OA showed clinically significant improvement occurring between 6 to 12 months despite showing no initial benefit. At 52 weeks, two patients were lost to follow-up, one patient from each group. No significant between-group differences were observed for any of the outcome measures. As no clinical efficacy was found, no cost-effectiveness analysis could be performed. Annual indirect cost (based on absenteeism, presenteeism and productivity loss of unpaid work) was calculated to be €2908 ±€6679 per patient per year. An estimation of total annual economic burden of a patient with ankle OA was projected to be €4500. Following the 52 week follow-up it was concluded that PRP injections, compared to placebo injections, still did not significantly improve ankle symptoms and function in patients with ankle OA. The results of the PRIMA trial therefore do not support the use of PRP injections in the treatment of ankle OA.

The current literature for randomised controlled trials on intra-articular injections for the treatment of ankle OA is assessed in **chapter 8**. In total seven studies were included: three studies on hyaluronic acid (HA) vs saline, one compared four different regimens of HA, one on PRP vs saline and one on botulinum toxin type A (BoNT-A) vs HA. The level of evidence was moderate for PRP and very low for both HA and BoNT-A. No clinically relevant differences were found between HA, PRP and BoNT-A and their control groups at 3, 6 or 12 months. Therefore the current literature does not support the use of HA, PRP or BoNT-A in the treatment of ankle OA.

In **Chapter 9** we reflect on the main findings of this thesis as well as limitations and potential clinical implications. Several studies have found promising changes from baseline with PRP injections. As presented in the PRIMA trial, comparison to a placebo group is important to determine efficacy. Methodological quality is of the utmost importance in order to contribute robust evidence.

NEDERLANDSE SAMENVATTING

Enkelartrose (OA) is een invaliderende aandoening, waarbij een meerderheid een enkeltrauma heeft doorgemaakt. Momenteel zijn er beperkte behandelopties voor enkelartrose, waarbij artrodese de gouden standaard is voor eindstadium enkelartrose. De impact op de kwaliteit van leven van deze aandoening is aanzienlijk. In **hoofdstuk 1** wordt een inleiding gegeven op dit proefschrift waarin we de epidemiologie, pathogenese, financiële en sociale impact van enkelartrose bespreken. Vervolgens gaan we in op de anatomie, biomechanica en biologie van de enkel. Er wordt ook achtergrondinformatie gegeven over behandelopties voor enkelartrose, evenals de methode die gebruikt is bij het dubbelblind, placebo-gecontroleerde gerandomiseerde trial dat in dit proefschrift wordt gepresenteerd.

In **hoofdstuk 2** wilden we de fysieke en mentale kwaliteit van leven van patiënten met enkelartrose bepalen. We voerden een case-control studie uit waarbij we 100 patiënten met enkelartrose koppelden aan 91 leeftijds- en geslachts-genoten, en de kwaliteit van leven hebben gemeten met behulp van de fysieke en mentale componentscores van de Short Form-36. We vonden een klinisch relevante lagere fysieke (P=0.003; 95% CI −6.7 to −1.3) en mentale kwaliteit van leven (P < 0.001; 95% CI −10 to −6). Patiënten met enkelartrose hadden een mediaan van 45 punten (controle groep 52 punten) en 43 punten (controle groep 53 punten) voor respectievelijk de fysieke en mentale componentscores.

In **hoofdstuk 3** wilden we de prevalentie van enkelartrose bij voormalige professionele voetbal- en rugby-spelers bepalen en de associatie tussen enkelblessures of enkeloperaties met enkelartrose onderzoeken. We voerden een cross-sectioneel op observatie gebaseerde vragenlijststudie uit bij voormalige professionele voetbal- (n=401) en rugby-spelers (n=152). We ontdekten dat voormalige professionele voetbal- (9,2%) en rugby-spelers (4,6%) een hogere prevalentie enkelartrose hadden ten opzichte van de algemene bevolking (3,4%). Ook bleken voetbalspelers vaker enkelartrose te ontwikkelen na elke doorgemaakte enkelblessure en/of enkeloperatie.

In **hoofdstuk 4** wilden we de meeteigenschappen en minimally important change (MIC) bepalen van een volledig door de patiënt gerapporteerde versie van de AOFAS (PR-AOFAS) bij patiënten met enkelartrose. In totaal werden de PR-AOFAS van 112 patiënten, geïncludeerd in de PRIMA-trial, beoordeeld op betrouwbaarheid, validiteit en responsiviteit. De meeteigenschappen werden beoordeeld met behulp van de AOFAS, FAOS, AOS VAS en SF-36. De MIC werd geschat met behulp van het optimale afkapniveau van de receiver operating characteristic (ROC) curve. De

meeteigenschappen van de PR-AOFAS bleken voldoende te zijn (validiteit, betrouwbaarheid en responsiviteit) in tegenstelling tot de AOFAS die onvoldoende bleken in dezelfde populatie. Aangezien de MIC kleiner was dan de kleinste detecteerbare verandering, is de PR-AOFAS geschikter voor gebruik in groepen patiënten zoals in onderzoeksverband.

Hoofdstuk 5 bevat het protocol van een dubbelblind, placebo-gecontroleerde gerandomiseerde trial (PRIMA trial) waarin we de effectiviteit van plaatjesrijk plasma (PRP) in de behandeling van enkelartrose hebben beoordeeld. In totaal werden 100 patiënten met enkelartrose geïncludeerd in 6 centra en gerandomiseerd in twee groepen. De ene groep kreeg PRP-injecties en de controlegroep kreeg een placebo (zoutoplossing) injectie. Beide groepen kregen twee injecties van PRP of placebo met een tussenpoos van 6 weken. De primaire uitkomstmaat was de American Orthopaedic Foot and Ankle Society (AOFAS) score gedurende 26 weken. Secundaire uitkomstmaten werden afgenomen bij baseline, 6, 12, 26 en 52 weken en waren de Ankle Osteoarthritis Score, Foot and Ankle Outcome Score (FAOS), pain subscale of (0–40), Visual Analogue Scale score (VAS; 0–100), Ankle Activity Score (AAS; 0–10), subjective patient satisfaction, Short Form Health Survey-36 (SF-36), Global Attainment Scaling (GAS) en de EuroQol-5 dimensions-3 levels utility score (EQ5d3l). Indien PRP effectief zou blijken, zou een kosteneffectiviteitsanalyse worden uitgevoerd na 1 jaar. Patiënten, artsen en beoordelaars waren geblindeerd. Resultaten werden pas gedeblindeerd na de geblindeerde analyse en interpretatie van de resultaten. In **hoofdstuk 6** presenteren we de 26 weken resultaten van de PRIMA-trial. Na randomisatie waren er 48 patiënten in de PRP-groep en 52 patiënten in de placebogroep (zoutoplossing). Er was geen verlies aan follow-up. In vergelijking met de baseline werd een verbetering van 10 punten gezien in de PRP-groep ten opzichte van een verbetering van 11 punten in de placebogroep voor de primaire uitkomst (AOFAS-score) gedurende 26 weken. Na correctie voor eventuele meewegende variabelen, werden er geen statistische verschillen gevonden voor de primaire of secundaire uitkomstmaten. We concludeerden daarom dat PRP-injecties niet tot verbetering heeft geleid van enkelklachten en enkelfunctie gedurende 26 weken ten opzichte van placebo injecties. In **hoofdstuk 7** presenteren we de 52 weken resultaten van de PRIMA-studie. Studies over de effectiviteit van PRP bij de behandeling van knieartrose toonden klinisch significante verbeteringen aan tussen de 6 en 12 maanden, ondanks het ontbreken van een initiële verbetering. Bij 52 weken waren twee patiënten uitgevallen voor follow-up, één patiënt uit elke groep. Er werden geen significante verschillen waargenomen tussen de groepen. Aangezien geen klinische effectiviteit werd gevonden, kon geen kosteneffectiviteitsanalyse worden uitgevoerd. De jaarlijkse indirecte kosten (gebaseerd op absenteïsme, aanwezigheidslijden en productiviteitsverlies van onbetaald werk) waren €2908 ± €6679 per patiënt per jaar. Een schatting van de totale jaarlijkse economische last van een patiënt met enkelartrose werd geschat op €4500. Na de follow-up van 52 weken werd

geconcludeerd dat PRP-injecties, ten opzichte van placebo injecties, nog steeds niet tot significante verbetering van enkelklachten en enkelfunctie leidt bij patiënten met enkelartrose. De resultaten van de PRIMA-trial ondersteunen daarom niet het gebruik van PRP-injecties in de behandeling van enkelartrose.

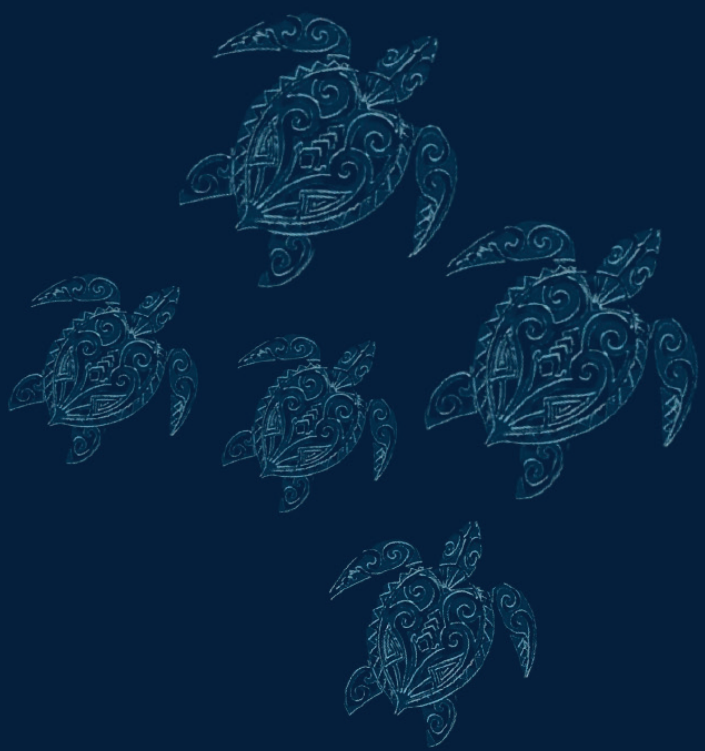
In **hoofdstuk 8** beoordelen we de huidige literatuur voor gerandomiseerde onderzoeken naar de effectiviteit van intra-articulaire injecties voor de behandeling van enkelartrose. In totaal werden zeven studies geïncludeerd: drie studies over hyaluronzuur (HA) vs zoutoplossing, één vergeleek vier verschillende regimes van HA toediening, één over PRP vs zoutoplossing en één over botulinumtoxine type A (BoNT-A) vs HA. Het niveau van bewijs was matig voor PRP en zeer laag voor zowel HA als BoNT-A. Er werden geen klinisch relevante verschillen gevonden tussen HA, PRP en BoNT-A en hun controlegroepen op 3, 6 of 12 maanden. Daarom ondersteunt de huidige literatuur het gebruik van HA, PRP of BoNT-A niet bij de behandeling van enkelartrose.

In **hoofdstuk 9** reflecteren we op de belangrijkste bevindingen van dit proefschrift, evenals beperkingen en mogelijke klinische implicaties. Een aantal studies over PRP-injecties hebben veelbelovende resultaten gerapporteerd. Zoals gepresenteerd in de PRIMA-trial, is vergelijking met een placebogroep belangrijk om effectiviteit te bepalen. Methodologische kwaliteit is van groot belang om het niveau van bewijs te verbeteren.

CHAPTER

11

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APPENDIX

I

Fast-Tracked Rehabilitation and Return to Sport of an Elite Rugby Player with a Complicated Posterolateral Corner Injury and Associated Peroneal Paralysis

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Abstract

Acute posterolateral corner injuries of the knee with associated hamstring avulsions and peroneal paralysis are rare in rugby. Regain of motor function following a complete paralysis is documented to be 38%. To our knowledge, only one case describes return to preinjury level of competitive sport taking up to 27 months. A 24-year-old international level rugby player, a medical student, sustained an acute posterolateral knee injury with associated anterior cruciate ligament tear, bicep femoris and semimembranosus avulsions as well as a complete peroneal paralysis. The patient returned to full-time medical rotation work weeks at 5 months. At 10 months, the patient was considered to have returned to preinjury level of activity having managed a 5 km run, participated regularly in non-contact rugby and performed exercises at 140% of his preinjury maximum. This case report describes the successful outcome of a high-frequency high-intensity rehabilitation.

BACKGROUND

This case report describes an elite rugby player with a complex posterolateral corner (PLC) injury sustained while playing rugby. A rare occurrence in the aforementioned contact sport, with the most common knee injury comprising anterior cruciate ligament (ACL) and medial collateral ligament (MCL) tears.[1–3] The main contributors of stabilisation to the posterolateral corner of the knee include the lateral collateral ligament, arcuate ligament, posterolateral capsule as well as the popliteus muscle-tendon-ligament unit (including the popliteal muscle and tendon in addition to the popliteofibular ligament). The aforementioned structures provide restraint to varus and external rotation.[4–8] LaPrade *et al* observed a multiple ligament knee injury to be present in 87% of cases with posterolateral structure damage, of which 13% was associated with an ACL injury.[9–11] As the common peroneal nerve is situated in the posterolateral corner, it is understandably consistent with 26% of multiple ligament knee injuries.[12] Furthermore, peroneal palsy is present in 44% of cases with an associated biceps femoris avulsion fracture or tendon tear.[13] According to Niall *et al*, 10% of patients with peroneal palsy had complete loss of sensibility and motoric function at initial presentation of which 50% would not regain peroneal nerve function. In 29% of the aforementioned group, partial recovery was seen. Only 21% would eventually regain full motoric function. Recovery was associated with the damaged length of the nerve being less than 7 cm, more extensive damage was met with a poorer prognosis.[10] Ridley *et al* observed similar statistics, with only 38% of patients recovering from an initial complete paralysis presentation.[12] Furthermore, it was observed that the superficial branch, innervating the peronei muscles, was the first to recover. The deep branch, facilitating dorsiflexion of the foot, would often take longer to recover if at all.[10 14 15] Cases comprising a biceps femoris avulsion fracture, complete peroneal palsy and multiple ligament knee injury have a poor prognosis regarding return to sports. Although return to sports is a wide concept, our goal is returning to preinjury level of sports without contact, not just being able to achieve functionality or physical exercise.[16] However, the obstacle is overcoming the peroneal paralysis and the manner in which it inhibits rehabilitation, and regaining propriocepsis, strength, speed and explosiveness associated with the preinjury level of knee functionality. To our knowledge, there is only one case report describing an actual return to elite level competitive sports taking up to 27 months.[17] Although the 'figure-of-8 posterolateral knee reconstruction according to Fanelli and Larson' is among the several techniques most frequently used, there is still no clear consensus regarding the swiftest return to sports.[18 19] We hypothesise that an all-out rigorous rehabilitation programme, where the athlete is pushed to his limits, will provide a faster return to work and preinjury level sports as opposed to adversely affecting the recovery.

Case presentation

A 24-year-old international level rugby player, fifth year medical student and an author of this paper, presented himself at the emergency department following a rugby-related trauma involving a posterolateral hyperextension of the left knee with considerable hydrops. The patient was 1.95 m in length and weighed 115 kg with a fat percentage of 16%. Examination showed a positive Lachman and varus stress test with a range of motion (ROM) noted as flexion/extension 100/0/0. Furthermore, complete loss of dorsiflexion and eversion of the left foot was observed as well as sensibility loss of the lateral half of the lower left leg and dorsum of the foot. Left knee flexion strength was graded at 2/5 on the Medical Research Council (MRC) scale for muscle power. The MRI, shown in figure 1, revealed an avulsion fracture of the semimembranosus, a torn ACL and a complex complete PLC injury comprising a distal biceps femoris tendon avulsion fracture, grade 3 LCL, arcuate ligament and popliteus muscle-tendon-ligament unit tear as wells as extensive injury to the peroneal nerve consisting of a longitudinal tear. An electromyography (EMG), performed the same week showed possible continuation of the peroneal nerve, yet minimal to no signal conduction. Due to the short time postinjury at which the EMG was performed, it was repeated at 6 weeks postinjury. This EMG showed denervation of the tibialis anterior and minimal movement of the peroneus brevis following stimulation. Due to the considerable haemarthrosis, the reconstruction of the PLC and ACL repair was set for 8 weeks postinjury.

Treatment

Preoperative rehabilitation

The patient underwent a rigorous training and diet programme at his own initiative, starting 6 days postinjury, to facilitate the well-known elite athlete's need to fast-track the return from injury. The following goals were set to attain this:

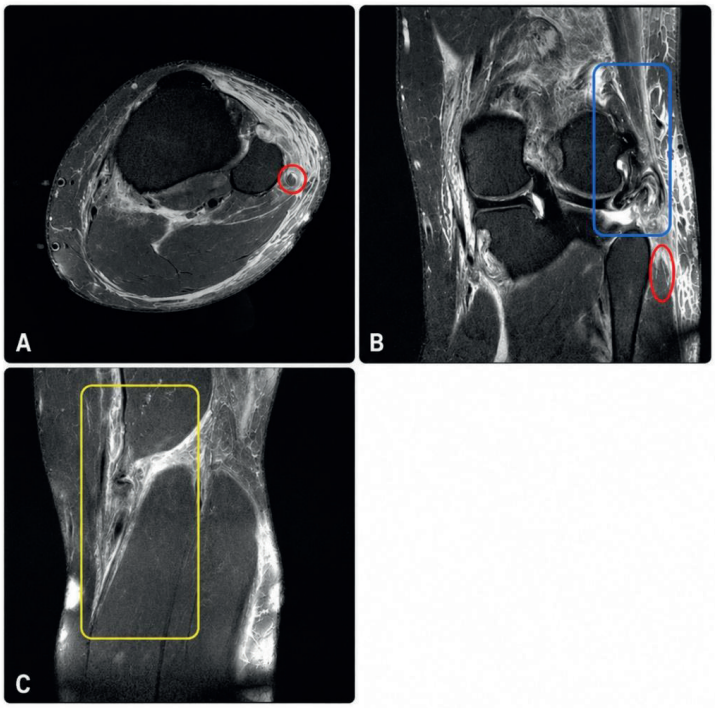
1. Pain management
2. Increase in ROM
3. Increase of overall leg strength and minimisation of atrophy
4. Stimulation of the elite athlete's mental drive during rehabilitation.

Goals 1, 2 and 4 were similarly applied postoperatively and will therefore be described in more detail further on. Goal 3 was considerably restricted due to the paralysis, reduced range of motion and pain. However, preoperative fitness was considered a major factor contributing to a successful postoperative rehabilitation. In addition, training of the non-immobilised leg was deemed beneficial

due to cross-education. This is a phenomenon where training of the non-immobilised limb was implicated to promote hypertrophy in the immobilised leg as well as cortical adaptations regarding functionality concerning both legs.[20] The paralysed peronei muscles, tibialis anterior and hallucis longus as well as the quadriceps underwent transcutaneous neuromuscular electrical stimulation (NMES) in two settings (30 min at 5 Hz, 400 µs and 30 min at 30 Hz, 160 µs) one to two times a day. Additionally, NMES was applied at 1–150 Hz on the posterior aspect of the fibular head to act as a neurostimulator for the paralysed peroneal nerve to stimulate function.[21] Ten days post-injury, the pain and strength was acceptable enough to start lower body weighted exercises in addition to the daily NMES. This included suspension cord (TRX) stabilised own body-weighted squats. Two weeks postinjury, the patient upgraded leg exercises to TRX stabilised single-leg squats to 90 degrees on the injured leg. Upper and lower body training sessions were alternated six times a week. This was eventually upgraded to eight training sessions when an increase in range of motion of the knee permitted two additional aerobic/anaerobic interval training sessions weekly in the form of outdoor cycling. Six weeks postinjury, the patient proceeded to jog a distance of 2 km twice, mainly due to the patient's own extreme stubbornness at the sudden dramatic reduced functionality. This was done using a peroneal orthosis to counter the foot-drop and tape to stabilise the knee. On both occasions, there was no subsequent swelling of the knee or pain.

To support the training regimen, a high-protein diet was undertaken.[22] The patient used supplements frequently used in the elite athlete world. These included 60 g of whey isolate and 10 g of Branched Chain Amino Acids (BCAA's) throughout the day in addition to magnesium, zinc as well as omega-3 supplementation. This was initiated as whey protein has been seen to increase muscle mass, performance and enhance recovery.[22] Although there is no medical evidence to support the use of magnesium, zinc and omega-3 supplementation, these were documented in order to remain transparent. It must be mentioned that the elite athlete used these supplements on his own initiative.

Figure 1. MRI findings of the left knee



Depicts the cross-sectional (A) and sagittal (B and C) view of the left knee, illustrating the extent of the damage as seen on the MRI. A and B show a longitudinal hyperintensity in the centre of an enlarged peroneal nerve encircled with red. The blue (B) and yellow (C) boxes mark areas of hyperintensity displaying marked loss and retracted muscle structure of the biceps femoris and semimembranosus, respectively.

Reconstruction of the knee

Eight weeks postinjury, an ACL reconstruction using a Bone-patellar Tendon-bone (BTB) allograft and a figure-of-8 Posterolateral Corner (PLC) reconstruction using an Achilles tendon allograft, first described by Fanelli and Larson, was performed as seen in figure 2.[23] The latter is a fibular head-based technique where the graft is passed through a tunnel made in an anterior to posterior direction. By using the figure-of-8 construct, the graft recreates the popliteofibular-ligament-complex and Lateral Collateral Ligament (LCL) stability due to the posterior and anterior arms of the graft respectively protruding from the fibular head tunnel.

Figure 2. Posterolateral reconstruction technique

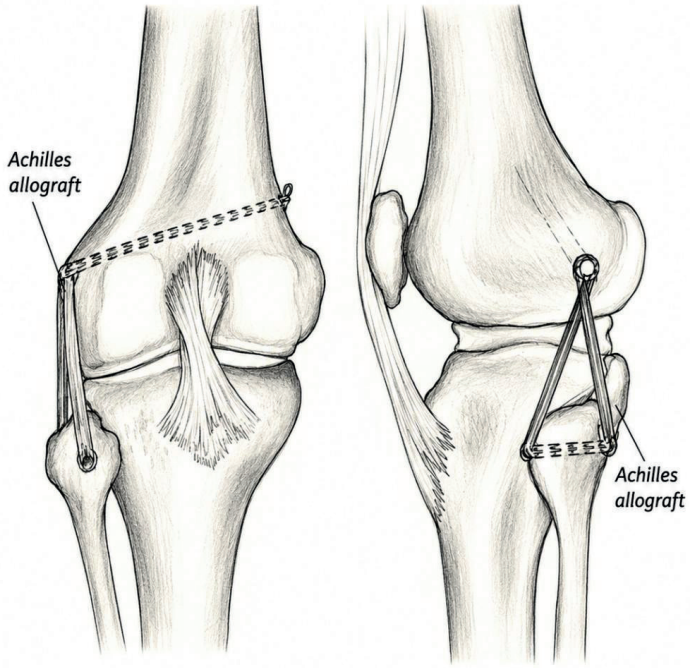
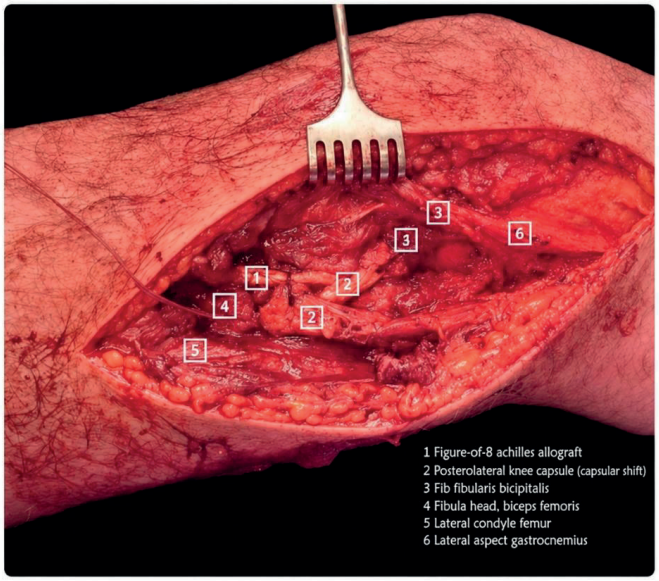


Illustration of the posterolateral reconstruction technique described by Fanelli and Larson, using an Achilles allograft which is passed through the tunnel of the fibular head. The figure-of-8 construction mimics the absent LCL and popliteofibular ligament stability.

On opening the posterolateral corner, the surgeon encountered an 'exploded' area making it a complex repair as seen in figure 3. A neurolysis of the peroneal nerve was performed with the injured nerve spanning a distance of 15 cm. Four centimetres proximal to the fibular head, the surgeon encountered a part of the peroneal nerve which seemed to have shown discontinuity or a longitudinal tear, as is described in the MRI report. Then, an ACL reconstruction was performed[24] During the aforementioned procedure, a healed longitudinal tear of the medial meniscus was encountered.

Figure 3. Intraoperative view of the posterolateral corner of the left knee



The state of the posterolateral corner of the left knee, with the Achilles tendon allograft set in place in a figure-of-8 according to Fanelli.

Postoperative rigorous rehabilitation phase

Regular rehabilitation protocols for multiligament knee injuries dictate maintaining the knee, non-weight bearing, in a full extension brace for 5 weeks. From week 6 through to week 10, weight bearing is progressively increased by 20% body weight each week. Closed kinetic chain strength, ROM and proprioceptive exercises are slowly started from week 11 onwards. Return to sports and heavy labour occur at least 9 months postsurgery.[18 25] However, return to preinjury level of sports following multiligament knee injuries with associated hamstring avulsions and peroneal palsy has been documented to take 27 months.[17] As our hypothesis suggests, we strived to fast-track the recovery period and assess whether a rigorous rehabilitation protocol would benefit or adversely affect the convalescent period.

Our patient was interned for 6 days after the PLC and ACL reconstruction, following which, the rehabilitation was started immediately according to the previously mentioned goals:

1. Pain management
2. Increase in ROM
3. Leg strength and minimisation of atrophy
4. Stimulation and support of the elite athlete's mental drive during rehabilitation.

Goal 1: pain management

The first goal was mainly set on hydrops reduction. Ice packs, pressure bandages and lymph drainage massage were used daily to decrease swelling in the operated limb. This was supported by 10 min sessions of whole body cryotherapy to reduce swelling, alleviate muscle soreness and facilitate recovery.[26 27] The patient was in considerable discomfort sleeping 4 hours a night the first 8 weeks.[28] The pain was located primarily along the lateral part of the leg including the biceps femoris, vastus lateralis, tractus ileotibialis and peronei muscles. As the patient became increasingly active around week 9 postsurgery and the peroneal function had started to return, the paralysed peronei muscles and calve became increasingly tender. At 27 weeks, the highest area of pain once again shifted to the lateral side of the leg, involving predominantly the gluteal muscles as well as the vastus lateralis and tractus ileotibialis. At week 30, the sensation slowly started to return which resulted in sharp stabbing pains, even with light touch such as clothes or bedlinen.

Pain medication consisted of novalgin, paracetamol and oxycodone for the first couple of weeks. For severe local pain, Transcutaneous Electrical Neuro Stimulation (TENS) was applied. Sport massages and dry needling were used daily to relax sensitive trigger points in the problem muscles.[29 30] As the rehabilitation progressed, dry needling played an increasing role as main pain relief treatment. As many intensely painful myofascial trigger points limited the frequency and intensity at which the rigorous rehabilitation could be upheld, the patient was taught how to dry needle himself. This was deemed responsible regarding his own medical background. The patient now tended to his own sensitive trigger points permitting better pain control which possibly facilitated muscle recovery and a more unrestricted training frequency. Pain throughout the rehabilitation stemming from muscle imbalances, such as the gluteal muscles, were treated with stability exercises.

Goal 2: increase in ROM

Particularly in the initial weeks, goal 2 focused primarily on a week by week increase in ROM. Our patient was equipped with a valgus locking brace for a period of 2 weeks at 0–30 degrees flexion at discharge. The degree of flexion was to be expanded by 15 degrees every week for 4 weeks until reaching 90-0-0. In the seventh week, the knee brace was discarded. Apart from the factors facilitating hydrops reduction as described under goal 1: pain management, ROM increase was

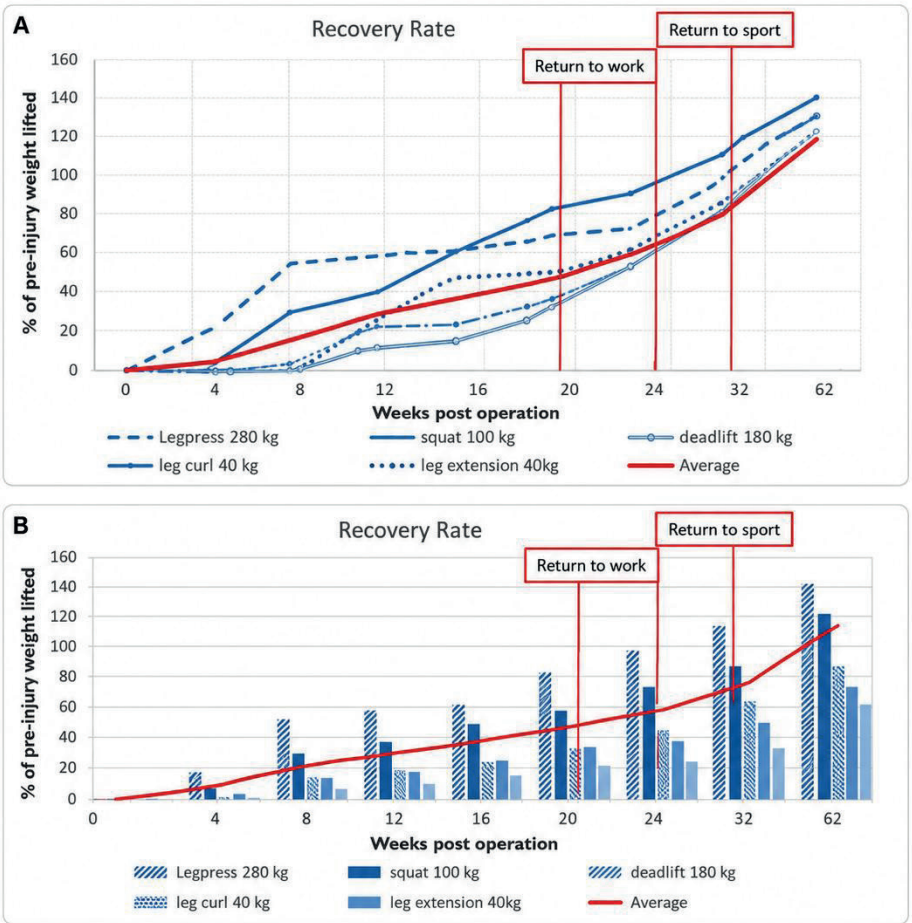
further managed through stretching, manipulation and massage of the scar tissue, knee capsule, quadriceps and its tendon. This was performed daily by physiotherapists until ROM had progressed sufficiently to allow cycling outdoors in week 15.

Goal 3: leg strength and minimisation of atrophy

Our patient had lost 20 kg since the injury, bringing him to 95 kg, despite the preoperative training. The postoperative training got off to a difficult start. The lack of sleep made it difficult to recover sufficiently, both physically and mentally during the rigorous rehabilitation.[28] Goal 3 was facilitated by way of electrical muscle stimulation starting 2 days postoperation.[31–33] The same settings were used as described in the preoperative rehabilitation section. Our patient started with upper body weight training every second day 2.5 weeks postoperation. In week 5, the patient performed leg exercises from Monday to Friday, which eventually allowed him to walk without crutches by week 7. Exercises were initially done 7 min continuously while receiving electrical stimulation on the muscles being trained.[31–33] Therefore during leg press and squats, NMES was applied on both the quadriceps and hamstrings simultaneously. This was then upgraded to 4 sets of 10 repetitions and eventually progressed to even fewer sets and repetitions with heavier weights.[34] Two months following the operation, the patient started using the AlterG daily. This is an antigravity treadmill, allowing the patient to run at 65% of his own body weight. By week 7, our patient started feeling physically exhausted, suffering from severe tiredness, nausea and mood swings. Our patient opted to increase the intensity and frequency of the rehabilitation, working towards a complete break in week 11 and 12. Thus, two additional high-intensity cardio sessions consisting of several low-weighted Tabata protocols were added. The aforementioned are high-intensity interval training protocols consisting of eight sets of 100% intensity bouts of activity of 20 s followed by 10 s of rest. One protocol lasts for 4 min, with the amount of protocols (usually 4–8) depending on symptoms such as dizziness and nausea. The exercise used in the protocols varied and included low weights, cycling, rowing, heavy rope training and the use of a cross-trainer. Due to the increased intensity and ever-reducing rate of recovery, extra focus was put on nutrition and the earlier described supplements to uphold the intensity. In addition, the patient used creatine for the remaining 3 weeks. After 2 weeks of a complete rest in Greece, the patient felt mentally and physically recharged. In the meantime, peroneal function allowed the patient to perform a weak dorsiflexion of the foot several times a day. Furthermore, the patient was able to do a 90 kg single-leg press continuously for 7 min at high intensity with NMES stimulation. The progression of the exercises as well as other exercises performed are illustrated in figure 4A,B. The figure does not illustrate the weights in kg but a percentage of the preinjury level of activity. The preinjury '100%' weight is documented in the legend beside its respective exercise. So, in week 16, our patient performed a leg extension at 50% of

preinjury level. In the legend, 40 kg marks the preinjury level of leg extension, making our patients level of leg extension in week 16, 20 kg.

Figure 4. Recovery rate



Illustrates, in two different variations, the progress per exercise over the weeks, with the operation taking place at week 0. The vertical axis shows the percentage of the pre-injury weight the patient was capable of lifting. The red line represents the average progress of all exercises throughout rehabilitation. The exercises presented in the legend indicate the amount of weight (kg) the patient was capable of lifting pre-injury. Week 22.5 marks return to work. Furthermore, the average of all exercises shows accelerated progression particularly between 24 and 32 weeks.

In addition to working on hypertrophy, power and explosiveness, particular attention was paid to stability exercises, such as balancing on an unstable surface (eventually while hopping) with one leg,

clamshell and Dynaband lateral walk. When ROM permitted, the patient proceeded to do an hour of outdoor cycling a day in addition to the current training regimen. The intensity was upheld, making it 5 weighted leg sessions a week, 3 upper body weighted sessions a week, 2 cardio sessions as well as 1–2 hours of cycling a day.

The paralysed muscles continued to be stimulated and the peroneal nerve at the fibular head underwent neurostimulation daily using NMES for 15 min. However, as the hallucis longus, tibialis anterior and peronei muscles did not initially react to the transcutaneous electrode pads, it was opted to conduct NMES intramuscularly. With this method, needles were inserted into the belly of the muscle allowing for a more direct stimulation of the paralysed muscles. This was done at a pulse frequency of 1/30–10 Hz. One week following the start of this intervention, the patient noticed a rapid progression in muscle growth and eventually function in the paralysed muscles.

Throughout the rehabilitation, additional sport massages, dry needling, hydration and diet were used to uphold the ever-increasing intensity and meet the demands needed for recovery. This was crucial as several periods of a marked drop in ability to maintain the intensity and recover were associated with a reduced adherence to the earlier mentioned interventions.

In figure 4A,B, all quadriceps-associated exercises seem to initially progress faster before slowing down between week 8 and week 16. In contrast, hamstring-associated exercises start slow and undergo an accelerated progression around week 16. Both muscle groups reach a comparable standard at 32 weeks. No obvious blunted progression could be seen during weeks 6–10 when the athlete suffered symptoms of exhaustion.

Goal 4: mental drive

With the impact of a sudden dramatic reduction in functionality in sport and work in comparison to the usual day-to-day activities of an elite athlete as well as further future uncertainties, focus on the mental state and energy levels was seen as imperative to achieve a successful rehabilitation. Emotional lability, low mood, irritability and sleep were closely monitored. Following discharge from the hospital, the patient underwent a reasonably strict daily structure, including getting up between 8:00 and 10:00 and upper body training programme. Although upper body training sessions are less relevant to the rehabilitation of the knee, it focusses on creating a sense of achievement rather than the limited functionality. Diet was deemed essential to maintaining high physical and mental energy levels, focussing on a high vitamin, mineral and protein intake. In addition, whole body cryotherapy was initially undertaken frequently when the mood and motivation was high. This intervention was

then implemented during low mood and motivation episodes, acting as a conditioned reset to uphold and continue the high-intensity, high-frequency regimen.

Several periods, either due to lack of sleep, over-reaching, reduced focus on dietary intake or a combination of the aforementioned, were considered mentally challenging and required considerable discipline. During these periods, the patient would suffer from physical and mental exhaustion, chronic nausea, emotional lability, irritability and a depressed mood. Whole-body cryotherapy was considered effective to reset the discipline, followed by extra attention to interventions facilitating recovery,[26 35] such as sport massages and diet. Furthermore, the support, attitude and involvement of partner, family, friends and medical staff played a considerable role in upholding discipline and motivation as well as training intensity and frequency.

Outcome and follow-up

Reintegration phase

Just over 5 months following the operation, the patient returned to work as a medical intern doing generally non-sedentary full-time rotations, including full days standing in the operation theatre. Rehabilitation was downscaled significantly to three full body sessions a week. By week 27, the patient seemed to have reacted well to the intramuscular NMES as the peroneal orthosis was no longer necessary. Although a minimal drop-foot was still evident, especially following a day of work or exercise, it was barely obvious by week 32. Sensation had recovered to half-way down the lower leg, predominantly on the lateral side.

Furthermore, the patient proceeded to undertake more dynamic exercises such as rope skipping and speed-agility-quickness ladder drills. In the 35th week, the patient managed to start running. This was followed by a game of touch (non-contact) rugby, including sudden rapid directional changes and short ranged accelerations. At 10 months postsurgery, the patient was considered to have 'returned to preinjury level of sports without contact' when a jog of 5 km was achieved, without the peroneal orthosis, with little hydrops or pain the following day. By week 39, normal sensation had expanded to the ankle on the lateral side and just above the ankle on the anterior side. The lower anterior part of the lower leg exhibited altered but an intact sensation. The dorsum of the foot was no longer numb, yet far from normal sensation. By 15 months, our patient managed to perform a 370 kg leg press and a 140 kg free squat, meaning he had achieved 132% and 140%, respectively, of his preinjury maximum. Furthermore, the patient could perform a TRX-stabilised unilateral leg squat followed by an explosive jump and 90-degree landing, something the patient was not capable of preinjury. This demonstrates the level of proprioceptive skills, strength and explosiveness acquired throughout the

rehabilitation as well as the ability to take repetitive stress on the knee. Moreover, our patient had reached a similar physique as before the injury, weighing 117 kg.

DISCUSSION

Despite the poor prognosis due to the serious associated injuries, including the peroneal palsy, PLC injury and avulsion fractures of the biceps femoris and the semimembranosus, a successful return to work and 'return to preinjury level of sports without contact' was achieved. Progress was achieved markedly faster than any other described cases of complex posterolateral knee injuries as far as the authors are aware. Ridley *et al* describes the earliest recovery from complete peroneal paralysis at 14 months.[12] Furthermore, the extent of muscular damage, such as additional hamstring avulsion fractures, inhibiting return to preinjury level of knee function is not taken in to account. In this case report, physical activities were assessed by performance–based tests instead of using patient-reported outcome measures as was done by Ridley *et al*.[12] Therefore, this case report is more comparable to the case described by Oshima *et al* but with a much faster actual return to sports: 10 versus 27 months.[17] However, it must be mentioned that at 27 months, the athlete described by Oshima *et al* return to competitive sport, as opposed to our athlete who returned to preinjury level of sports without contact. The following factors probably contributed to the described result, grouped according to the International Classification of Functioning model.[36]

Multiple clinical interventions were performed, some of them are non-evidence based and were initiated by the athlete himself. To be as transparent as possible, we also reported these non-evidence-based interventions without suggesting that these contributed to the positive outcome and therefore should be followed-up in future similar cases. First, an ACL reconstruction using a BTB allograft and a figure-of-8 PLC repair using an Achilles allograft were performed. Second, the patient underwent a rigorous training regimen. Numerous interventions were used to facilitate recovery throughout the rehabilitation, focusing on increase in ROM and pain reduction.[26] These were targeted by way of lymph-drainage massage, sports massage, dry needling, low-intensity training sessions and TENS.[29 30] In addition, protein diet and supplements like whey isolate, magnesium, zinc as well as omega-3 were taken. However, only protein supplementation has minor literary support.[22] Muscle tenderness was treated with pain medication, sport massages and whole body cryotherapy, yet dry needling remains unsurpassed.[26 27 29 30] NMES was performed to enhance muscle growth throughout the intense regimen but also to continue to stimulate the paralysed muscles, reducing atrophy.[21 31–33] Our patient considered the whey isolate supplementation, whole body cryotherapy,

dry needling and NMES to be the most enhancing and facilitating interventions throughout the rehabilitation.

With regard to personal factors, our patient was a medical student functioning as an elite athlete, used to training six to eight times a week on top of matches in addition to his medical rotations. The rapid progression is also attributed to the state of fitness preinjury as well as the state of fitness preoperation. Not only was our patient motivated to beat the odds, he was used to a high-frequency training regimen and the important role diet plays. Furthermore, he already had experience from many previous injuries for which he had undergone rehabilitation. The patient anticipated the training regimen to be mentally and physically challenging, including hard work and confrontational setbacks. He was pushed intrinsically even harder by the poor prognosis and the prospect of not fully recovering. The biggest motivation being that whatever the outcome, he could resign himself to it, as long as he had done everything possible.

Extrinsic factors upholding the patient's motivation are also attributed to a large contingency of family and friends as well as a professional, motivated and much involved medical staff committed to the road to recovery. The attitude, involvement and role of the medical staff as well as family and friends cannot be underestimated. In addition, the decision to go abroad during the 2 weeks of complete rest was seen as beneficial. It allowed the patient to physically recover and mentally recharge due to the completely different setting.

As a result, the patient managed to return to work as a medical intern at 5.5 months, doing full work weeks. The days included predominantly non-sedentary work with a lot of walking and standing. Return to sports without contact was achieved at 10 months, when he managed to do full-intensity non-contact rugby at preinjury level for 30–40 min and was able to jog 5 km. This is in contrast to the documented return to sport, if at all, taking up to several years. Furthermore, the achievement of 132% and 140% of the patient's preinjury leg press and squat weight, respectively, in addition to continuous unilateral single legged squat jumps, illustrates the strength, power and explosiveness acquired through rehabilitation. Our patient feels physically capable of returning to his own standard of rugby. Though mentally, due to fear of reinjury, another 6 months of receiving knocks would be needed to comfortably return. However, his retirement from rugby remains definite, as having fought back against the odds, it has allowed him to choose to retire rather than be forced to retire. Our patient feels proud he has been able to regain the ability to make that choice. In conclusion, our patient admits the rehabilitation was extremely heavy and on multiple occasions confrontational. However, with a return to work at 5.5 months and a return to preinjury level sports without contact

at 10 months, this rapid road to recovery can be seen as successful showing that on this occasion a high-intensity, high-frequency regimen resulted in a successful outcome. Whether this is due to the implemented interventions, intrinsic motivation or extrinsic support from family, friends and medical staff, a considerably reduced convalescent period was achieved. Future implementation may not only be limited to elite athletes but also for weekend warriors and non-athletes.
Patient's perspective.

I found the rehabilitation extremely heavy and on multiple occasions confrontational. However, following the rehabilitation period, I felt physically capable of returning to my former standard of rugby. Mentally, mainly due to fear of reinjury, another 6 months of receiving knocks would be needed in order to comfortably return. However, my retirement from rugby remains definite, as having fought back against the odds, it has allowed me to choose to retire rather than be forced to retire. I feel proud to have been able to regain the ability to make that choice.

ACKNOWLEDGMENTS

In memory of Terence Paget. The patient is pleased to acknowledge Keith Paget, Carmel Flood, Daphne Psaltaki, Jamie Rowell, Daan van Dongen, Yordi de Wit, Dirk Uittenbogaard, Elizabeth Flood in addition to the physiotherapists of Manual Fysion and fysio.com and the medical staff of the Radiology, Trauma and Orthopaedic department of the academic medical center—Amsterdam for their valuable contribution towards the successful rehabilitation.

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Lord Paget: “By God, sir, I’ve lost my leg!”
Duke of Wellington: “By God, sir, so you have!”

To the surgeon during a subsequent mid-thigh amputation on the dining table in a cottage at headquarters in Waterloo.

“The knives appear somewhat blunt”

— Henry William Paget, 2nd Earl of Uxbridge — later Field Marshal, 1st Marquess of Anglesey, Lord Lieutenant of Ireland — after being struck in the right leg by cannon shot at the Battle of Waterloo while near Field Marshal Arthur Wellesley, 1st Duke of Wellington.

"Clinical science has as good a claim to the name and rights and self-subsistence of a science as any other department of biology"

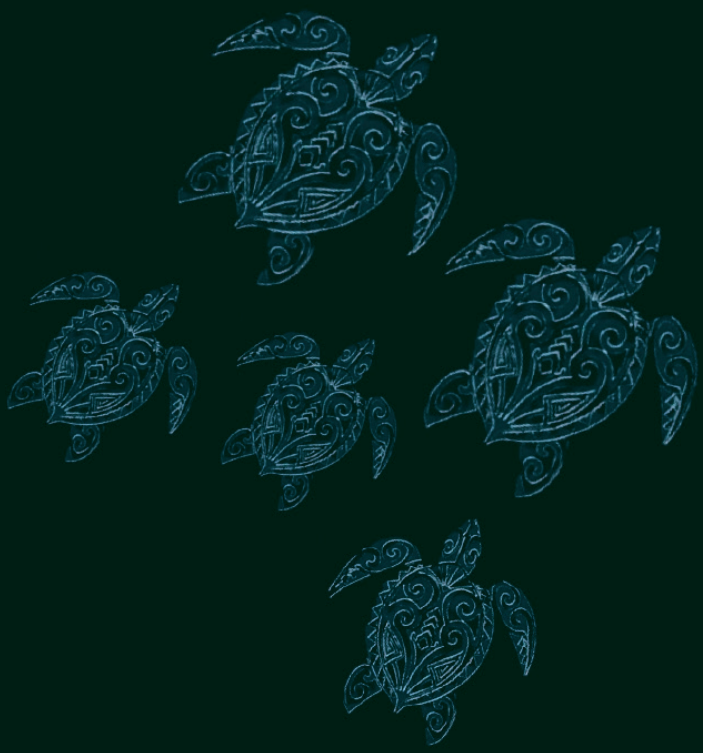
— Sir James Paget - Surgeon

APPENDIX

II

About the Author

PhD Portfolio · Acknowledgements



About the Author



Liam Paget, of Irish and Scottish descent, was born and raised in Amsterdam. After Het Amsterdams Lyceum he studied Biomedical Sciences at VU University Amsterdam and Medicine at the University of Amsterdam (AMC). Growing up he competed in swimming, judo (at national level) and football, before rugby took over from his mid-teens. He went on to play international rugby at youth and senior level, representing the Irish Exiles and the Netherlands.

A career-ending rugby injury led to his first publication: a case report on his own fast-tracked rehabilitation. In 2017 he started as a non-training resident (ANIOS) in Orthopaedic Surgery at Spaarne Gasthuis, followed in 2018 by a PhD at the Department of Orthopaedic Surgery and Sports Medicine, Amsterdam UMC, where he managed the PRIMA trial, a multicentre randomised controlled trial across six clinical centres. In 2020 he entered the Orthopaedic Surgery Residency Programme of Amsterdam UMC, with placements at OLVG, Tergooi Ziekenhuis, Amsterdam UMC and Spaarne Gasthuis. Liam's passion for optimising injury treatment, rehabilitation, and return to performance has led him to undertake several elective elite sports medicine and orthopaedic surgery fellowships. These included Champions League football clubs in London and Manchester, United Rugby Championship teams in Cape Town and Dublin, and Groote Schuur Hospital and the South African Sports Science Institute in Cape Town.

Rugby has remained a constant. As head or assistant coach, board member and Director of Rugby at Dutch premiership clubs, he was involved in several domestic and Belgian-Dutch championship titles, and he has been assistant coach to Dutch national selections at European championships. He currently serves on the medical committees of Rugby Europe and Rugby Nederland, is medical consultant to RC Eemland and Mixed Hockey Club HBS. Academically he is dedicated to improving player welfare currently setting-up an injury surveillance network and a head acceleration events study within Dutch Rugby. He is also medical and scientific advisor to Stichting Nazorg Sport Gehandicapten, a foundation supporting people who have sustained serious injuries in sport. Liam is married to Daphne Psaltaki, of Dutch and Greek descent. Together they have three children: Zoë, Nikki and Chris.

PhD PORTFOLIO

Name: L.D.A. Paget

Promotores: Prof. Dr. G.M.M.J. Kerkhoffs; Prof. Dr. J. L. Tol

Copromotor: Dr. G. Reurink

Courses	Host/Institution	Year	Workload (ECTS)
Hip and Knee Arthroplasty Cours	Zimmer-Biomet	2026	1.0
Hip Arthroplasty Course	Radboud MC Nijmegen	2025	0.5
Training Physiology in Sports Medicine	Dutch Sports Medicine Association	2025	1.0
Foundation Course Sports Medicine	Dutch Sports Medicine Association	2025	1.0
Anatomy, Arthroscopy and Approaches of the Knee	Arthrex/München	2025	1.0
AO Advanced Principles of Fracture Management	AO/Leeds	2025	2.0
Ankle Arthroscopy course	European Ankle Federation	2025	1.0
Advanced Trauma Life Support (ATLS) Refresher Course	ALSG	2025	1.5
Anatomy, Arthroscopy and Approaches of the Knee	Arthrex/München	2024	1.0
Basic Skills, Knee and Shoulder Arthroscopy Course	Dutch Association of Arthroscopy	2024	1.5
Knee Arthroplasty Course	Amsterdam UMC	2024	0.5
Foundation Laparoscopic Skills Course	Erasmus MC	2023	0.5
Trauma of the Shoulder, Arm, Wrist & Hand Anatomy Cadaver Course	Radboud MC, Nijmegen	2023	0.5
Recertification BROK		2022	0.5
Radiation Protection for Medical Specialists	Boerhaave	2022	1.0
AO Basic Principles of Fracture Management	AO/Oysterwijk	2022	2.0
Basic Surgical Skills	Catharina Ziekenhuis	2022	0.5

Advanced Trauma Life Support (ATLS)	ALSG	2021	2.0
BROK	Amsterdam UMC	2018	1.0
Practical Biostatistics	Amsterdam UMC	2018	1.0
Clinical Epidemiology: RCT	Amsterdam UMC	2018	0.3
Research Data Management	Amsterdam UMC	2018	0.3
Clinical Epidemiology: Systematic Review	Amsterdam UMC	2018	0.3

Podium Presentations	Year	Workload (ECTS)
Keynote speaker: VVAA congress – Head Injuries and concussion.	2026	0.5
Keynote speaker and moderator: Amsterdam Sports Medicine Congress (ACES) – A gentlemen's game played by ruffians, why rugby matters in medicine.	2026	0.5
Keynote speaker: Dutch Association for Sports Medicine (VSG) – Beyond the Game of Rugby: Bruises, Teamwork and Using Innovation in Player Welfare.	2025	0.5
Keynote speaker: DIESturbia, Pharmaciae Sacrum Symposium – Psychological Tactics in Elite Sports.	2024	0.5
European Society for Sports Traumatology Knee Surgery and Arthroscopy (ESSKA) – Platelet-Rich Plasma Injections for the Treatment of Ankle Osteoarthritis (52 week follow-up).	2024	0.5
European Society for Sports Traumatology Knee Surgery and Arthroscopy (ESSKA) – Platelet-Rich Plasma Injections for the Treatment of Ankle Osteoarthritis (26 week follow-up).	2022	0.5
World Rugby Medical Commission Conference – Discussion panel on mental health in elite rugby players	2022	0.5
European Society for Sports Traumatology Knee Surgery and Arthroscopy (ESSKA) – Effect of Platelet-Rich Plasma Injections vs Placebo on Ankle Symptoms and Function in Patients With Ankle Osteoarthritis: A Randomized Clinical Trial.	2022	0.5
European Society for Sports Traumatology Knee Surgery and Arthroscopy (ESSKA) – Ankle Osteoarthritis and its association with severe ankle injuries, ankle surgeries in former professional football and rugby players	2021	0.5

Dutch Association for Sports Medicine (VSG) – Ankle Osteoarthritis and its association with severe ankle injuries, ankle surgeries in former professional football and rugby players	2019	0.5

Organizing Committees	Year	Workload (ECTS)
Amsterdam Sports Medicine Congress (ACES): Rugby block including three speakers, of which two international speakers.	2026	1.5
3rd Lowlander conference: The Athlete's Shoulder: Rugby block including one international speaker and the physiotherapists of Dutch Rugby.	2025	1.5
The Amsterdam Movement Sciences congress	2020	1.5
The Amsterdam Movement Sciences congress	2019	1.5

Lecturing	Year	Workload (ECTS)
Residency Programme Dutch Association of Sports Medicine: Rugby: The Game, the injuries and the road to recovery.	2024	1.0
Supervision of Milo Mokkenstorm, Scientific Internship/Master thesis: Injectables in the Treatment of Ankle Osteoarthritis	2022	2.0
Guest lecturer for both Bachelor of Medicine Module Orthopaedic surgery and Sports Medicine – Fast-tracked Rehabilitation and Return to Sport of a Rugby Player	2016-2019	1.0
Guest lecturer elective minor 'Arts & Topsport' (Medicine bachelor, UvA) – Fast-tracked Rehabilitation and Return to Sport of a Rugby Player	2016-2019	1.0

Awards and Grants	Year
Dutch Orthopaedic Association (NOV) – Nomination van Rens Prize (best Abstract): Platelet-Rich Plasma Injections for the Treatment of Ankle Osteoarthritis (52 week follow-up).	2023
Dutch Association for Sports Medicine (VSG) – Prize: Best abstract: Effect of Platelet-Rich Plasma Injections vs Placebo on Ankle Symptoms and Function in Patients With Ankle Osteoarthritis: A Randomized Clinical Trial.	2022

Dutch Association for Sports Medicine (VSG) – Nomination best abstract: Platelet-rich Plasma Injections for the Treatment of Ankle Osteoarthritis (52 week follow-up).	2022
Sport Kongres Scandinavian Sports Medicine Congress – Nomination best abstract Effect of Platelet-Rich Plasma Injections vs Placebo on Ankle Symptoms and Function in Patients With Ankle Osteoarthritis: A Randomized Clinical Trial.	2021
Grant: Marti-Keuning Eckhardt Foundation	2021

Publications (Journal Articles and Book Chapters)	Year
Book Chapter J. Nienke Altink, **Liam D. A. Paget,** Robin P. Blom, Jari Dahmen, Miki Dalmau-Pastor & Gino M. M. J. Kerkhoffs. **Ankle Sprains and Instability.** In: Gian Luigi Canata, Pieter D'Hooghe, Kenneth J. Hunt, Gino M. M. J. Kerkhoffs, Umile Giuseppe Longo, **Management of Track and Field Injuries.** Springer Cham; 2021.	2021
Journal Articles	
Low annual revision rate in ankle distraction for ankle osteoarthritis: A systematic review and meta-analysis. J J Hollander, **L D A Paget,** J Dahmen, T Stornebrink, Q G H Rikken, I N Sierevelt, G M M J Kerkhoffs, S A S Stufkens. Knee Surg Sports Traumatol Arthrosc. 2024 Feb;32(2):344-351.	2024
Platelet-Rich Plasma Injections for the Treatment of Ankle Osteoarthritis: Response. L D A Paget, G Reurink, G M M J Kerkhoffs, J L Tol. Am J Sports Med. 2024 Feb;52(2):NP4-NP5.	2024
Improving Injectable Orthobiologics Reporting Guidelines Adherence: Response. L D A Paget, G Reurink, G M M J Kerkhoffs, J L Tol. Am J Sports Med. 2023 Dec;51(14):NP67.	2023
The completely patient-reported version of the American Orthopaedic Foot and Ankle Society (AOFAS) score: A valid and reliable measurement for ankle osteoarthritis. L D A Paget, I N Sierevelt, J L Tol, G M M J Kerkhoffs, G Reurink. J ISAKOS. 2023 Oct;8(5):345-351.	2023
What Is the Efficacy of Intra-articular Injections in the Treatment of Ankle Osteoarthritis? A Systematic Review. L D A Paget, M J Mokkenstorm, J L Tol, G M M J Kerkhoffs, G Reurink. Clin Orthop Relat Res. 2023 Sep 1;481(9):1813-1824.	2023
Platelet-Rich Plasma Injections for the Treatment of Ankle Osteoarthritis (52 week follow-up). L D A Paget, G Reurink, R J de Vos, A Weir, M H Moen, S M A Bierma-	2023

Zeinstra, S A S Stufkens, S Goedegebuure, R Krips, M Maas, D E Meuffels, P A Nolte, J Runhaar, G M M J Kerkhoffs, J L Tol. Am J Sports Med. 2023 Aug;51(10):2625-2634.	
Platelet-Rich Plasma Injections vs Placebo for Patients With Ankle Osteoarthritis-Reply. L D A Paget, G Reurink, J L Tol. JAMA. 2022 Feb 22;327(8):781.	2022
Health-Related Quality of Life in Ankle Osteoarthritis: A Case-Control Study. L D A Paget, J L Tol, G M M J Kerkhoffs, G Reurink. Cartilage. 2021 Dec;13(1_suppl):1438S-1444S	2021
Effect of Platelet-Rich Plasma Injections vs Placebo on Ankle Symptoms and Function in Patients With Ankle Osteoarthritis: A Randomized Clinical Trial (26 week follow-up). L D A Paget, G Reurink, R J de Vos, A Weir, M H Moen, S M A Bierma-Zeinstra, S A S Stufkens, G M M J Kerkhoffs, J L Tol; PRIMA Study Group. JAMA 2021 Oct 26;326(16):1595-1605.	2021
Letter to the Editor on "Treatment of lateral ankle sprain with platelet-rich plasma: A randomized clinical study". J Dahmen, **L D A Paget,** G Reurink, J L Tol, G M M J Kerkhoffs. Foot Ankle Surg. 2019	2019
Ankle osteoarthritis and its association with severe ankle injuries, ankle surgeries and health-related quality of life in recently retired professional male football and rugby players. L D A. Paget, H Aoki, S Kemp, M Lambert, C Readhead, K Stokes, W Viljoen, G Reurink, J L Tol, G M M J Kerkhoffs, V Gouttebarge – BMJ Open 2020	2020
Platelet-Rich plasma Injection Management for Ankle osteoarthritis study (PRIMA): protocol of a Dutch multicentre, stratified, block-randomised, double-blind, placebo-controlled trial. L D A Paget, S M A Bierma-Zeinstra, S Goedegebuure. G M M J Kerkhoffs, R Krips, M Maas, M H Moen, G Reurink, S A S Stufkens, R J de Vos, A Weir, J L Tol. BMJ Open 2019 Oct 7	2019
Assessment of Isometric Knee Flexor Strength Using Hand-Held Dynamometry in High-Level Rugby Players Is Intertester Reliable. A D van der Made, **L D A Paget,** J N Altink, G Reurink, W R Six, J L Tol, G M M J Kerkhoffs. Clin J Sport Med. 2019 Dec 12	2019
Fast-tracked Rehabilitation and Return to Sport of a Rugby Player with a Complicated Posterolateral Corner Injury with Associated Peroneal Paralysis. L D A Paget, P P F M Kuijer, M Maas, G M M J Kerkhoffs – BMJ case reports. 2017	2017

Other PhD-related activities	Year	Workload (ECTS)
Journal Club	2018-2021	2

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Throughout the years I have had the privilege to stand on the shoulders of absolute giants and work with inspiring people. I am truly grateful for the generosity, the mentorship, the grounded conversations, the opportunities, but most importantly, the laughs we have shared. They are the cornerstone of not only this thesis but have made this journey an absolute joy. I would like to thank a few in particular.

Prof. Dr. G.M.M.J. Kerkhoffs, dear Gino, as a patient, PhD student and resident you have guided me through different facets of my life, from rehabilitation days to clinical, academic and general mentorship. Your leadership but also your take on treatment of elite athletes sets a true example, not only treating the injury, but a full multifaceted packaged guidance on return to elite performance, with attention to the smallest of details along the way. However, I have had the privilege of learning far more than just clinical aspects. Your ability to see opportunities, connect people, lift projects to a higher level and juggle multiple responsibilities is truly inspiring. You recognize how to get the best out of people and their talents, facilitating confidence and autonomy. But what I appreciate above all is the banter and the long chats on sports, sport tactics, good food, leisure, family. Thank you for the laughs, your ever present mentorship, guidance and unwavering support throughout the years.

Prof. Dr. J. L. Tol, dear Hans, my experience with you from PRIMA trial set-up to finish has been absolutely brilliant. You set a completely different standard with regards to scientific standards of studies and I am privileged to have been allowed to learn from you. Your critical questions and attention to detail but also your no-nonsense approach whilst also being able to put all into perspective, were ever present: “It is only a study Liam, no one is going to die”. This meant celebrating the little wins and every milestone inclusion accompanied by your famous catchphrase “PRRRRIMAAA….”. We celebrated each time the PRIMA trial ended, and as it got unended three times, we celebrated three times. As with all your PhD students, each manuscript returned completely red making me doubt whether I had sent the draft in the wrong font colour to begin with. But it was exactly that, that gave us the confidence to set-up and manage research projects and manuscripts and be critical. Your ability to push me to think outside the box and encourage me to take the lead whilst always giving the feeling that you are 100% behind me gave me an enormous amount of confidence. I am grateful to have had you in my corner.

Dr. G. Reurink, dear Guus, your door was always open. There is no storm, chaos or pressure that seems to rock your boat. And in the middle of a storm, a raised eyebrow, a steely stare into the distance and a muttered tja…, is the most flustered I have seen you, before we got back to fixing whatever needed fixing. Your calmness, wise words, critical view, genuine involvement and solutions

were ever present during my PhD and was a large part in bringing it to a next level. You knew better than almost anyone what it means to manage a trial and then have the evidence say *no*, and you taught me to regard that not as failure but as the entire point.

Anne van der Made and **Jari Dahmen**, my paranymphs. It means a lot to have the two of you standing beside me on the day. In over 10 years, the constant banter, outdoing each other in practical jokes and jeering as well as being my sounding board and mirror are a true testament of our friendship. **Anne** your critical eye is as sharp as a sword and has always brought every project we have done together to another level. I would still advise some work on your Scottish accent. **Jari**, your sheer productivity is the stuff of legend and admirable how attentive you are to all around you. That I get to defend this thesis with the two of you at my side is exactly as it should be. **Anne** and **Jari**, Thank you for your unwavering support, the chats, the banter and your friendship.

Dear doctoral committee, your time and effort is very much appreciated. Thank you for taking part in the committee: **Prof. dr. J.A.M. Bramer, Prof. dr. R.J. Oostra, Prof. dr. S.A. Bus, Dr. M. Zengerink, Dr. Y.L. Hiemstra and Prof. dr. V. Gouttebarge.** Dear **Vincent**, I very much enjoy working together, whether it is football, rugby or hockey. Thank you for always being up for a chat, the mentoring, the opportunities and your guidance.

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