Medial Tibial Stress Syndrome

Diagnosis, Treatment and Outcome Assessment

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Mediaal Tibiaal Stress Syndroom

Diagnose, Behandeling en Uitkomstbepaling

(met een samenvatting in het Nederlands)

Proefschrift

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Chapter 01

General introduction

Medial tibial stress syndrome (MTSS) is one of the most frequently seen overuse injuries in modern sports medicine and physiotherapy practices.[1,2] Yet it seems that MTSS may have been around for a long time. Investigators from the University of Athens found a 500-800 year old skeleton, from a Byzantine graveyard in Rhodes, Greece. They observed surface cortical lesions along the posteromedial tibial border, and excessive cortical tissue deposition. The researchers concluded that this person probably suffered from bilateral MTSS.[3]

While the problem of MTSS may have been around for a while, its terminology has a relatively short history. M.B. Devas, an orthopaedic surgeon from the Middlesex Hospital in London, was one of the first to write about "shin soreness" or "shin splints".[4] Others followed with distinct names for MTSS, most including variations to shin splints (e.g. shinsplint[5], shin splint syndrome[6] and posterior tibial syndrome[7-9]). Presently, the most commonly used name is medial tibial stress syndrome. A 'syndrome' is "a concurrence of several symptoms in a disease...".[10] Syndrome means that we recognise a set of symptoms as a clinical entity, however, it also implies the absence of a known and clearly defined pathogenic process.

Incidence rates vary from 4 to 35% in young athletic and military populations.[11-15] Yates and White's definition for MTSS is commonly used: "pain along the posteromedial border of the tibia that occurs due to exercise...", and in addition, the pain has "...to be spread over a minimum of 5 centimetres..." when the posteromedial tibial border is palpated.[13]

1.1. THE IMPACT OF MTSS

Presently, MTSS is a well recognised and commonly seen sporting overuse injury. However, there seems to be a lack of understanding regarding the best way to manage MTSS. Multiple studies have shown that injury duration is often protracted. For example, in a study by Moen et al.,[16] the duration of symptoms prior to study participation was close to two years in one of the groups. In studies by Rompe et al. and Brinkman et al. the duration of pain was 6 - 30 and 2 - 56 months prior to study enrolment, respectively.[17, 18] At this point, it is unclear to what extent athletes can be treated effectively in the long-term. Multiple studies by Moen et al. suggest that the recovery time can take up to 90 - 120 days.[16, 19] Recovery in these studies was defined as being able to run 18 minutes on a pace while speaking became difficult. It is likely that many athletes' ideal level of sporting activity lies far beyond this point. Athletes seem to endure multiple episodes of MTSS after their recovery.[15, 20, 21]

In summary, MTSS is a common injury with a seemingly long recovery time and may cause athletes to reduce sporting activities and limits their performance. Once symptom-free, the risk of a new episode of MTSS seems high.

1.2. MTSS AND GAPS IN THE BODY OF KNOWLEDGE

There are many gaps in the literature regarding MTSS that impede the further study

in the field. Currently, the underlying pathogenesis of MTSS is unclear and it is also unknown how best diagnose it. Importantly, we do not how to treat MTSS best and there is no instrument to measure injury severity and treatment outcomes. It seems difficult to target preventative and treatment interventions for MTSS with limited understanding about the pathogenesis, diagnosis and measurement of outcomes. These gaps need to be addressed before further studies can investigate areas such as (secondary) prevention, prognostic factors and treatment of MTSS in epidemiological and randomised controlled studies with long-term follow-up.

In this chapter we will introduce the following topics:

1. Pathogenesis
2. Diagnosis
3. Treatment
4. Outcome assessment

We will discuss the gaps in the existing knowledge regarding these areas and how this thesis seeks to address them.

1.3. PATHOGENESIS

Several theories regarding the pathogenesis of MTSS exist. It is suggested that MTSS is a "traction-induced" periostitis,[22, 23] a crural fasciitis[24] or a local tibial bone overload injury.[25] Others have stated that a combination of these two or three structures are affected in MTSS.[26, 27] Here, we will introduce these theories and the available evidence supporting these premises.

1.3.1. TRACTION-INDUCED PERIOSTITIS

Multiple authors have stipulated that the periosteum may become inflammatory in athletes with MTSS.[25, 28] This is thought to be due to repeated contractions of the (deep) ankle plantar flexors pulling on the muscles' origin; the tibial periosteum. When the loads applied exceed a certain threshold, the periosteum could become inflamed. There is debate as to whether the proximal origins of the lower leg muscles insert at the site where MTSS occurs.[22, 27]

Beck et al. investigated the insertions of the soleus, flexor digitorum longus, tibialis posterior onto the tibia.[22] They found connections of the soleus and flexor digitorum longus along the medial aspects of the posterior side of the tibia, and concluded that these muscles could induce traction onto the posteromedial tibial periosteum (fig. 1). However, connections were found only between the junction of the proximal and distal 1/2 of the tibia and the junction of the mid and distal 1/3 of the tibia; this leaves the common pain site of the distal 1/3 of the tibia in MTSS unexplained. No connection of the tibialis posterior to the posteromedial aspects of the tibia was found.[22] Saxena et

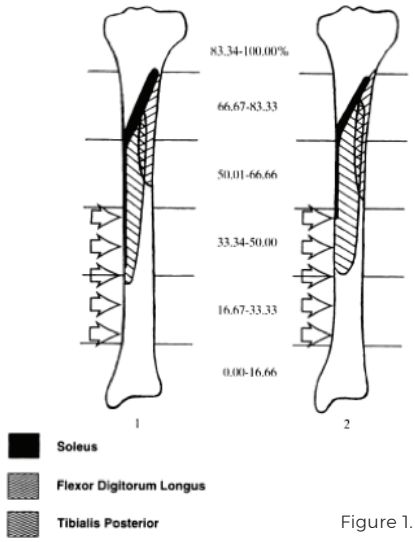

Figure 1.

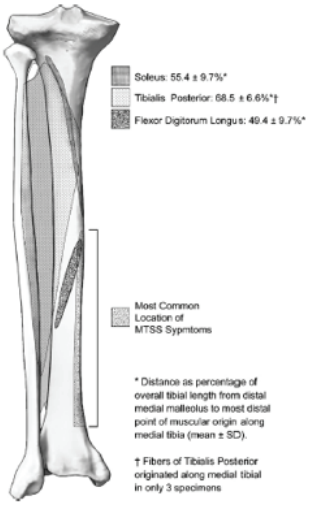

Figure 2.

Figure 1. Origins of the soleus, tibialis posterior and flexor digitorum longus in the lower leg, according to Beck et al. 1994 (with permission)[22] Percentage ranges 6 equal parts of 16.67% of the tibia. Open arrows = MTSS area Figure 2. Origins of the soleus, tibialis posterior and flexor digitorum longus in the lower leg, according to Stickley et al., 2009[30]

al. investigated the most distal location of where the tibialis posterior muscle was attached to the tibia in 5 cadaveric legs and 5 below-the-knee-amputated limbs.[29] Soleus muscle attachments and connection of the crural fascia were also evaluated for their presence in the distal 1/3 of the tibia. The tibialis posterior was found to be attached medially, a mean 7.7 cm proximal to the medial malleolus. It would seem this is within the distal 1/3 of the tibia. In addition to the tibialis posterior, the crural fascia was also found to be attached posteromedially to the tibia. No connections of the soleus to the tibia were found in the distal 1/3 of the tibia.[29] Upon personal communication, the first author A. Saxena said their results may have been found due to a mistake while performing the study (personnel communication dr. A. Saxena with dr. M.H. Moen).

Stickley et al. investigated the connection of the ankle plantar flexors (tibialis posterior, flexor digitorum longus, soleus, the soleus aponeurosis and the deep crural fascia) to the tibia in 16 fresh cadaver limbs.[30] No connections of the tibialis posterior or flexor digitorum longus were found along the medial aspect of the posterior tibia, in the distal 1/3 of the tibia (fig. 2). They found a soleus aponeurosis along the medial aspects of the tibia in three cadaver limbs, but this was mostly proximal to the junction of the mid and distal 1/3 of the tibia. The deep crural fascia attached along the entire length of the tibia in all but three specimens.[30] The authors concluded that the deep crural

fascia may cause inflammation of the periosteum.

Brown (2015) investigated the anatomical location of the tibialis posterior, flexor digitorum longus and soleus muscle in 22 legs of 11 male and 2 female cadavers (fig. 3).[31] He also looked at the location of the deep crural fascia along the medial aspects of the tibia. He found that the tibialis posterior was not attached to the MTSS area; it was attached to the posterior surface of interosseous membrane, the lateral aspect of the posterior surface of the tibia and the medial aspect of the posterior surface of the fibula. The soleus was attached to the medial aspects of the posterior surface of the tibia, but only in the proximal half of the tibia. The flexor digitorum longus was found to be attached to the medial aspects of the posterior surface of the tibia, just distal to the soleal line; also in the proximal half of the tibia. The deep crural fascia was found to be attached along the proximal 2/3 of the medial border of the tibia.[31]

Edama et al. investigated the location of the tibialis posterior, soleus, flexor digitorum longus, flexor hallucis longus and deep crural fascia in 100 legs of 55 cadavers.[32] They found that the tibialis posterior and flexor hallucis longus had no connection to the medial margins of the tibia. Additionally, they found that the flexor digitorum longus was connected to the mid or distal 1/3 of the tibia in 97% of the cadaveric legs, and the soleus in 49% of the cadaveric legs. However, none of these covered the entire MTSS area (fig. 4). Only the crural fascia was attached along the entire medial tibial border.[32]

In summary, studies did not find a relationship between the anatomic position of muscles in the lower leg and the location where MTSS occurs, except for that of Saxena et al.[29] The deep and superficial crural fascia, however, are attached to the tibia at the location where MTSS occurs.

A cadaveric study by Bouché and Johnson (2007) studied the traction-mechanism and shows how fascial traction may work.[23] They attached the tibialis posterior, flexor digitorum longus and soleus aponeurosis to three pneumatic actuators that pulled upward, simulating muscle pull, in three cadaveric legs. Four strain gauges measured the medio-lateral strain while the three muscles were pulled to superior. A linear relation was seen between muscle pull and strain measured in the fascia. Visual inspection revealed a fascial tenting effect while pulling the muscles. The authors speculated that if MTSS is related to a traction-induced periostitis, the deep crural fascia is the medium through which this traction is applied.[23]

Histological studies have examined the traction periostitis theory in athletes with MTSS. Johnell et al. were the first to investigate the traction theory in patients with MTSS.[24] They obtained 33 soft-tissue biopsies, including periosteum and crural fascia from athletes with MTSS. They found inflammatory changes in 13 (39%) fascia biopsies; plasma cell infiltration, aggregates of lymphocytes, histocytes and mast cell surrounding and infiltrating the walls of small arteries were seen. Periosteal inflammation (i.e. plasma cell infiltration surrounding wide lymphatics) was seen in one athlete with MTSS only.[24] Bhatt et al. found that 21/32 (66%) of periosteal biopsies showed abnormalities, such as thickening, fibrosis and vascular ingrowth. However, only a few cases showed signs of

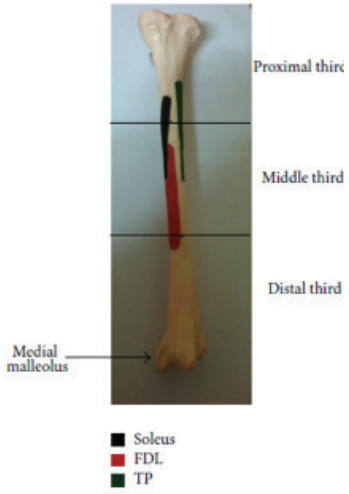

Figure 3

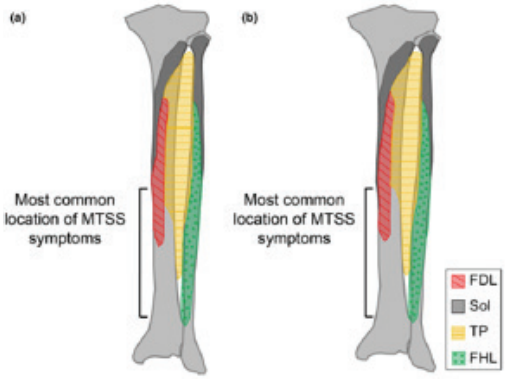

Figure 4.

Figure 3. Illustration of the anatomical origins of the deep ankle plantar muscles in the lower leg according to Brown AA, 2015.[31] FDL = flexor digitorum longus, TP = tibialis posterior.

Figure 4. Illustration of the anatomical origins of the deep ankle plantar flexors in the lower leg according to Edama et al., 2015.[32] A = men, B = women, FDL = flexor digitorum longus, Sol = soleus, TP = tibialis posterior, FHL = flexor digitorum longus.

inflammation; mucin production and iron deposition.[28] Changes in the periosteum may resemble normal physiological responses to traction forces, causing tissue adaptation and strengthening. There have been no studies investigating periosteal abnormalities in a population with MTSS and non-injured controls. Such a study may elucidate on the relationship between periostitis and MTSS.

1.3.2. LOCAL TIBIAL BONE OVERLOAD

In recent years the bony overload theory, a pathogenic process similar to stress fractures, has been frequently cited. Moen (2012) linked insights from Frost's Utah paradigm to MTSS.[33 - 35] In this paradigm (figure 5), bone strains that exceed the minimal effect strain for modelling (i.e. the modelling threshold), but remain below the microdamage threshold (i.e. minimal strain to produce microdamage), cause remodelling and strengthen the bone. However, repetitive or large strains may exceed the microdamage threshold and the osteoclast activity may outpace osteoblast activity, the bone strength decreases and an injury occurs.[33, 34] Studies in mice found that repeated bending leads to adaptation of the tibial bone, predominantly at sites where strains are highest; the

junction of the mid- and distal 1/3 of the tibia, where MTSS occurs,[36, 37] confirming the susceptibility of this area to injury.

Histological examination has provided some preliminary evidence that bone changes may be associated with MTSS. Johnell et al. took 35 tibial bone biopsies at the medial border from 33 cases with MTSS.[24] Six patients having surgery for acute ankle injuries served as control biopsies, along with four cadaver biopsies. Most of the MTSS cases' (63%) biopsies showed signs of osteoblast-activity (active-cubical-osteoblasts covering an area of bone formation, vascular ingrowth into the surface of the cortical bone or osteoid seams covering more than half of the cortical bone surface). No changes were seen in any of the control biopsies, although it is not reported if any of the controls were physically active.[24]

The bone overload theory is most convincingly supported by two studies from a Swedish group. Magnusson et al. investigated the bone mineral density (BMD) in 5 regions in the tibia, by means of dual energy x-ray absorptiometry (DEXA) scans, in 18 athletes with long-standing MTSS symptoms (median 31 months), and compared these to sex- and age-matched controls from the hospital staff, and to athletic controls without MTSS.[38] They found that the BMD in the painful region along the medial tibia was 15% (SD 9%) lower than controls and 23% (SD 8%) lower than athletic controls without MTSS.[38] On follow-up, after a mean of 5.7 years, when symptoms had disappeared, the BMD had increased by 0.32 g/cm^2 in athletes with MTSS. Their BMD values upon follow-up were similar to those of athletic controls.[39]

Moreover, the BMD in the MTSS area was the only region that changed; other areas in the tibia, femur and lumbar spine did not change. This seems to strongly support the bone overload theory. Yet, it is unknown if this phenomenon occurs in all athletes with MTSS, and if it is related to a prolonged failing of local tibial bone remodelling. Özgürbüz et al. also performed a case-control study, in athletes with MTSS with a short period of symptoms (mean duration 5 weeks).[40] They obtained BMD values by means of DEXA scans in 11 athletes with MTSS and compared these to 11 athletic controls without current or previous shin pain. They found no differences in BMD between athletes with and without MTSS.[40] As bone changes probably start at the bone structure level, relevant changes may not be detectable on DEXA scans in the initial phase of the injury.[27, 41] The sample size in both studies was small; Magnusson et al., N = 14; Özgürbüz et al., N = 11. To what extent their findings apply to all athletes with MTSS remains unclear.

1.3.3. MTSS: MORE THAN ONE PATHOGENESIS?

Some authors have stipulated that there is more than one type of MTSS. Detmer distinguished four types of MTSS: stress fracture (type 1a), stress microfracture/diffuse stress reaction in the tibia (type 1b), chronic periostalgia (type 2), and chronic exertional compartment syndrome of the deep or superficial compartment.[26] Stress fracture, chronic exertional compartment syndrome and MTSS are presently acknowledged as

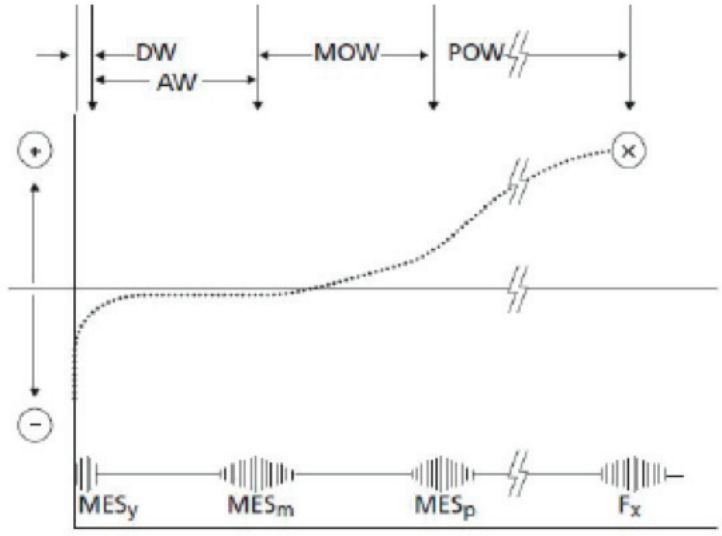

Figure 5. Modelling, remodelling and microdamage according to Frost, 1997 (with permission).[34] DW = disuse window; AW= adapted window as in normally adapted young adults; MOW = mild overuse window; POW = pathologic overload window; MESy = minimum effect strain for remodelling; MESm = minimum effect strain for modelling; MESp = minimal effect strain for microdamage, Fx = the fracture strain range.

separate entities.[42] However, type 1b (stress reaction) and type 2 (chronic periostalgia) in this system may co-exist as separate entities (i.e. a combination of the traction and bone theory), or point to the same pathogenic process. The periosteum is not only a structure to which the fascia or lower leg muscles may be attached in the region of MTSS, it also plays an important role in the homeostasis and remodelling of bone tissue.[43, 44]

We performed a study to investigate the pathogenesis of MTSS. In Chapter 2 we investigated the bone, periosteum and deep ankle plantar flexor muscles for abnormalities, in a case-control study, with athletes with and without MTSS. We hypothesised that if MTSS would be related to periosteal or tendinous changes, this could be detected with musculoskeletal ultrasonography.

1.4. DIAGNOSIS

In sports medicine, history and physical examination are considered the cornerstone for making the diagnosis. Multiple studies have shown that imaging modalities such as X-rays, magnetic resonance imaging, computed tomography or bone scans do not accurately differentiate between athletes with and without clinically diagnosed MTSS.[45-47] The underlying pathogenesis of MTSS is equivocal; MTSS is considered a clinical condition. As long as the pathogenesis of MTSS is not fully understood, it does

not seem logical to use imaging in the diagnosis of MTSS. While the clinical diagnosis is the cornerstone of diagnosing MTSS, its reliability has never been investigated. Clinicians making reliable diagnoses forms a good foundation for the discussion of expectations and planning treatment. A reliable diagnosis is also important for clinical research. Multiple researchers often include athletes in clinical trials, especially if they are multi-centre studies. For clinical practice and research settings it is important to reliably identify co-existed lower leg injuries, as this may change prognosis and treatment in practice, and it may alter the eligibility of a candidate athlete for participation in a clinical trial.

1.4.1. THE CLINICAL DIAGNOSIS MTSS

In lower leg overuse injuries, several entities share features with MTSS; predominantly in their location, pain provoking activities and the nature of the pain. MTSS can be recognised in patient history when exercise-induced diffuse pain is present along the medial aspects of the lower leg, during or after exercise. When recognisable pain along the posteromedial tibial border can be provoked over ≥ 5 centimetres, the presence of MTSS is likely; the diagnosis can be confirmed when there are no other entities present that could also explain the recognisable pain.[13] In the diagnosis of MTSS it seems thus important to consider differential diagnoses.

1.4.2. DIFFERENTIAL DIAGNOSES OF MTSS

There are several differential diagnoses to take into account when assessing the lower leg for the presence of MTSS, of which tibial stress fracture (TSF) and chronic exertional compartment syndrome (CECS) are considered to be the most important.[42]

1.4.2.1. TIBIAL STRESS FRACTURE

Tibial stress fracture (TSF) is a form of bone fatigue damage due to repetitive loading.[48] It presents as exercise-induced lower leg pain, often along the anteromedial surface of the tibia or along the anterior tibial crest. It usually has an insidious onset, with pain perceived during prolonged strenuous activities. Pain may be felt during the onset and after cessation of exercise when the injury progresses. Pain is often more focal than in athletes with MTSS, and can be pin-pointed with one finger. Weight-bearing activities, such as jumping and running, provoke the recognisable pain in TSF, and rest leads to a reduction of pain.[42, 48] Focal pain on palpation and pain upon tapping may further contribute to the suspicion of TSF.

1.4.2.2. CHRONIC EXERTIONAL COMPARTMENT SYNDROME

Chronic exertional compartment syndrome (CECS) is an overuse injury that is frequently seen in the lower leg, particularly in military personnel.[49] The pain seems to be associated with an increased pressure in the affected compartment leading to

ischaemia, in some cases leading to a vascular occlusion.[50] Others state that CECS may be the effect of an angiogenesis imperfecta, or a crural fascia that is too tight/not able to stretch.[51] CECS usually presents as cramping, burning pain over the affected compartment. With regard to location, the pain is expected to be felt on the anterior (in case of the anterior CECS) or posterior side (in case of the posterior CECS) of the lower leg. The pain usually ceases quickly upon stopping the provoking activity, where pain in MTSS tends to linger for a couple of hours to a couple of days.[42] In some athletes with CECS, a fascial hernia may occur. A focal subcutaneous mass is seen and felt upon palpation. Fascial hernia's usually occur when there is too much pressure in the affected compartment. A focal fascial defect may then develop. Most fascial hernias do not usually cause pain.[52]

1.4.2.3. POPLITEAL ARTERY ENTRAPMENT SYNDROME

A popliteal artery entrapment syndrome (PAES) is rarely seen in athletes, but seems an important differential diagnosis to bear in mind while examining athletes with lower leg pain. It's speculated that PAES is a result of an anatomic variation of the triceps surae, which can lead to compression of the artery in popliteal fossa during exercise. It's particularly seen in those athletes that have a sudden increase of sporting activities, which may cause the gastronemius and/or popliteal muscle to hypertrophy. Athletes report pain during exercise, a cramping or burning pain in the calf muscle group. Some report paraesthesia in the calf.[51]

1.4.2.4. SOLEUS STRAIN

The soleus muscle is directly posteriorly/postero-laterally located to the typical area of MTSS (the posteromedial border of the tibia).[54] A soleus muscle strain is therefore one of the differential diagnoses to consider when an athlete perceives pain in the medial side of the lower leg. It seems rather easy to distinguish MTSS from an acute soleus strain. There is a distinct onset; MTSS develops gradually. It is more challenging to distinguish MTSS from a medially located chronic soleus strain with a gradual, insidious onset. This type of injury can be differentiated from MTSS by its location, and by palpating the calf and bone to identify the area with recognisable pain. Resistance testing of the soleus muscle may help to distinguish the two entities. However, a previous study showed that this test is positive for pain in 3.8% of the athletes with MTSS, which means one should be cautious when using this test to distinguish the two entities.[47]

In conclusion, it seems that the location of the pain, the size of the pain location, and provocation and reduction are most important when differentiating between the various lower leg overuse injuries. Several lower leg injuries may co-exist in the lower leg. Identifying possible co-existing lower-leg injuries may be important to target the right intervention. The reliability of making the clinical diagnosis MTSS warrants investigation. Therefore, we investigated the inter-rater reliability of making the diagnosis MTSS using history and physical examination in a cross-sectional study (Chapter 3).

We also evaluated if raters were able to identify co-existing injuries to MTSS reliably.

1.5. TREATMENT

A critical review, published in 2009, highlighted the existence of only 3 RCTs.[25] The first RCT from 1974, had 5 intervention groups (ice application, aspirin intake, phenylbutazone, calf-stretching exercises, a plaster walking cast).[55] The second investigated the effectiveness of orthoses in addition to a walk to running program versus a walk to running program only.[56] In the third trial the difference between low-energy laser treatment and placebo laser treatment was investigated.[57] No significant differences were found between any of the investigated interventions in these 3 RCTs.

Between 2009 and 2014 several new studies emerged, investigating the effects of extracorporeal shockwave therapy, lower-leg stockings and strengthening and stretching exercises in addition to a graded running program.[16, 17, 19] However, it remains unclear which intervention is the most effective in the treatment of MTSS. Firstly, we evaluated the evidence regarding the treatment of MTSS in a systematic review (Chapter 4). In the subsequent Chapter 5 we report on two MTSS cases that were treated with corticosteroid injections.

1.6. OUTCOME ASSESSMENT

A major issue for MTSS research is the lack of an instrument to evaluate injury severity and outcomes of treatment interventions. It's challenging to compare MTSS populations and outcomes between MTSS studies as most of the treatment studies use different measures to evaluate injury severity and treatment outcomes. For example, the study by Rompe et al. uses pain and Likert Scales,[17] the studies by Moen et al. use 'pain free running distance' and time to recovery,[16, 19, 58] the latter is defined as "being able to run for 18 consecutive minutes at a speed where speaking becomes difficult". Other studies use visual analogue scales to evaluate treatment outcomes.[55, 59] One can question the use of such measures to assess outcomes, as these measures have not been validated for use in athletes with MTSS.

Many researchers, [60 - 62] and organisations such as The American Food and Drug Administration, advocate that the perception of the patient should play a central role in the assessment of treatment outcomes.[63, 64] Over the past 10 years, patient reported outcome measures (PROMs) have gained popularity and they are now considered to be the cornerstone of outcome assessment in both sports clinical practice and randomised controlled trials.[60, 61] In Chapter 6 we report on the item generation for a new PROM for MTSS: the MTSS score. Subsequently, we evaluated which items were best for the MTSS score and evaluated the MTSS score for its validity, reliability and responsiveness (Chapter 7). Its aim is to measure injury severity and treatment outcomes in clinical studies in the field of MTSS.

Finally, all of our findings are discussed in the general discussion in Chapter 8.

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Chapter 02

Are ultrasonographic findings like periosteal and tendinous edema associated with medial tibial stress syndrome? A case-control study

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2.1. ABSTRACT

2.1.1. OBJECTIVES

Medial tibial stress syndrome (MTSS) is one of the most common sporting injuries. As of yet, the development of effective therapeutic interventions to treat MTSS is hindered by the fact that its pathology is unknown. Our aim was to explore the pathology of MTSS, by assessing whether the presence of MTSS is related to periosteal, bony or tendinous abnormalities in the lower leg.

2.1.2. DESIGN

Case-control study.

2.1.3. METHODS

Participants with MTSS and athletic control participants were recruited from the same (high-risk) base population. Musculoskeletal ultrasonography was performed on the posteromedial tibialborder and deep plantar flexor muscles by an experienced radiological specialist who was blinded togroup membership. Associations between MTSS and tissue abnormalities were expressed in odds ratios(OR).

2.1.4. RESULTS

A total of 42 participants, 15 MTSS cases and 27 control athletes completed the study. Overall, periosteal and tendinous abnormalities were common in cases with and without MTSS. Periosteal edema was present in 8 (53.3%) MTSS cases and in 10 (37.0%) control athletes, in specific painful spots in the distal 2/3 of the posteromedial tibial border OR = 1.9 (95% CI 0.54–6.99, p = 0.35). Also, tendinous abnormalities in the tibialis posterior muscle were frequently seen in MTSS cases (N = 7, 46.7%) and in control athletes(N = 13, 48.1%) (OR = 0.97, 95% CI 0.27–3.51, p = 0.96). No bone abnormalities were observed in either group.

2.1.5. CONCLUSION

Periosteal and tendinous findings seem to be common in both athletes with and without MTSS, and consequently are not associated with MTSS.

2.2. INTRODUCTION

Medial tibial stress syndrome (MTSS) is one of the most commonly seen exercise-induced leg injuries.[1] MTSS is clinically diagnosed when exercise-related pain is present along the posteromedial tibial border and, in addition, when pain is provoked on palpation of the posteromedial tibial border over 5 or more consecutive centimetres.[2]

Presently, there is no treatment proven to be effective for patients with MTSS. For the development of new interventions or preventive strategies it is important that the underlying pathology of MTSS is better understood.[3]

Conventionally, it is thought that MTSS is due to a traction-induced periostitis or to a local tibial bony overload.[4,5] With regard to the traction theory, the rationale is that the deep ankle plantar flexor muscles induce traction onto the periosteum by repetitive contraction. When this is of excessive nature this may lead to an inflammation or overload of the periosteum.[6–8] In concordance with this, a study by Moen et al. suggests that deep plantar flexor muscles play a role in pain perceived along the posteromedial tibial border. They found that 31.5% of their MTSS cases perceived pain on palpation of the muscles and tendons medial to the tibial border.[9] The bony overload theory is an alternative hypothesis for MTSS's pathology. This theory assumes that the tibial bone responds to (high-impact) loads exerted onto the bone during sports activities.[10,11] Bone strains cause micro dam-age in the cortical bone which under a certain threshold can be repaired, and consequently, the bone is strengthened.[12] Osteoclast may, however, outpace osteoblast activity when strains exceed thisthreshold.[11]

Hard evidence for any of the theories is lacking, as no high-quality studies investigating MTSS' pathology have been per-formed. Previous studies have assessed histological and imaging findings in relation to MTSS but none of these studies included a non-injured control group.[11] This could be important as some abnormalities (e.g. periosteal edema) are also common in asymptomatic legs.[13] Musculoskeletal ultrasonography (MSU) allows for valid and reliable assessment of pathological findings in the periosteum and tendons and enables comparison of its findings with pain locations identified through physical examination (i.e. palpation of the posteromedial aspects of the tibia).[14]

Our aim was to assess if the presence of MTSS could be related to periosteal, bony or tendinous abnormalities in the lower leg using MSU.

2.3. METHODS

A case-control design was used to assess whether abnormalities in posteromedial tibial periosteum and bone, and the tendons of the deep ankle plantar flexor muscles were associated with MTSS. We also report on an adjacent cross-sectional study, in which we assessed the inter-observer reliability of the musculoskeletal ultrasonography methods used in this study. (see appendix 2)

The study was performed at the Inholland University of Applied Sciences in Haarlem, The Netherlands. Athletes were recruited from the adjacent Dance College (Nova,

Haarlem, The Netherlands) where they are schooled/educated to become dancers (or dance teachers). The study program involves many pivoting and plyometric activities. The average amount of weekly sports activities may add-up to around 25h. Existing and new cases with MTSS, and control athletes from the same base population (all dance students) were informed about the study and requested to participate through oral presentations, flyers, email and by phone prior to the study's start. Between the 1st of March 2015 and the 10th of April 2015, one physiotherapist (MW) assessed whether participants were eligible to participate in the study based on our inclusion and exclusion criteria. Candidates without lower leg pain(controls) were eligible if they were ≥16 year of age, not injured and involved in sporting activities for ≥5h a week. Those candidates with lower leg pain were further screened for the presence of MTSS. Patients were classified as MTSS patients if exercise-induced pain was present for ≥3 weeks along the posteromedial border of the tibia and pain could be provoked on palpation over 5 or more consecutive centimetres along the posteromedial tibial border.[2] All athletes with a history of crural fracture were excluded. Also, a tibial stress fracture or MTSS in the previous 6 months, a concurrent sporting injury, or a clinical suspicion of (concurrent) chronic compartment syndrome or stress fracture was reason for exclusion.[15] Healthy control athletes were eligible for participation when they performed sporting activities for ≥5 h a week, and if they had not suffered a lower leg injury in the previous 6 months. Athletes who met our inclusion criteria were included in the study after signing informed consent. The Medical Research Ethics Committees United, Nieuwegein, The Netherlands (W15.029), provided approval before the study's commencement.

Background information was obtained regarding participants' age (years), height (centimetres), weight (kg), body mass index(calculated as kilograms/(length in metres)^2), sport that they were involved in next to their academic sports activities, hours of weekly sports activities, and, in case of presence of MTSS, duration of complaints (months) and side of complaints. In addition, cases with MTSS were asked to fill out the MTSS score. This is a recently validated disease-specific outcome measure with good validity, reliability and responsiveness.[16,17] In athletes with MTSS, the two most painful spots along the diffusely painful distal 2/3 of the posteromedial tibial border were identified through palpation by one physiotherapist (MW). In control athletes, two spots along the posteromedial tibial border were randomly selected by a computer. Next, athletes were referred to a MSU specialist to have their lower leg assessed.

One investigator (PB) who was educated for 4 years to become a medical imaging and radiation specialist, performed an extensive familiarization session of five hours to adopt the protocol. This investigator performed the musculoskeletal ultrasonography(MSU) assessment. We kept the specialist blinded to the participant to be assessed (case or control).

- For all athletes, the physiotherapist briefed the medical imaging and radiation specialist on the leg to assess and which specific spots to assess (see painful/specific spots to be assessed—section):
- In case the participant had bilateral complaints the most painful leg was assessed.

- In case of equally affected legs, a computer randomly picked a leg to assess.
- For the healthy, non-injured athletes, the leg to assess was similarly allocated, with the computer randomly allocating a leg for MSU assessment.
- Participants were asked not to reveal whether they had lower leg pain to the specialists.

The posteromedial tibial periosteum and cortical bone, and the tendons of the deep ankle plantar flexor muscles (tibialis posterior, flexor hallucis longus and flexor digitorum longus) were assessed with a musculoskeletal ultrasonography device (Siemens, ACUSONS1000, linear transducer 14L5). To this end, the posteromedial tibial border was divided into three equal parts: the proximal, middle and distal third, as follows: a tape measure assisted in determining tibial length, defined as the distance between the upper edge of the tibial plateau, palpated in the medial aspect of the articular knee joint space (directly distal to the femoral epicondyle), and the most distal palpable aspects of the medial malleolus. The total tibial length was taken as the reference and the tibia was divided into three parts of 33%. At 33% and 67% of the total tibial length the borders for each third of the posteromedial tibial border were marked with a water-resistant marker. A layer of ultrasound gel (Parker Aquasonic® Clear® Ultrasound gel) was applied onto the area to be investigated. We placed a musculoskeletal probe (14 MHz) perpendicular onto the middle and distal third of the posteromedial border to be scanned. We used the following settings to optimize contrast and depth: dynamic range: 55, space time: 2, edge: 4, tint 1, maps B, Dynamic TCE: high, Sie clear: 5, and image: detail of contrast. Settings were adjusted to enhance contrast and depth.

First, the ultrasonographic specialist assessed the two specific spots on palpation along the distal 2/3 of the posteromedial tibial border – as identified by the physiotherapist beforehand – for periosteal and bony abnormalities. For control athletes, a computer generated two random percentages (as set between 15 and 50%) of the tibial length to be investigated specifically, along the posteromedial tibial border. To assure blinding of the medical imaging and radiation specialist, the sports physiotherapist briefed the assessor which spots to assess for all athletes. The middle and distal third of the posteromedial border were scanned for periosteal abnormalities (i.e. periosteal thickening, periosteal edema or vascularization). Subsequently, the posteromedial cortical bone was screened for irregular bony contours(erosions and spurs) and cortical edema.[14,18]

The tibialis posterior, flexor hallucis longus, and flexor digitorum longus tendons were examined for pathological changes, in the distomedial aspect of the posterior surface of the lower leg. Typically, tendinopathies manifest themselves as focal or diffuse thickening (sometimes with calcifications), the presence of intra-tendinous hypoechoic areas, hypoechoic edema distending from the tendon sheath or hypoechoic tendon sheath.[14,18]

Data analysis was performed by one of the investigators (MW)using SPSS version 20.0 (IBM SPSS Inc., Chicago, USA).

We present demographic data with their adequate estimates and measures of disper-

sion. Differences between the groups were assessed using a student's t-test, or when the assumptions were violated, the Mann–Whitney U test for continuous variables, and, Fisher's exact test for nominal data. An univariable logistic regression analysis was run between the dependent variable (MTSS yes/no) and the various tissues' abnormalities. The odds ratio(OR) with 95% confidence interval (CI) expressed the association between the dependent (MTSS yes/no) and independent variables. We planned a multivariable logistic regression analysis (backward Wald) to run on those variables that showed a relation to the presence of MTSS. Threshold for entering the multivariable model was set to $p < 0.1$. Overall significance was set to $p < 0.05$ for all analyses.

To the best of our knowledge, this is the first study to assess the pathology of MTSS with MSU. For our sample size calculation, we hypothesized that if periosteal or tendinous abnormalities were associated with MTSS, this would be a prevalent feature, i.e. present in ≥67% participants with MTSS. Additionally, we considered that these findings would be only sparsely, and randomly, present in non-injured participants (<33%). Then, with the alpha set at 0.05,and a power of 80%, a sample size of N = 16 was required. To verify this hypothesis, we a posteriori performed a sample size calculation for our main finding, the presence of abnormalities on the specific measured (painful) spots.

2.4. RESULTS

Forty-six candidates were willing to participate in our case-control study. A total of 42 participants, 15 cases and 27 control athletes, met the inclusion criteria and signed informed con-sent for participation (see Fig. 1 for the study flow diagram). All demographic variables of our studied population (Table 1) were comparable except for weekly hours of sports activities ($p = 0.04$).Given the mean MTSS score, the severity of MTSS was moderate in our MTSS cases.

None of our participants dropped out in the course of our study. No data was missing, except for one MTSS score that was not completed by one athlete.

Periosteal edema at the painful/specific spots was present in 8 (53.3%) MTSS cases and in 10 (37.0%) control athletes, at both spots evaluated. These differences were not statistically significant, $p = 0.35$ (see Appendix 1). No bony edema, bony irregular surface or periosteal thickening or vascularization was observed at these specifically measured spots, in any participant (N = 0).

We found periosteal abnormalities along the posteromedial tibial border in 4 cases (26.7%) with MTSS and in 9 control athletes (33.3%). This difference was not significant, $p = 0.74$. We did not find a significant difference between groups for any of the specific periosteal abnormalities. Edema was present in 3 athletes with MTSS (20%) and in 8 control athletes (29.6%), $p = 0.72$. Two athletes with MTSS and one control athletes had periosteal thickening, $p = 0.28$. No signs of vascularization were found in any participant with or without MTSS (N = 0). One healthy control athlete did have an irregular bone surface along the posteromedial tibial border whereas another healthy control athlete had cortical edema. The Fisher's exact test revealed that these differences were not

Table 1. Demographic information

Demographic variable	MTSS group (N=15)		Control group (N=27)	P-value‡
Male/female, *n*	1/14 (6.7%/93.3%)		7/20 (25.9%/74.1%)	0.22†
Age, *mean ± SD*	20.3 ± 2.4		21.1 ± 3.4	0.46
Length in cm, *mean ± SD*	169 ± 7.0		173 ± 9.1	0.18
Weight in kg, *mean ± SD*	63.9 ± 8.6		63.6 ± 10.5	0.98
BMI, *mean ± SD*	22.3 ± 2.5		21.1 ± 2.5	0.23
Hours of sporting activities, *mean ± SD*	12.5 ± 10.6		18.7 ± 8.2	0.04#
Duration of complaints in months, *median with range (min-max)*	5 (0.75 - 66)		NA	NA
Side of complaints, *n (%)*	Both legs:	11 (73%)	NA	NA
	Only left leg:	0 (0.0%)		
	Only right leg:	4 (27%)		
MTSS - Score, *mean ± SD*	4.21 ± 1.58		NA	NA
Side assessed, *n (%)*	Left leg:	10 (67%)	15 (56%)	0.53†
	Right leg:	5 (33%)	12 (44%)	
Tibial length in cm, *mean ± SD*	39.4 ± 2.3		40.6 ± 2.9	0.26
Painful/specific spot 1*, *mean percentage ± SD*	30.4 ± 7.5		31.6 ± 10.7	0.61
Painful/specific spot 2*, *mean percentage ± SD*	33.3 ± 11.7		32.3 ± 10.6	0.74

n = number, SD = standard deviation, cm = centimetre, kg = kilograms, BMI = body mass index (calculated as kilograms /(length in meters)^2), min = minimum, max = maximum, % = percentage, NA = not applicable ‡ = all tests were performed by means of an student t-test, except for † : † = calculated with a Fisher's exact test. # = significantly different between groups. * = Mean distance f the most distal tip of the medial malleolus, as expressed in percentage of the total tibial length.

Table 1: Demographic information, n = number, SD = standard deviation, cm = centimetre, kg =kilogram BMI, body mass index (calculated as kilograms/ (length in meters)^2), min = minimun, max, maximum, % = percentage, NA = not applicable, + = all tests were preformed by means of an studen t-test, ex

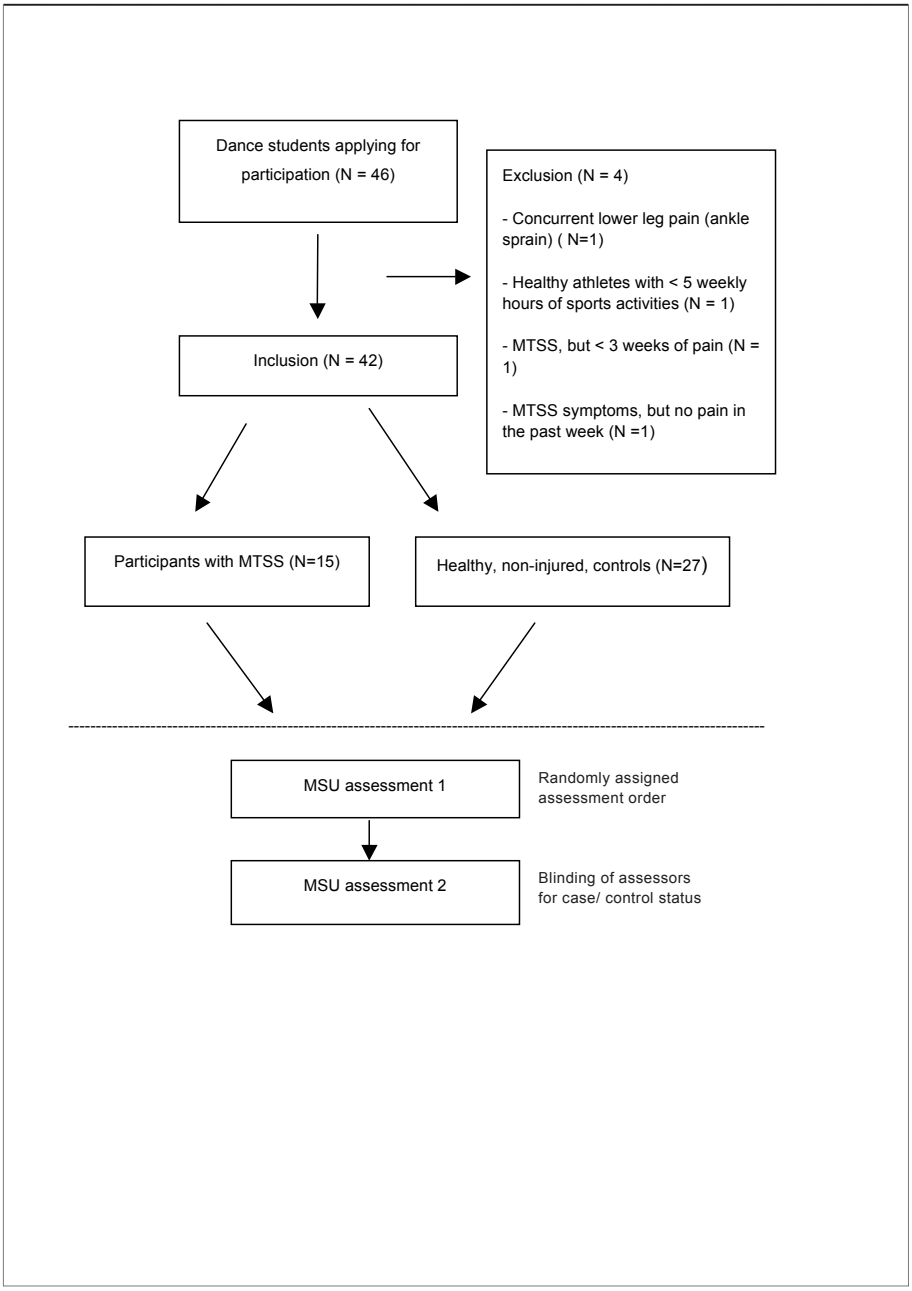

Figure 1: flow diagram. MTSS = medial tibial stress syndrome, MSU = musculoskeletal ultrasonography

significant between groups, p was 1.00 for both variables.

Tendinous abnormalities were commonly found in athletes with MTSS and in control athletes; in 7 (46.7%) and 13 (48.1%) respectively. This was not a significant difference, p = 1.00. Six (40%) of the MTSS athletes had tendinous edema in the tibialis posterior muscle. However, this was also found in 11 control athletes (41.7%) without MTSS, p = 1.00.

Other abnormalities were only incidentally observed: 1 athlete with MTSS had a tendinous tibialis posterior thickening (p = 0.36), in 1 control athlete the tibialis posterior tendon was hypoechoic, whereas in 1 control athlete the tendon sheath was hypoechoic, p = 1.00 for both findings. In contrast to the tibialis posterior tendon, the flexor digitorum longus tendon showed hardly any abnormalities. In 1 athlete with MTSS and 2 control athletes tendinous edema was seen, this was not significant, p = 1.00. The flexor digitorum longus did not show other abnormalities. One control athlete had tendinous edema in the flexor hallucis longus tendon, p = 1.00. No other findings were present in MTSS or control athletes.

To determine if our findings were associated with MTSS, we assessed each variable in a separate univariable logistic regression analysis. Unfortunately, many variables could not be assessed with logistic regression analysis due to 0-counts in one of the groups(see Table 2). The presence of abnormalities at specific painful spots were not significantly associated with MTSS, odds ratio (OR) = 1.9; 95% confidence interval (CI) 0.54–6.99, p = 0.31 for both spots (see also Table 2).

The presence of 'any abnormality in the tibial periosteum' was not significantly associated with MTSS, OR = 0.73; 95% CI 0.18–2.94, p = 0.66. Also, specific abnormalities such as periosteal edema and periosteal thickening were also not associated with MTSS: OR = 0.59; 95% CI 0.13–2.69, p = 0.50 and OR = 4.00; 95% CI0.33–48.30, p = 0.28, respectively.

The logistic regression analysis revealed that tendinous abnormalities were not associated with MTSS, OR = 0.94; 95% CI0.27–3.34, p = 0.93. More specifically, the OR for tendinous edema was 0.97; 95% CI 0.27–3.51, p = 0.96. For other tendinous abnormalities no OR could be calculated due to 0-counts in one of the two groups.

Findings in the flexor digitorum longus tendon were not associated with MTSS, OR = 0.89; 95% CI 0.07–10.75, p = 0.93. None of our findings fulfilled the threshold for entering a multi-variable model. Consequently, no multivariable logistic regression model was built.

We used the findings of the specific painful spots to calculate the power of this study. Post-hoc analysis showed that the power for these tests was 5.6%. Given the effect size (w = 0.152), constructing a 2-sided confidence interval with a 5% chance on type-1 error and a power of 80%, a sample size of >336 athletes would be necessary to detect differences for these tests.

Table 2. Univariable logistic regression analysis

Tissue	Type of abnormality	Odds ratio (95% CI)	P - value
Painful/specific spot 1, *n (%)*	Periosteal edema	1.9 (0.54 - 6.99)	0.31
Painful/specific spot 2, *n (%)*	Periosteal edema	1.9 (0.54 - 6.99)	0.31
Periosteum, *n (%)*	Any abnormality	0.73 (0.18 - 2.94)	0.66
	Abnormality in the middle 1/3 PM tibial border	1.04 (0.25 - 4.35)	0.96
	Edema PM tibial border	0.59 (0.13 - 2.69)	0.50
	Thickening PM tibial border	4.00 (0.33 - 48.30)	0.28
Tibialis posterior, *n (%)*	Any abnormality	0.94 (0.27 - 3.34)	0.93
	Tendinous edema	0.97 (0.27 - 3.51)	0.96
Flexor digitorum longus, *n (%)*	Any abnormality	0.89 (0.07 - 10.75)	0.93
	Tendinous edema	0.89 (0.07 - 10.75)	0.93

Table 2, number, CI = confidence interval, pm = posteromedial. N.b. The following variables were not assessed in the logistic regression because odds ratios could not be calculated due to a 0-count for MTSS cases and/or control athletes: periosteum: 'abnormality in the distal 1/3 PM tibial border' and 'periosteal vascularization'; bone: 'any abnormality', 'bone edema', 'irregular bone surface'; tendons: tibialis posterior/flexor digitorum longus: 'tendon thickening', 'intratendinous hypoechoic areas' and 'hypoechoic tendon sheath'; flexor hallucis longus: 'any abnormality', 'tendinous edema', 'tendon thickening', 'intratendinous hypoechoic areas' and 'hypoechoic tendon sheath'.

2.5. DISCUSSION

To the best of our knowledge, this is the first study to assess the pathology of MTSS with musculoskeletal ultrasonography (MSU) in a population with MTSS and with comparable athletic controls from the same base population. This case-control study showed that periosteal edema along the posteromedial tibial border, and tendinous edema in the crural aspects of the tibialis posterior insertion tendon are common as well as in cases with MTSS as in healthy athletic controls from the same base population.

We specifically assessed the two as most painful perceived spots along the posteromedial tibial border. Periosteal edema was present in 8 (53.3%) MTSS cases and in 10 (37.0%) control athletes, at both spots. As expected, a majority of athletes with MTSS had periosteal edema and tendinous abnormalities in the tibialis posterior muscle. How- ever, both these abnormalities were found to be equally present in control athletes (both p's > 0.3). Hardly any abnormalities were found in the posteromedial tibial bone, nor in the tendons of the flexor hallucis longus- and flexor digitorum longus mucles. Finally, we also assessed the reliability of our MSU assessment's methods in a cross-sectional study (see Appendix 2). In sum, the presence of periosteal and tendinous edema can be assessed with sufficient reliability, however, their presence seems not to be associated with MTSS.

The high prevalence of periosteal edema may indicate bone remodeling activity.[19] This hypothesis is supported by Mammoto et al., who found the presence of periosteal reactions to be related to earlier bone marrow changes on MRI assessment of tibial bones.[20] Similar conclusions were reported by Moen et al., who found periosteal edema in 34.6% cases with MTSS. Furthermore, the presence of tibial bone marrow or periosteal edema shortened time to recovery.[9] Also, Bergman et al. found that 43% of their asymptomatic runners had tibial stress reactions, suggesting that periosteal edema is indeed a sign of a normal bone remodelling process, and not necessarily related to MTSS.[13] Our study supports all of these findings: periosteal edema does not seem to be related to MTSS but could be considered as a physiological bone remodelling of the tibial bone due to repetitive loading. We did not find any cortical changes (cortical edema or cortical irregular surfaces)along the posteromedial tibial border in athletes with MTSS. We found it difficult to distinguish cortical edema from the bone as both are hypoechoic on musculoskeletal ultrasonography. Also, bone changes in patients with MTSS may not reach a visible endpoint (i.e. cortical spurs/erosions) that is detectable for MSU.[21]

A second explanation for presence of periosteal edema is the presence of a periostitis. However, with periostitis one would also expect signs of periosteal vascularisation and thickening.[14,18] In our study, very few findings that are suggestive for periostitis were found. Two athletes with MTSS (13.3%) and one control athlete showed periosteal thickening, and this difference was not significant. Only one athlete with MTSS had both periosteal edema and thickening. Furthermore, no signs of increased periosteal vascularisation were found upon MSU assessment. These results suggest it is unlikely that a periostitis is a plausible cause for MTSS.

Previous studies did relate their findings to the traction theory. Saxena et al. found that the connection of the tibialis posterior muscle is connected 7.8 cm proximal to the most distal tip of the medial malleolus, on average.[8] With a mean tibial length of 40.1 cm in our study it is likely that this distance was within the distal 1/3 of the posteromedial tibial border. Others, however, did not find connections of the tibialis posterior to the posteromedial tibial border.[6,22] Beck et al. found that the flexor digitorum longus muscle was connected to the posteromedial tibial border in 50 cadavers but only in the middle and proximal 1/3, making the traction theory less likely.[6] Bhatt et al.[7] took 32 periosteal biopsies of 20 patients with MTSS. Twenty-one of those biopsies showed periosteal changes, including thickening, fibrosis, vascularisation, iron deposition and mucin production.[7] However, there was no control group and it is unknown to what extent these findings are normal in a healthy, athletic, population. Johnell et al.[23] also took periosteal biopsies(N = 33), in 20 patients with MTSS. This study found periosteal changes in only one symptomatic biopsy.[23]

Thirty-one percent of the athletes with MTSS in the study by Moen et al. reported to feel, besides pain on palpation of the posteromedial border, pain on palpation of the muscles in the distal posteromedial aspects of the calf.[9] Therefore, we were also interested in possible abnormalities in the deep plantar flexor muscles, more specifically, in the tendinous parts. We found tendinous edema in the tibialis posterior muscle in 40.5% of our athletes, but no significant differences between athletes with or without MTSS, OR = 0.94 (95% CI 0.27–3.34), p = 0.93. Thus, our results suggest that the presence of tendinous edema is not related to the presence of MTSS or, as it seems, to any musculoskeletal injury, as our control athletes were free of any other lower leg pain. To our best knowledge, no studies exist that report on tendinous edema in the tibialis posterior muscle in asymptomatic populations. In patellar and achilles tendons, though, such abnormalities are commonly found in asymptomatic populations.[24,25]

Strengths of this study concern the procedures imposed, that are sufficient for an unbiased estimate of effect in a population in which MTSS is a frequently seen injury. There are also some limitations to address, though. Firstly, the power of the study seems limited, given the between group difference found. Thus, one may argue that we could have missed relations between abnormalities and MTSS due to a type-2 error. However, we speculated that if periosteal or tendinous abnormalities are associated with MTSS these would be frequently found in MTSS patients (>67%) whereas these findings would be minimally present, and randomly, in non-injured athletes (<33%). Given the very small effect size observed, a sample size of >336 subjects was needed to detect a significant difference. However, with such a small effect size it is unlikely that the presence of periosteal or tendinous pathological entities resemble the pathology of MTSS. Another limitation of our study, that maybe judged as such, is that MSU assessments were performed by medical imaging and radiation specialists instead of radiologists. In The Netherlands musculoskeletal ultrasonography assessments are commonly performed in hospitals by these specialists. Also, given their extensive training prior to the study's start, we are confident that their assessments are valid, and, given the results from the reliability study, sufficiently reliable. A minor

limitation that should be addressed is the criterion for periosteal thickening. We do not know of any studies that describe the normal thickness of the posteromedial tibial periosteum. In our experience the periosteal thickness cannot be measured reliably, and therefore we decided to refrain from measuring this systematically in the study. Instead, we followed the periosteum in longitudinal direction and visually inspected the presence of apparent thickening. This could have underestimated the number of participants with periosteal thickening. However, we are confident that we examined the periosteum very thoroughly in order to not miss any abnormality. Lastly, we found no cortical bone abnormalities in MTSS cases, and only two control participants had cortical abnormalities. These findings should be interpreted with caution. MSU is hardly able to detect intra-cortical changes. It cannot be excluded that bone abnormalities were present, but were not detectable for MSU.[26]

Noticeable were our findings that MTSS athletes did not engage in exercise as much as control athletes, on a weekly basis (6 versus 20 h), $p = 0.04$. This difference is likely to be due to the presence of MTSS. This difference may have affected our results. Perhaps, when MTSS cases would have continued training to the same extent as control athletes, their abnormalities may have further progressed. Otherwise, if the difference in exercise load was already present before the start of the academic program, MTSS may be an effect of loading the medial aspects of the tibial structures insufficiently prior to starting the academic program. Consequently, for athletes that have had insufficient loading prior to the academic program's start, the academic program may be 'a step too big' to deal with. Prospective cohort studies are needed to examine the relation between the onset of abnormalities, the onset of MTSS and pre-academic programs' exercise load.

The evidence regarding the pathological process of MTSS remains equivocal. Our findings suggest that MTSS is not related to signs of a posteromedial tibial periostitis. Alternatively, the bony overload could be more likely but needs to be further investigated, e.g. in a prospective cohort study investigating the local tibial bone health in a population at risk for MTSS. Furthermore, more invasive methods (e.g. micro CT-scans evaluating in-vivo obtained bone biopsies for micro cracks) could be considered while investigating the pathology of MTSS.

2.6. CONCLUSION

Periosteal, tendinous and bony abnormalities were not associated with the presence of MTSS. Therefore, we did not find evidence for any theory regarding the histology or pathological process of MTSS. Given our results, a posteromedial tibial periositis as an pathological explanation for MTSS seems not to be likely.

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2.7. APPENDIX 1 : PRESENCE OF ABNORMALITES

Tissue	Type of abnormality	MTSS group (N = 15)	Control group (N = 27)	P - value
Painful/specific spot 1, *n (%)*	Periosteal edema	8 (53.3%)	10 (37.0%))	0.35
Painful/specific spot 2, *n (%)*	Periosteal edema	8 (53.3%)	10 (37.0%)	0.35
Periosteum, *n (%)*	Any abnormality	4 (26.7%)	9 (33.3%)	0.74
	Abnormality in the middle 1/3 PM tibial border	4 (26.7%)	7 (25.9%)	1.00
	Abnormality in the distal 1/3 PM tibial border	0 (0%)	2 (7.4%)	0.53
	Edema PM tibial border	3 (20.0%)	8 (29.6%)	0.72
	Thickening PM tibial border	2 (13.3%)	1 (3.7%)	0.29
	Vascularization	0 (0%)	0 (0%)	NA
Bone, *n (%)*	Any abnormality	0 (0%)	2 (7.4%)	0.53
	Edema	0 (0%)	1 (3.7%)	1.00
	Irregular bone surface	0 (0%)	1 (3.7%)	1.00
Tibialis posterior, *n (%)*	Any abnormality	7 (46.7%)	13 (48.1%)	1.00
	Distensible edema tendon sheath	6 (40.0%)	11 (40.7%)	1.00
	Tendon thickening	1 (6.7%)	0 (0%)	0.36
	Intratendinous hypoechoic areas	0 (0%)	1 (3.7%)	1.00
	Hypoechoic tendon sheath	0 (0%)	1 (3.7%)	1.00
Flexor digitorum longus, *n (%)*	Any abnormality	1 (6.7%)	2 (7.4%)	1.00
	Distensible edema tendon sheath	1 (6.7%)	2 (7.4%)	1.00
	Tendon thickening	0 (0%)	0 (0%)	NA
	Intratendinous hypoechoic areas	0 (0%)	0 (0%)	NA
	Hypoechoic tendon sheath	0 (0%)	0 (0%)	NA
Flexor hallucis longus, *n (%)*	Any abnormality	0 (0%)	1 (3.7%)	1.00
	Distensible edema tendon sheath	0 (0%)	1 (3.7%)	1.00
	Tendon thickening	0 (0%)	0 (0%)	NA
	Intratendinous hypoechoic areas	0 (0%)	0 (0%)	NA
	Hypoechoic tendon sheath	0 (0%)	0 (0%)	NA

Appendix 1: Predence of abnormalities. MTSS = medial tibial stress syndrome, N = number, CI = confidence interval, NA = not applicable, could not be calculated because of absence of abnormality

2.8. APPENDIX 2

2.8.1. METHODS

This cross-sectional study was adjacent to the case-control study. For this study all methods (recruitment, selection, procedure, musculoskeletal ultrasonographic (MSU) assessment) were followed as documented in the full text content. In addition to the methods described in the full printed content: the first MSU assessment was immediately followed-up by the second assessment, which was performed by another medical imaging and radiation specialist. This short follow-up period was chosen to avoid possible alterations in injury status (i.e. possible changes in the presence or degree of abnormalities). A computer randomly assigned an assessment order (without a prefixed block) for each athlete to be assessed, so that the athlete was either assessed first by assessor 1 (PB) or 2 (SB). In addition to the blinding for group membership, as described in the methods section of the full text paper, we imposed some other methods to control for bias:

We kept assessor two blinded to the assessment results as obtained by the first assessor. We organised this as follows:

- Only one specialist was in the room when assessing the lower leg

- The medical imaging and radiation specialists used separate forms to note their results. Those forms were stored in separate opaque envelopes and were kept closed until the end of the study.

As for the statistical analysis, we present data regarding the prevalence, percentage of agreement, the observed percentage of positive agreement (Ppos), the observed percentage of negative agreement (Pneg) and the chance-corrected ratio for agreement, the Kappa-statistic. Kappa was interpreted as follows: poor (k <0.00), slight (k = 0.00-0.20), fair (k = 0.21-0.40), moderate (k= 0.41-0.60), substantial (k= 0.61-0.80) or almost perfect (k = 0.81-1.00).[1] Kappa can be inflated by bias between examiners and deflated by a low or high prevalence.[2, 3] We calculated the Bias index (BI) and prevalence index (PI) to evaluate how kappa was affected by bias between examiners and prevalence. BI ranges from -1 to +1. In case both raters find an equal proportion of 'yes' (i.e. 'prevalence') the BI is 0, and consequently, the kappa-statistic is not affected by bias between examiners. The closer to -1 or +1 the more the Kappa -statistic is inflated. PI ranges also between -1 and +1. Opposite to the BI, a value closer to -1 or +1 results in a deflated Kappa. A value of 0 (the average prevalence across the two raters is 50%) indicates that prevalence does not affect Kappa (please see appendix 3 for all calculations).[4] For inter-examiner reliability of the MSU assessment a sample size of 50 subjects was required, with an expected Kappa of 0.6, a 50% proportion success (i.e. prevalence), constructing a two-sided 95% confidence interval (95% CI), with a distance from kappa to the limit of the 95% CI of 0.2.[5] Missing data was handled by imputing sample medians.

2.8.2 TABLE 1: INTER-OBSERVER RELIABILITY FOR SPECIFIC ABNORMALITIES, FOR EACH TYPE OF TISSUE ALONG THE POSTEROMEDIAL TIBIAL BORDER

Tissue	Type of abnormality	Prevalence (%)	Percentage of Agreement (%)	Ppos (%)	Pneg (%)	PI	BI	Kappa (95% CI)	P- value
Periosteum	Edema	29.8%	78.6%	64.0%	84.7%	-0.40	0.07	0.49 (0.21 - 0.78)	0.001
	Thickening	9.5%	85.7%	25.0%	92.1%	-0.81	0.05	0.18 (-0.24 to 0.59)	0.23
	Vascularization	0%	100%	0%	100%	-1	0	NA*	NA*
Bone	Edema	1.2%	97.6%	0%	98.8%	-0.95	0.95	NA*	NA*
	Irregular bone surface	4.8%	90.5%	0%	95.0%	-0.88	0.05	-0.04 (-0.09 to 0.02)	0.78
Tendon	Tendinous thickening	0%	97.6%	0%	98.8%	-0.98	-0.02	NA*	NA*
	Intratendinous hypoechoic areas	1.2%	97.6%	0%	98.8%	-0.98	-0.02	NA*	NA*
	Distensible edema tendon sheath	48.8%	69.0%	71.1%	66.7%	0.07	0.12	0.39 (0.22 - 0.66)	0.01
	Hypoechoic tendon sheath	1.2%	97.6%	0	98.8%	-0.98	-0.02	NA*	NA*

Appendix 2. The inter-examiner reliability musculoskeletal ultrasonographic assessment of the posteromedial region of the tibia: a cross-sectional study. Ppos= percentage of positive agreement, Pneg = percentage of negative agreement, PI = prevalence index, BI = bias index, 95% confidence interval, NA = not applicable, * = empty row.

2.8.3. RESULTS

Concurrent with the case-control study: the same 42 participants (15 with MTSS, 27 control athletes) were included in this study. There was no missing data. We found moderate Kappa's for periosteal edema, k = 0.49 (95%CI 0.21 - 0.78), p = 0.001, and, for edema that distends from the tendon sheath, k = 0.40 (95%CI 0.14 - 0.66), p = 0.006. Possibly the low prevalence may have deflated kappa for periosteal edema (PI = -0.40) whereas for "distending edema from the tendon sheath" this effect was negligible (PI =0.07). Bias between observers seems not to have inflated kappa for both findings (BI= 0.12 and 0.07 respectively). Kappa's for other findings could either not be calculated or be regarded as good estimations; very low prevalence was found for these findings. This was confirmed by the PI - values that were all close to -1. See table 1 of this appendix for all inter-observer reliability statistics.

In sum, we found moderate kappa's for inter-observer assessment of periosteal and tendinous edema (k = 0.39 and 0.49 respectively). The prevalence of other findings was too low for good estimations of inter-observer agreement

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2.9. APPENDIX 3

Measures of prevalence, agreement and bias according to Byrt et al., 1993.[4]

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		Examiner 1		
		+	-	
Examiner 2	+	A	B	G1
	-	C	D	G2
		F1	F2	N

Prevalence = (A + ((B+C)/2))//N x 100

Percentage of agreement = (A + D)/ N X 100

Percentage of positive agreement = A/((F1+G1)/2)) X 100

Percentage of negative agreement = D /((F2+G2)/2)) X 100

Prevalence index = (A-D)/N

Bias index = (A+B)/N - (A+C)/N = (b-c)/N

Kappa - statistic = (Po - Pe) / (1- Pe) = 1 - ((1-Po)/(1-Pe))

Chapter 03

Medial tibial stress syndrome can be diagnosed reliably using history and physical examination

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3.1. ABSTRACT

3.1.1. BACKGROUND

The majority of sporting injuries are clinically diagnosed using history and physical examination as the cornerstone. There are no studies supporting the reliability of making a clinical diagnosis of medial tibial stress syndrome (MTSS).

3.1.2. AIM

Our aim was to assess if MTSS can be diagnosed reliably, using history and physical examination. We also investigated if clinicians were able to reliably identify concurrent lower leg injuries.

3.1.3. METHODS

A clinical reliability study was performed at multiple sports medicine sites in The Netherlands. Athletes with non-traumatic lower leg pain were assessed for having MTSS by two clinicians, who were blinded to each others' diagnoses. We calculated the prevalence, percentage of agreement, observed percentage of positive agreement (Ppos), observed percentage of negative agreement (Pneg) and Kappa-statistic with 95%CI.

3.1.4. RESULTS

Forty-nine athletes participated in this study, of whom 46 completed both assessments. The prevalence of MTSS was 74%. The percentage of agreement was 96%, with Ppos and Pneg of 97% and 92%, respectively. The inter-rater reliability was almost perfect; k=0.89 (95% CI 0.74 to 1.00), p<0.000001. Of the 34 athletes with MTSS, 11 (32%) had a concurrent lower leg injury, which was reliably noted by our clinicians, k=0.73, 95% CI 0.48 to 0.98, p<0.0001.

3.1.5. CONCLUSION

Our findings show that MTSS can be reliably diagnosed clinically using history and physical examination, in clinical practice and research settings. We also found that concurrent lower leg injuries are common in athletes with MTSS.

3.2. INTRODUCTION

Medial tibial stress syndrome (MTSS) is defined as exercise-induced pain along the posteromedial tibial border, and recognisable pain is provoked on palpation of this posteromedial tibial border over a length of ≥5 consecutive centimetres.[1] MTSS is a common overuse sports injury,[2, 3] with incidence rates from 4% to 19% in athletic populations.[4]

MTSS is diagnosed clinically using history and physical examination. Various imaging techniques have been studied for their ability to identify athletes with and without MTSS. These studies used the clinical diagnosis as the gold standard and examined if imaging compared with this.[5, 6] In this case, imaging's accuracy will always be less than the clinical diagnosis. Studies into imaging of other sports injuries, such as patellofemoral pain syndrome and groin pain, have also shown to lack discriminatory ability between symptomatic and asymptomatic athletes.[7, 8] In MTSS, the underlying pathology is equivocal, with both bony overload or periosteal inflammation being reported.[4, 9] There seems to be a need for a shift in the diagnostic paradigm for sports injuries where the pathogenesis is unclear; from making a diagnosis based on imaging or histological findings towards a diagnosis based on clinical findings.[10]

While history and clinical examination are the cornerstones of the diagnostic process in MTSS, the reliability of this approach has never been examined. Making a reliable clinical diagnosis forms a good foundation for planning treatment and discussing expectations. Ascertaining that clinicians are able to make a reliable diagnosis is also essential for research purposes.[11] We aimed to investigate the inter-rater reliability of using standardised history and physical examination to diagnose MTSS.

3.3. METHODS

3.3.1. DESIGN

Cross-sectional study.

3.3.2. SETTING

Four locations in The Netherlands (Inholland University of Applied Sciences, Haarlem; Academy for Physical Education, The Hague; the Sports Medical Advice Centre Haarlem and a handball club (HV Hellas) in The Hague), from March 2015 to August 2016.

3.3.3. PARTICIPANTS

Athletes (≥16 years) (i.e., students at Inholland University of Applied Sciences, Haarlem and Academy for Physical Education, The Hague; athletes at the Sports Medical Advice Centre Haarlem and HV Hellas, The Hague) who presented with a gradual onset of any lower leg pain (i.e., pain between the tip of the medial malleolus and the tibial plateau) for at least 1 week were potentially eligible for inclusion. No further restrictions with

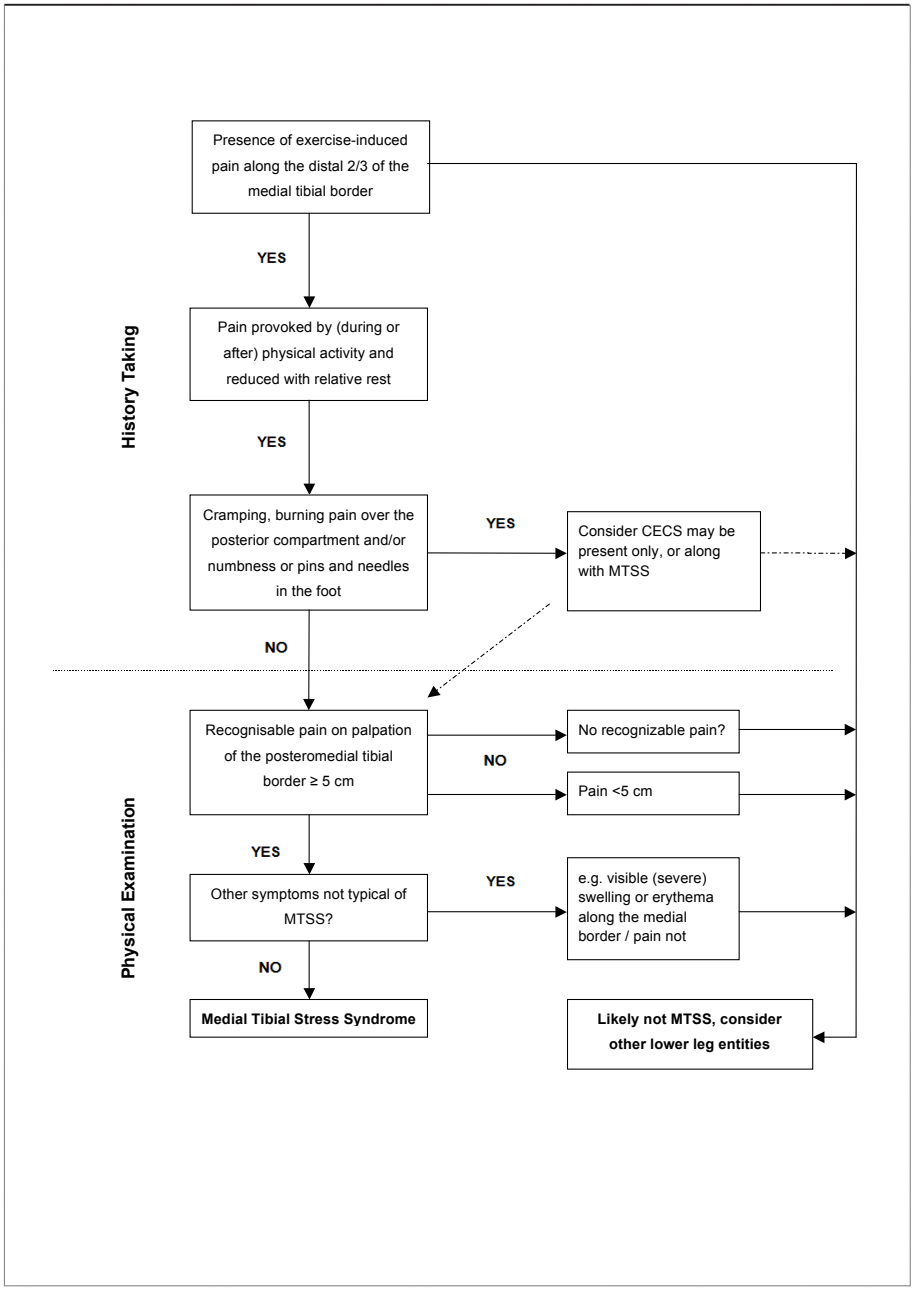

Figure 1. History taking and physical examination tool for lower leg pain in clinical sports medicine practice

MTSS = medial tibial stress syndrome, CECS = chronic exertional compartment syndrome

regards to the location of the pain were imposed. Exclusion criteria were a traumatic cause for the pain or a history of tibial fracture.

Potential candidates were informed about the study by a clinician or trainer/coach. Those athletes that were potentially willing to participate were provided with written and verbal information about the study by one of the medical professionals or trainers/coaches. All athletes were asked to sign informed consent after which they were included in the study. The Medical Research Ethics Committees United, Nieuwegein, The Netherlands (W15.029) provided approval.

3.3.4. DEMOGRAPHIC INFORMATION

After inclusion, athletes filled out a demographic information form: gender (male/female), height (cm), weight (kg) and injury duration (months). The MTSS score was filled out by athletes with MTSS to assess injury severity. The MTSS score is a new valid, reliable and responsive patient reported outcome measure. Scores range from 0 to 10, 0 means having no pain/limitation, whereas 10 is maximal severity.[12, 13]

3.3.5. PROCEDURE

Eight clinicians (five sports physiotherapists and three sports physicians; mean (SD) years of experience 8 (9); median (range) 5.5 years (1–23)) were available to assess the included athletes. For most cases, there were more than two clinicians available to make the diagnosis MTSS. In those cases, two clinicians were randomly selected by a computer from the pool of available clinicians. The assessment order was also randomly determined by a computer in all cases. The person that performed the randomisation procedure was not blinded to the clinician to be selected, nor to the athlete that was to be assessed. The two assessments took place on the same day to prevent the athlete's condition changing.

3.3.6. DIAGNOSIS MTSS, BASED ON HISTORY TAKING AND PHYSICAL EXAMINATION

We used a standardised history and physical examination to diagnose MTSS clinically (figure 1). We used six steps for the confirmation of the diagnosis MTSS, based on the previous work by Yates and White and Edwards et al. (2005).[1, 14] We explained this to the clinicians before the study commencement. The clinicians were not specifically trained for the study purpose.

3.3.7. HISTORY

The standardised history comprised questions on the onset and location of the pain. If there was exercise-induced pain along the medial tibial border, the athlete was asked what aggravated and relieved their pain. Athletes were also asked about pain in adjacent areas, or remote areas in the lower leg. Then, athletes were also specifically asked

for the presence of any signs of chronic exertional compartment syndrome (CECS), which could be a concurrent injury or the sole explanation for their pain. Athletes were asked about cramping, burning and pressure-like calf pain; pain that was primarily present during exercise, which quickly decreased after exercise. Athletes were also asked whether they experienced any pins and needles in the foot or a cold foot during exercise, especially when pain in the calf area was reported.

3.3.8. PHYSICAL EXAMINATION

If MTSS was suspected after the history, the posteromedial tibial border was palpated and the athletes were asked for the presence of recognisable pain (i.e., from painful activities). If no pain on palpation was present, or the pain could be palpated over less than 5 cm, other lower leg injuries (e.g., a stress fracture) were considered to be present and the athlete was labelled as not having MTSS. When recognisable pain was present on palpation over 5 cm or more and no atypical symptoms were present, the diagnosis MTSS was confirmed. When the length of perceived pain along the posteromedial border was equivocal, a tape measure was used to determine the exact length. During physical examination, athletes were specifically asked for pain in adjacent structures. If so, those structures were palpated and athletes were asked if recognisable pain was present.

We did not specifically define other injury conditions, that is, we did not define CECS, a tibial stress fracture or soleus strain. The clinicians were free to use their own preferred terms to describe other diagnoses (e.g., calf pain/CECS/suspicion of tibial stress fracture). This study solely focused on the reliability of making the diagnosis MTSS (present yes/no) and the presence of co-existed lower leg conditions (present yes/no).

3.3.9. BLINDING

The raters made their clinical diagnosis independently, and were blinded to the other clinician's assessment. Blinding of the raters was performed as follows: only one clinician was in the assessment room when the athlete's injury was examined. The first clinician examined the athlete but did not relate their findings to them, and only the second clinician communicated the diagnosis to the athlete. Each athlete was also instructed beforehand, not to share the findings of the first clinician with the second.

3.3.10. STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS V.22.0 (IBM SPSS, Chicago, USA). Demographic data are presented with their estimates and appropriate measure of dispersion. For the reliability analysis, we used the two diagnoses of each set of clinicians and aggregated these for the analysis to one set of two clinicians. Specifically, we calculated the reliability statistics over data collected by all sets of clinicians, in contrast to the calculation for each set of clinicians. We calculated the prevalence,

percentage of agreement, observed Ppos, Pneg and our primary outcome measure: the chance-corrected ratio for agreement, Kappa-statistic. Kappa was interpreted as follows: poor (k<0.00), slight (k=0.00–0.20), fair (k=0.21–0.40), moderate (k=0.41–0.60), substantial (k=0.61–0.80) or almost perfect (k=0.81–1.00).[15] Bias between clinicians can inflate Kappa whereas a low or high prevalence can deflate Kappa.[16,17] We calculated the Bias Index (BI) and Prevalence Index (PI) to evaluate how Kappa may have been affected by bias between clinicians, and by prevalence. BI ranges from −1 to +1. In case both clinicians label an equal proportion of the population as having MTSS (i.e., 'prevalence') the BI is 0, and consequently, the Kappa-statistic is not affected by bias between clinicians. The closer to −1 or +1 the more the Kappa-statistic is inflated. PI ranges also between −1 and +1. Opposite to the BI, a value closer to −1 or +1 results in a deflated Kappa. A value of 0 (the average prevalence across the two clinicians is 50%) indicates that prevalence does not affect Kappa (see appendix 1 for all calculations).[18] The sample size calculation showed that 51 athletes with lower leg pain were required for an expected Kappa of 0.6 and the prevalence to be 50%, constructing a two-sided 95% CI, with a distance from the estimated Kappa to the limit of the 95% CI of 0.2.[19] Missing demographic, continuous data were handled by imputing sample means. Missing sports activity data were labelled as 'unknown'. If athletes failed to attend their second assessment they were excluded from the reliability analysis.

3.4.1. RESULTS

A total of 52 athletes agreed to participate, of which 49 met our inclusion criteria. Three athletes were excluded; two due to lower leg pain after acute ankle trauma, one who had insertional Achilles tendinopathy. Three athletes failed to attend their second assessment. Figure 2 shows the study flow.

We included 14 (29%) males and 35 (71%) females. Injury severity was moderate in the athletes with MTSS; the mean (SD) MTSS score was 3.82 (1.42). Table 1 provides further demographic information.

3.4.2. MISSING DATA

There were missing demographic data for eight athletes (3.2% of all data), as they did not fill out the demographic information form. No data regarding the diagnosis making process was missing.

3.4.3. INTER-RATER RELIABILITY MTSS DIAGNOSIS

There were 34/46 (74%) athletes with MTSS, and 12/46 (26%) with other lower leg injuries. These other lower leg injuries were categorised as: anterior tibialis muscle pain (n=5), calf pain (n=3), tibial bony stress reaction (n=2) and peroneal muscle pain (n=2).

The percentage of agreement, Ppos and Pneg were 96%, 97% and 92%, respectively. The Kappa was almost perfect: k=0.89, 95% CI 0.74 to 1.00, p<0.000001 (see table

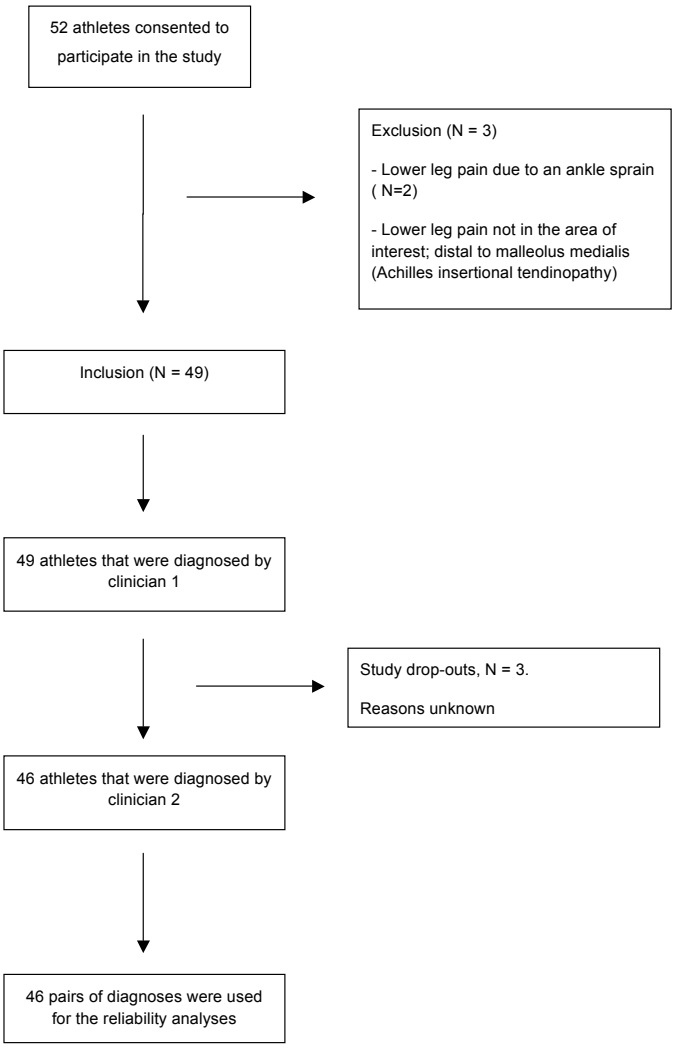

Figure 2: Flow diagram

Table 1. Demographic information

Demographic variable		MTSS cases (N = 34)	Non-MTSS cases with lower leg pain (N = 15)
Male/female, *n (%)*		7 (21%) / 27 (79%)	7(47%) / 8 (53%)
Age in years, *mean ± SD*		20.3 ± 2.3	20.6 ± 2.8
Length in cm, *mean ± SD*		173 ± 8	177 ± 9
Weight in kg, *mean ± SD*		66 ± 8	69 ± 7
BMI in kg/m^2, *mean ± SD*		22 ± 2	22 ± 2
Sports category *n (%)*	Dance	15	3
	Handball	8	2
	Football	2	1
	Other	6	3
	Unknown	3	6
Duration of complaints in months, *median with range (min-max)*		5.8 (0.25 - 108)	3.0 (0.25 - 72)
Side of complaints, *n (%)*	Both legs:	20 (59%)	12 (80%)
	Only left leg:	3 (9%)	2 (13%)
	Only right leg:	11 (32%)	1 (7%)
MTSS Score, mean ± SD		3.82 ± 1.42	NA

BMI = body mass index

Table 1. Demographic information

2A and table 3). Clinicians did not make the same diagnosis in 2/46 cases (4%). One was labelled as having only MTSS by one clinician, and as having pain in the flexor hallucis longus by the other. The second athlete was labelled as having MTSS and a tibial stress reaction by one clinician, and as only having a tibial stress reaction by the other. The reliability may have been deflated by the high prevalence of MTSS in our sample, that is, an underestimation of Kappa, PI=0.48. Kappa was not affected by bias between clinicians, BI=−0.04.

3.4.4. INTER-RATER RELIABILITY PRESENCE OF CONCURRENT LOWER LEG INJURY

Of the 34 athletes with MTSS, 11 (32%) had a concurrent lower leg injury. These were anterior tibial muscle pain (n=5), calf pain (n=5) and a tibial stress reaction (n=1). The percentage of agreement, Ppos and Pneg for the identification of a concurrent lower leg injury (yes/no) were 88%, 82% and 91%, respectively. The Kappa for the identification of concurrent lower leg injuries (yes/no) was substantial, k=0.73, 95% CI 0.48 to 0.98, p<0.0001 (see table 2B and table 3).

In four athletes with MTSS, the clinicians did not agree whether there was a concurrent lower leg injury present. The first clinician identified three cases with MTSS plus a concurrent injury: one anterior tibial stress reaction, one calf pain and one anterior tibialis muscle pain. These concurrent injuries were not noted by the second clinician.

Table 2a. Reliability data MTSS diagnosis

		Clinician 2		
	MTSS	**Yes**	**No**	**Total**
Clinician 1	**Yes**	33	0	33
	No	2	11	13
	Total	35	11	46

Table 2b. Reliability data presence of concurrent lower leg injuries

		Clinician 2		
	Concurrent lower leg injury	**Yes**	**No**	**Total**
Clinician 1	**Yes**	9	3	12
	No	1	21	22
	Total	10	24	34

Table 3. Reliability analysis MTSS diagnosis & Presence of concurrent lower leg injuries (N = 46)

Inter-rater reliability statistic	**MTSS diagnosis**	**Concurrent lower leg injury**
Prevalence	74%	32%
Percentage of agreement	96%	88%
Ppos	97%	82%
Pneg	92%	91%
Prevalence bias	0.48	-0.35
Bias index	-0.04	0.06
Kappa, p -value	**0.89 (95%CI 0.74 - 1.00), p < 0.000001**	**0.73 (95%CI 0.48 - 0.98), p < 0.0001**

Table 2a. Reliability data MTSS diagnosis

Table 2b. Reliability data presence of concurrent lower leg injuries

Table 3. Reliability analysis MTSS diagnosis & Presence of concurrent lower leg injuries (N = 46). Ppos = percentage of positive agreement, Pneg = percentage of negative agreement, 95% confidence interval

The second clinician identified one MTSS athlete as having MTSS plus concurrent calf pain. This additional calf pain was not noted by the first clinician. Reliability may have been deflated by the low prevalence of concurrent lower leg injuries, PI=−0.35, but was not affected by bias between clinicians, BI=0.06.

3.5.1. DISCUSSION

This is the first study to assess the inter-rater reliability of diagnosing MTSS using standardised history and physical examination. Our results show that MTSS can be diagnosed with almost perfect reliability in clinical practice. Concurrent lower leg injuries were often present (32%) in athletes with MTSS and the presence of concurrent injuries could also be identified reliably. Our findings support the use of standardised history and clinical examination for diagnosing MTSS in clinical practice and research settings.

3.5.2. CLINICAL DIAGNOSIS OF MTSS: THE LOGICAL APPROACH?

Although MTSS is mainly considered a bony overload injury,[4, 20, 21] some studies suggest it being related to traction periostitis,[22–24] meaning evidence for its pathogenesis is equivocal.[9] Previous studies investigated the accuracy of MRI and CT for diagnosing MTSS.[5, 6] In these studies, the clinical diagnosis of MTSS was used as the gold standard to determine it being present. In this approach, the diagnostic accuracy of imaging will always be lower than that of clinical examination. The more common text book approach in diagnostic research is when clinical tests/diagnoses are compared with imaging, surgery or histological findings. This is useful when the pathogenesis of an injury is known. This is, however, not the case in most overuse sports injuries. An alternative approach in this paradigm is the use of imaging in the diagnosis of sports injuries to examine its ability to accurately discriminate symptomatic from asymptomatic subjects. In the majority of cases for overuse sports injuries, imaging has been found to have a poor discriminatory ability.[7, 8] Imaging leads to uncertainty in sports medicine practice, trying to identify which imaging 'abnormalities' are related to the clinical condition, rather than clarifying a patient's condition. This has also been highlighted by others recently.[10]

The role of imaging could focus on whether it provides prognostic information or predicts treatment response rather than diagnostic accuracy. However, clinical findings should also be accounted for when assessing the prognostic value of imaging, as shown by a recent study of acute hamstring injuries. MRI did not add to the predictive value when clinical parameters were used to estimate the prognosis of time to recovery.[25] For diagnostic purposes, imaging may be used to rule out other entities with a known pathogenesis (e.g., stress fractures, or suspicion of another rare condition like osteosarcoma,[26] i.e., if there is doubt in the source of lower leg pain).

There seems a need for a paradigm shift in the diagnosis of clinical conditions, like MTSS. They can be diagnosed clinically, without wasting resources using additional investigations. This paradigm shift seems to be increasingly adopted in sports medicine, where the clinical diagnosis is now considered the cornerstone in the diagnosis making of many sports injuries.[27, 28]

We consider MTSS a clinical diagnosis with mixed evidence for its pathogenesis. Therefore, making the diagnosis MTSS clinically seems the most logical approach. Our findings suggest that diagnosing MTSS clinically can be achieved reliably.

3.5.3. STRENGTHS AND LIMITATIONS

A strength of this study is that our methods allowed for an unbiased estimate of effect. We blinded our clinicians to each others' diagnoses and randomised the assessment order to control for a possible 'clinical experience' effect, which could have been present due to the great variation of experience in our sample of clinicians. We did not specifically train the clinicians to make the diagnosis of MTSS. This allows for a true estimation of the clinical diagnosis' reliability in daily practice. The Kappa's found in our study are likely an underestimation of the true Kappa-value, for two reasons: (1)

we used eight clinicians to form a pair of clinicians, this may have added variation in perception among clinicians of what MTSS really is; (2) the Kappa-statistic is usually an optimal presentation of agreement when the prevalence is around 50%. For the MTSS diagnosis, the PI showed that Kappa was deflated due to a high prevalence, whereas for the presence of concurrent lower leg injuries, Kappa was also deflated but in this case due to a low prevalence. A further strength of this study is the generalisability of our findings to multiple professions and years of clinical experience. MTSS is a clinical diagnosis, and as such, sports physicians and sports physiotherapists seem able to reliably diagnose the condition, irrespective of their years of clinical experience.

This study also has some limitations. Firstly, some of the participants also participated in two other studies.[29] This may have led to an increased risk of a type 1 error, due to multiple testing. However, considering the very high Kappa and subsequent p value ($p<0.000001$) found, we are confident that making the diagnosis clinically is truly reliable. We did not reach the a priori calculated sample size (n=51). However, we found a Kappa-value much higher than we estimated when planning the study. Therefore, we are confident that this sample size enabled for a robust estimation of inter-rater reliability, which is confirmed by the 95% CI, k=0.74–1.00. We used an arbitrary cut-off value (5 cm) to differentiate between focal pain (suspected of having a tibial stress fracture) and diffuse pain (MTSS) along the posteromedial tibial border, for the purpose of this study. Although this criterion is based on previous literature,[1, 14] there is no evidence for this specific cut-off value. One might consider imaging to rule out a tibial stress fracture when an athlete presents with <5 cm of pain in clinical practice. It is of note that no athlete was clinically suspected of having a tibial stress fracture, one of the more important differential diagnoses when assessing overuse injuries along the medial aspects of the tibia. However, tibial stress fractures are extremely rare in The Netherlands, even in the Dutch Royal Army.[30] We acknowledge that in other geographical areas (e.g., Australia,[31] Great Britain,[32] Israel[33] and the USA[34]) the prevalence of tibial stress fractures seems much higher, and, possibly this may affect the ease to distinguish between MTSS and tibial stress fracture. Future studies should investigate the reliability of the clinical diagnosis MTSS in other geographical areas and in military populations.

3.6. CONCLUSION

The clinical diagnosis MTSS can be made reliably using history and physical examination. Concurrent lower leg injuries were often present (32%) in athletes with MTSS and the presence of concurrent injuries could also be identified reliably. Our study supports the use of standardised history and clinical examination for diagnosing MTSS in clinical practice and research settings.

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Chapter 04

Treatment of medial tibial stress syndrome: a systematic review

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4.1. ABSTRACT

4.1.1. BACKGROUND

Medial tibial stress syndrome (MTSS) is a common exercise-induced leg injury among athletes and military personnel. Several treatment options have been described in the literature, but it remains unclear which treatment is most effective.

4.1.2. OBJECTIVE

The objective of this systematic review was to assess the effectiveness of any intervention in the treatment of MTSS.

4.1.3. STUDY SELECTION

Published or non-published studies, reporting randomized or non-randomized controlled trials of any treatment in subjects with MTSS were eligible for inclusion. Treatments were assessed for effects on pain, time to recovery or global perceived effect.

4.1.4. DATA SOURCES

Computerized bibliographic databases (MEDLINE, CENTRAL, EMBASE, CINAHL, PEDro and SPORTDiscus) and trial registries were searched for relevant reports, from their inception to 1 June 2012. Grey literature was searched for additional relevant reports.

4.1.5. STUDY APPRAISAL

The Cochrane Risk of Bias Tool was used to appraise study quality of randomized clinical trials (RCTs) whereas the Newcastle Ottawa Scale was used to appraise non-randomized trials. The 'levels of evidence', according to the Oxford Centre for Evidence-Based Medicine, addressed the impact of the assessed trials. Two reviewers independently performed the search for articles, study selection, data extraction and appraised methodological quality.

4.1.6. RESULTS

Eleven trials were included in this systematic review. All RCTs revealed a high risk of bias (Level 3 of evidence). Both non-randomized clinical trials were found to be of poor quality (Level 4 of evidence). RCTs, studying the effect of a lower leg brace versus no lower leg brace, and iontophoresis versus phonophoresis, were pooled using a fixed-effects model. No significant differences were found for lower leg braces (standardized mean difference [SMD] -0.06; 95 % CI -0.44 to 0.32, p = 0.76), or iontophoresis (SMD 0.09; 95 % CI -0.50 to 0.68, p = 0.76). Iontophoresis, phonophoresis, ice massage, ultrasound therapy, periosteal pecking and extracorporeal shockwave therapy (ESWT) could be

effective in treating MTSS when compared with control (Level 3 to 4 of evidence).

Low-energy laser treatment, stretching and strengthening exercises, sports compression stockings, lower leg braces and pulsed electromagnetic fields have not been proven to be effective in treating MTSS (level 3 of evidence).

4.1.7. CONCLUSION

None of the studies are sufficiently free from methodological bias to recommend any of the treatments investigated. Of those examined, ESWT appears to have the most promise.

4.2. INTRODUCTION

Among exercise-induced leg injuries, medial tibial stress syndrome (MTSS) is frequently seen, especially in jumping and running athletes and in military personnel.[1] Yates' definition for MTSS: ''pain along the posteromedial border of the tibia that occurs due to exercise…'' and in addition: ''pain by palpation of the posteromedial border of the tibia is present over a length of five or more consecutive centimeters'' is commonly used.[2] Currently, it is thought that MTSS is a bony overload injury; i.e., the tibial bone bends during weight-bearing activities causing strain in the tibia.[3-5] This strain normally causes micro damage in the bone, which leads to bone adaptation processes to strengthen the bone to resist tibial bending. When this strain exceeds a certain threshold and becomes overloaded, the osteoclast activity may outpace osteoblast activity, leading to local tibial osteopenia.[6]

Several conservative and surgical interventions have been described in the literature. Noteworthy is that very few interventional studies were performed up until 2009.1 Several trials have been conducted over the past 4 years;[7-10] however, which intervention is most effective in the treatment of MTSS remains unclear.

This review aims to assess the effectiveness of conservative and surgical interventions in subjects with MTSS.

4.3. METHODS

4.3.1. RESEARCH QUESTION

The research question was to assess the effectiveness of conservative and surgical treatment in subjects with MTSS.

4.3.2. INCLUSION CRITERIA FOR STUDIES

4.3.2.1. TYPE OF STUDIES

Published and non-published, randomized and non-randomized clinical trials in full text were eligible for inclusion

4.3.2.2. TYPE OF PARTICIPANTS

Subjects with exercise-induced pain on the medial border of the tibia and in addition presence of diffuse pain by palpation on the medial border of the tibia were included in this review.[2] Other causes of lower leg pain were excluded; e.g., stress fracture, acute and chronic exertional compartment syndrome, nerve or vascular entrapment.[11]

4.3.2.3. TYPE OF INTERVENTION

Any intervention that was compared with any another treatment or with 'wait-and-see' was included.

4.3.2.4. TYPE OF OUTCOME

Studies that assessed the effect of an intervention on time to recovery, global perceived effect and/or pain were eligible for inclusion.

4.3.3. SEARCH METHODS

4.3.3.1. DATABASES

Two reviewers (MW, ME) searched independently the following databases (from inception to 1 June 2012) for relevant studies: The National Library of Medicine, Washington DC (MEDLINE-PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), Excerpta Medical Database by Elsevier (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Physiotherapy Evidence Database (PEDro) and SPORTDiscus.

Our sensitive search strategy (see appendix 1) was based on controlled vocabulary (MESH terms) and free text terms and developed by a research librarian. No language restrictions were imposed.

4.3.3.2. ONGOING STUDIES

We searched the national (http://www.trialregister.nl) and international trial registries (http://www.controlled-trials. com); ClinicalTrials.gov and http://apps.who.int/trialsearch/ to identify ongoing studies. When an ongoing study was found, attempts were made to contact its primary investigator to collect further information.

4.3.3.3. GREY LITERATURE

Conference abstracts were searched to identify relevant unpublished studies in: OpenSigle (http://opensigle.inist.fr/); British Library Inside (http://www.bl.uk/inside); Web of Science and BIOSIS Previews (http://www.ovid.com).

4.3.3.5. HAND SEARCHING

We checked the reference lists of included studies and existing reviews to identify potentially relevant studies.

4.3.4. STUDY SELECTION

After removal of duplicates, two reviewers (MW, ME) independently scanned titles and abstracts of all papers identified by our search strategy for potentially eligible studies. Full text content was obtained for these studies, and the two reviewers independently applied the inclusion and exclusion criteria to assess the eligibility for inclusion in this study. In all cases of initial disagreement, the reviewers reached consensus on inclusion of the trials.

4.3.5. DATA EXTRACTION

Standardized data extraction forms were used which were adapted from the Cochrane Centre and slightly modified for the purpose of this study.[12] Two reviewers (MW, ME) independently extracted data on study design, subjects, intervention under study, outcome parameters and results. Discrepancies in the data extracted were resolved in a shared session of data synthesis by the two reviewers (MW, ME).

4.3.6. QUALITY ASSESSMENT OF INDIVIDUAL STUDIES

After data extraction, the methodological quality of each study was independently assessed by two reviewers (MW, ME).

4.3.6.1. RANDOMIZED CONTROLLED TRIALS

The Cochrane Risk of Bias Tool was used to appraise the methodological quality of randomized clinical trials (RCTs).[12] The five major domains of bias (selection bias, performance bias, detection bias, attrition bias and reporting bias) were assessed as proposed by the RCT checklist of the Dutch Cochrane Centre and completed using a priori formulated quality criteria (see appendix 2).

We labeled an aspect as 'low risk of bias'(?), 'high risk of bias' (-) or 'unclear risk of bias' (?), respectively.[12]

RCTs were considered as low risk of bias when on each domain of bias a '?' was scored, a moderate risk of bias was considered if studies scored a '-' or '?' on one or two domains. Studies with the presence of three or more '-' or '?' were considered as high risk of bias.

4.3.6.2. NON-RANDOMIZED CLINICAL TRIALS

The Newcastle Ottawa Scale was used and somewhat modified for the study purpose (see appendix 3).[13] Reviewers (MW, ME) awarded stars for each item where sufficient information was provided and was appropriate. When no information was provided or when the method used was not appropriate, no star was awarded.

Studies could be awarded a maximum of 10 stars when the method was appropriate on each item in the domains selection, performance and outcome. Studies that were

awarded ten stars were considered to be of good quality whereas studies missing one to three stars were considered to be of moderate quality and studies missing more than three stars were considered to be of poor quality.

Reviewers attempted to reach consensus when differences were present, and when no consensus could be reached the decision was made by a third reviewer (EB).

4.3.6.3. LEVELS OF EVIDENCE

In addition, the 'levels of evidence' of the Oxford Centre for Evidence-Based Medicine were used to assess methodological quality.[14] In this system, a Level 2 is assigned to randomized trials or observational studies with a large effect and Level 3 to non-randomized controlled cohort/follow-up studies. ''Level may be graded down on the basis of study quality, imprecision, indirectness, because of inconsistency between studies, or because of the absolute effect size is very small; Level may be graded up if there is a large or very large effect size''.[14]

4.3.7. DATA SYNTHESIS

We planned a meta-analysis if studies (or subgroups of studies) were considered clinically and statistically homogenous. Otherwise we considered a subgroup and meta-regression analysis to explore possible sources of heterogeneity. Results are presented in a descriptive summary of findings table.

4.4. RESULTS

4.4.1. STUDY SELECTION

This systematic review included eleven trials. Figure 1 provides the flow diagram of the search and selection procedure. All trials that met our inclusion criteria studied the effect of conservative interventions. No controlled trials with comparison groups that studied the effect of surgical interventions were identified by our search strategy.

Of the included studies, nine studies were written in English, one was written in Dutch and one was written in Danish. The Danish study was translated into Dutch by a native speaker with a medical background. Five studies were performed in military populations, five studies in athletic populations and in one study the population was not described. Studies varied in size from 15 to 78 subjects. All relevant data extracted is summarized in the summary characteristics and findings table (Table 1). Eight studies were excluded based on full text as they did not meet the inclusion criteria (Fig. 1).[15-21] Our search in the trial registers revealed that one trial investigating monochromatic near-infrared light energy in 'tibial stress reaction patients' was suspended.[22] Unfortunately, we were unable to attain additional information on inclusion criteria and reasons for trial suspension.

In view of the symmetric distribution of the studies in the funnel plot, we concluded

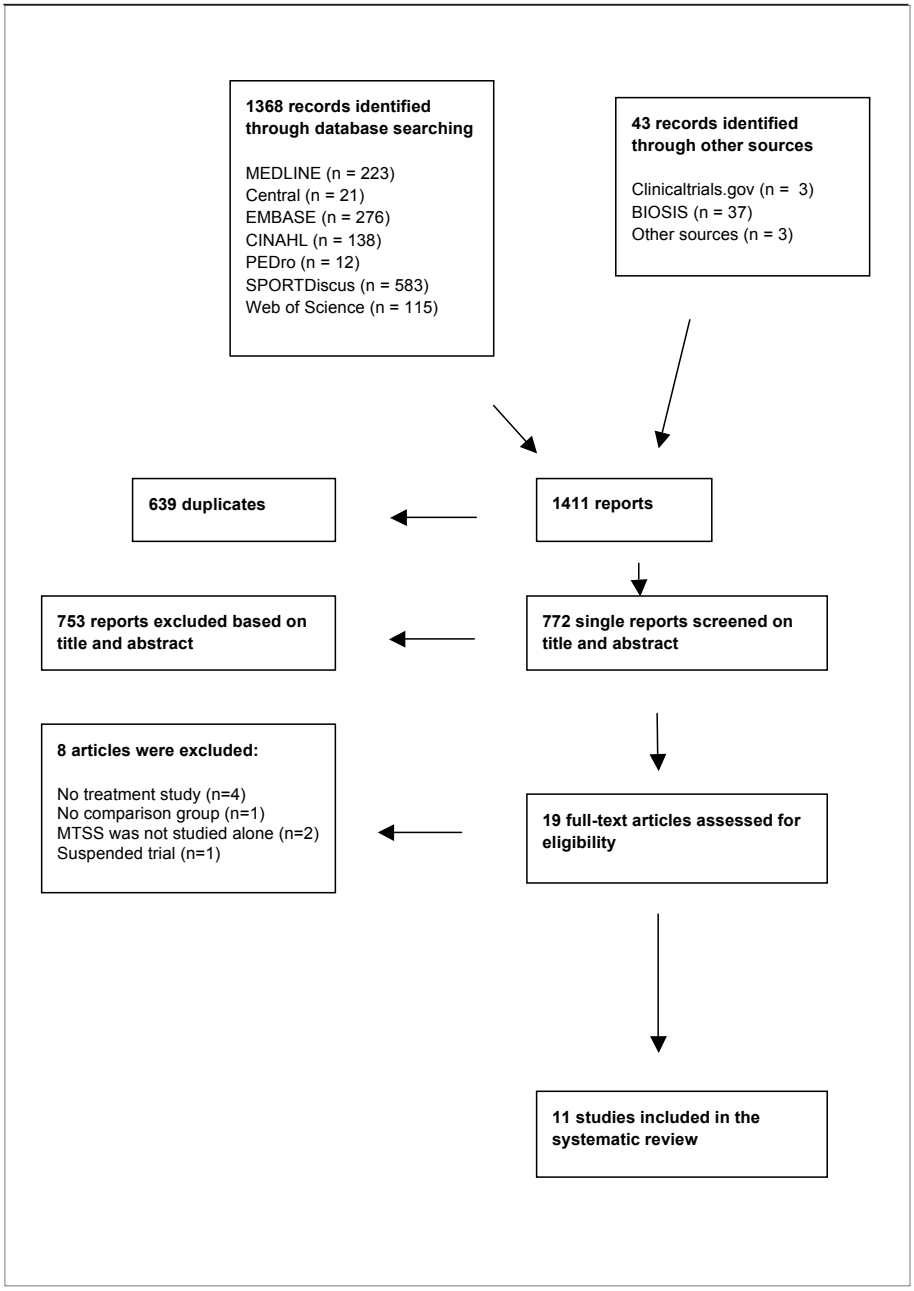

Figure 1. Flow diagram. MTSS = medial tibial stress syndrome.

Author/ Study design and Treatment	Inclusion criteria	Population	Baseline characteristics	Intervention	Outcomes	Results	Level of Evidence
Smith et al. (1986)[23] **RCT** **Iontophoresis, ice massage, phonophoresis and ultrasound versus control**	Palpable pain along the medial aspects of the tibia. X-rays ruled out TSF.	Military population; 50 subjects, 10 in each group.	"The subjects included both male and females, ranging 18-25 years of age." Height/Weight/BMI/Duration of complaints: ?	Group 1: Iontophoresis via a Phoresor iontophoretic drug delivery system. produced a constant current for iontophoresis. "The active electrode allowed for a fixed quantity of medication of 2 mL of dexamethasone sodium phosphate (4mg/ml) and 1 mL of 4% of lidocaine hydrochloride. The average current dosage was between 2.5-5 mA for 20 minutes depending on the patient's tolerance." Group 2: 10 minutes of ice massage in a circular motion at the pain site. Group 3: ultrasound and phonophoresis using a mixture of 33 mg of dexamethasone and 16 mL of lidocaine gel of 2% in 60mg of a water-soluble base. Ultrasound was continuous and set at an average of 1.5 watts/cm^2. Group 4: Ultrasound therapy as described above. Group 5: Control group, did not receive any modality. All groups performed heel stretching exercises and were placed on a limited duty basis.	Perceived pain on a 1-10 scale. The measure of interest was the difference between pre- and post-treatment program.	Perceived pain, change scores (mean ± SD) Group 1: 5.00 ± 1.15, Group 2: 5.60 ± 1.65, Group 3: 5.20 ± 1.14, Group 4: 4.80 ± 0.92, Group 5: -1.90 ± 2.46. P < 0.01. Control group differs significantly from the other groups. No treatment is significantly superior to another treatment.	**3**
Singh et al. (2002) [24] **RCT** **Iontophoresis versus Phonophoresis**	Subjects were included based on clinical history and physical examination. Radiographs were taken if TSF was suspected.	Population:? 25 subjects, 13 in group 1, 12 in group 2.	Age (range): 18-29 years. Sex: Group 1: 4 males. 9 females Group 2: 7 males. 5 females Height/Weight/BMI:? Duration of complaints:?	Group 1: Iontophoresis: Continuous direct current at 5mAmp for 15 minutes. 5 days a week, for 2 weeks. Drug delivery: ? Group 2: Phonophoresis: Continuous ultrasound, frequency of 1MHz at 1w/cm^2, for 10 minutes. 5 days a week, for 2 weeks. Drug delivery: ?	VAS after hop test on the affected leg, recorded on the 1st, 7th and 14th treatment. Functional score 6 meter hop test; distance without pain or discomfort.	VAS decrease between treatment 1 and 7 (mean ± SD): Group 1: 1.35 ± 0.427, Group 2: 1.17 ± 0.389; between 7th and 14th treatment (mean ± SD): Group 1: 2.96 ± 0.721, Group 2: 3.08 ± 0.515; between 1st and 14th treatment (mean ± SD): Group 1: 4.35 ± 0.591, Group 2: 4.17 ± 0.577. All: P > 0.05. Functional improvement in meters: Between 1st and 7th treatment (mean ± SD): Group 1: 0.81 ± 0.253, Group 2: 0.82 ± 0.246.	**3**

Table 1: Study characteristics and findings, RCT = randomized clinical trial, Cm= centimetre, cm^2= square centimetre, kg=kilograms, BMI= body mass index, calculated as (kg/(length in meters)2), ? = not described, MTSS= medial tibial stress syndrome, TSF= tibial stress fracture, CS= compartment syndrome, 95% CI = 95% confidence interval, VAS= visual analogue scale, Non-RCT = nonrandomized clinical trial, ESWT = extracorporeal shockwave therapy, approx. = approximately, NRS = numeric rating score

						Between 7th and 14th treatment (mean ± SD): Group 1: 1.65±0.376, Group 2: 1.63±0.311; Between 1st and 14th treatment (mean ± SD): Group 1: 2.54±0.380, Group 2: 2.50±0.369. All P >0.05	
Nissen et al. (1994) [25] **RCT** **Low-energy laser treatment**	Conscripts with recently induced pain and presence of pain by palpation on the posteromedial border of the tibia. Exclusion: "other conditions that caused pain in the legs like knee pain or pain caused by distortions."	Military population; 72 subjects. Unclear is how many were allocated to each group. 23 completed the trial in group 1, 26 in group 2.	Age/Sex/Height/Weight/BMI/ Duration of complaints: ?	Group 1: Low-energy laser treatment. Laser rays of wavelength of 840nm were administered. At each treatment 40mW for 60sec/cm along the medial tibial border was performed, equivalent to 2.4 J/cm for the laser probe. 6 sessions in 2 weeks was aimed to perform, with 1-2 days interval. Group 2: received sham low-energy laser treatment.	Primary outcome: Full functionality after 14 days (ability to fully function as a conscript) Secondary outcomes: Time to reaching 2/3 of initial VAS-value Time to reaching 1/3 of initial VAS-value	Full functionality after 14 days: Group 1: 78%, sham laser group: 73%. Difference: 5% (95% CI: -19 - 29). P > 0.05 The Kaplan Meier Curve revealed no difference between groups in time of reaching 2/3 and 1/3 of the initial VAS-value.	**3**
Robertson (2003) [26] **RCT** **Periosteal pecking + ultrasound therapy versus ultrasound therapy**	Subjects (16-52 year of age), with pain and tenderness localised to the distal 2/3 of the medial border of the tibia. Subjects with contra-indications to dry needling/periosteal pecking or ultrasound were excluded.	Sports athletes population; 44 subjects. Both groups 22 subjects.	Age (range): 20-52 years. Male: 72.7%. Height/Weight/BMI/Duration of complaints:?	Group 1: Periosteal pecking ultrasound therapy: acupuncture needles (25mm scale: Hwato needles-Suzhou medical instruments, Siuzhou, China) were inserted into the tender spots located at the medial border of the tibia. Ultrasound therapy: a one MHz applicator head set was used, set at 0.5 watts /cm^2 and pulsed at 2 milliseconds on and 8 seconds off. 4 treatments were provided over 2 weeks. Group 2: Solely Ultrsound treatment. 4 treatments were provided over 2 weeks.	Primary outcome: Pain disability index; 5 questions 1-10 answer, 1=no disability, 10= pain completely prevents patient from activity; obtained before treatment 4. Secondary outcomes: Numerical pain rating scale: perceived level of pain 0-100 scale. 0= no pain, 100=pain at its worst; obtained before treatment 4. McGill short form pain questionnaire: list of 15 words that described pain, for each word pain intensity scale was ranked: 0=none, 1= mild, 2=moderate, 3= severe; obtained before treatment 4.	Pain disability index: (accumulated scores of 5 items) ; (mean ± SD): Group 1: 8.05 ± 11.52, Group 2: 4.64 ± 13.54, P=0.02. Numeric pain rating scale (mean ± SD): Group 1: 2.16 ± 22.18, Group 2: 25.80 ± 15.86 P=0.311. McGill short form pain questionnaire (mean ± SD): Group 1: 1.47±12.01, Group 2: 1.42±12.75. P=0.963.	**3**

Moen et al. (2012) [10] **RCT** **Graded running program, stretching and strengthening exercises or compression stockings**	Subjects > 16 years old, active in sport ≥ 3 times a week, with exercise induced pain on the posteromedial border of the tibia and pain by palpation on the posteromedial border of the tibia ≥ 5cm. Exclusion when suspicion of TSF, CS or history of tibial fracture or paresthesia.	Sports athletes population; 74 subjects. Group 1: 25, group 2: 24, group 3: 25 subjects.	All data is presented as mean ± SD, except for sex. Group 1: Age (years): 22.2 ± 6.8 Sex (% female): 65.2%; Height (cm): 175.4±4.9, Weight (kg): 68.7±8.1, BMI: 22.2±1.8; Duration of complaints (days): 178.0±319.2. Group 2: Age (years): 20.7 ± 6.3 Sex (%female): 72.7%; Height (cm): 171.6 ± 5.2, Weight (kg): 68.3 ± 7.7, BMI: 22.9 ± 2.6; Duration of complaints (days): 174.0 ± 274.1. Group 3: Age (years): 23.0 ± 8.2 Sex (%female): 53.3%; Height (cm): 177.0 ± 9.9, Weight (kg): 70.4 ± 11.2, BMI: 22.3 ± 2.6; Duration of complaints (days): 213.7 ± 363.8.	Group 1: 6- phase graded running program Group 2: 6- phase graded running program, stretching and strengthening exercises for the calve muscles, 5 times a week Group 3: 6- phase graded running program, subjects wore a sports compression stocking while running and walking	Days from inclusion to completing phase 6 of the running program (ability of running 18 consecutive minutes at a pace at which speech becomes difficult).	Time to completion of the running program (mean ± SD): Group 1: 105.2 ± 54.6, Group 2: 117.6 ± 64.2, Group 3:102.1 ± 52.3. P > 0.05	**3**
Moen et al. (2010) [7] **RCT** **Lower leg brace versus no brace**	Exercise induced pain on the posteromedial border of the tibia and pain by palpation of the posteromedial border for ≥ 5cm. Exclusion: suspicion of TSF or CS	Military population: 15 subjects, all were men. Group 1: 8, group 2: 7 subjects	All data is presented with their mean ± SD Group 1: Age (years): 19.1 ± 1.9; Height/Weight:?; BMI: 24.5±2.0; Duration of complaints (days): 32.9±20.2. Group 2: Age (years): 18.6±1.2; Height/Weight:?; BMI: 23.1±2.0; Duration of complaints (days): 35.1±16.9.	Group 1: 6-phase graded running program, wearing a pneumatic leg brace (Aircast Inc. Summit, New Jersey, USA). Group 2: 6-phase graded running program, no brace	Days from inclusion to completing phase 6 of the running program (ability of running 18 consecutive minutes at a pace at which speech becomes difficult).	Time to completing the running program in days (mean ± SD): Group 1: 58.8±27.7 Group 2: 57.9±26.02 P=0.57.	**3**
Piantanida et al. (Unpublished)[28] **RCT** **Lower leg brace versus no brace**	Subject >17yr, non- pregnant subjects, ≥ 6 weeks of exertional lower medial leg pain and available for 6 months follow-up. Exclusion: suspicion of TSF or CS or	Military population; 77 subjects. Group 1: 37 Group 2: 40	Group 1: Age: 19-24yr: 19, 25-29yr: 8, 30-40yr: 7, > 40:3; Sex (% female): 73.0%, Height/Weight/BMI/Duration of complaints: ? Group 2: Age: 19-24yr: 20,	Both groups followed a non- supervised 4-phase rehabilitation program: stationary biking, stretching, strengthening, exercises, walking and running sessions. Group 1: pneumatic leg brace (Aircast Corporation, Summit, New Jersey, USA) Group 2: no brace	Primary outcome: 100mm VAS after a 5 minute running treadmill test after 4 weeks from baseline. Secondary outcomes: VAS after a treadmill test at 8 weeks Return to duty after 8 weeks	Difference VAS baseline - 4 weeks (mean ± SD): Right leg, group 1: 26.91± 28, right leg, group 2: 27.97±28. P=0.8728. Left leg, group 1: 16.65±27, left leg, group 2: 16.43±31, P= 0.9738 Difference VAS baseline – 8 weeks (mean ± SD): Right leg, group 1: 37.27±32, right leg, group 2: 26.93±32	3

	X-rays and pressure measurements revealed such.		25-29yr: 9, 30-40yr: 9, over 40:2; Sex (% female): 66.7%, Height/Weight/BMI/Duration of complaints: ? All subjects had bilateral complaints.			P=0.9698. Left leg group 1: 26.64±33, left leg group 2: 27.37±30. P=0.9348 After 8 weeks return to duty rate: Group 1: 59.1%, Group 2: 70.4%. P=0.41	
Johnston et al. (2006)[27] **RCT** **Lower leg brace versus no brace**	Shin splints, exclusion: TSF, < 6 weeks training remaining, concurrent lower extremity pathologies.	Military population; 25 subjects, group 1: 12 group 2: 13	Group 1: Age (mean years ± SD): 22.33 ± 3.89; Sex:?; Height (mean inches ± SD): 67.58 ± 3.53; Weight (lb) (mean lb ± SD): 159.08 ± 36.36; BMI:?; Duration of complaints:? Group 2: Age (mean years ± SD): 22.00 ± 5.05; Sex:?; Height (mean inches ± SD): 67.96 ± 4.05; Weight (mean lb ± SD): 169.96 ± 24.03; BMI:?; Duration of complaints:?	Both groups: activity modification and ice appliance after each training. Group 1: Walk-to-run program with a shin save orthosis Group 2: Walk-to-run program without a shin save orthosis.	Time to run 0.5 mile without 10 subsequent steps of pain. Global rating of change 10- cm VAS score	Time (days) to run 0.5 mile (mean ± SD): Group 1: 13.43 ± 4.5 Group 2:17.17 ± 16.5. P=0.575. Global rating of change (mean ± SD): Group 1: 4.71 ± 3.1. Group 2: 5.5 ± 1.4. P=0.578 VAS: Group 1:? Group 2: ? Not significant	**3**
Brinkman et al. (2013)[29] **RCT:** **Pulsed Electromagnetic Field**	Subjects (18-45yr) with complaints ≥ 6 weeks, exercise related pain on the posteromedial border and pain by palpation on the posteromedial border of the tibia for at least 5cm. Exclusion: Clinical suspicion of TSF or CS; pregnancy, use of anticoagulant medicine, pacemakers or insulin pump or present	Sports athletes population; 17 subjects. Group 1: 8, Group 2: 9. A total of 30 legs were analysed.	All data is presented by median and range, except for sex. Group 1: Age (years): 23.8 (18-35), Sex: 3 males, 5 females; Height/Weight:? BMI: 22.6 (19.9 - 24.8); Duration of complaints (months): 30.5 (2.5-56) Group 2: Age (years) 28.6 (19-45), Sex: 3 males, 6 females; Height/Weight:? BMI: 24.7 (19.6 - 28.7); Duration of complaints (months): 14.0 (2.5-56)	Group 1: Pulsed Electromagnetic Field (PEMF): "A pulsing electromagnetic field was activated by a flat coil in a portable PEMF device." Pulse width was 5 microseconds, pulse frequency was set at 100 kHz, the burst width was 5 milliseconds and the burst frequency was set at 15 Hz. The PEMF was worn for 6 weeks, 7 days a weeks, 8 hours a day. The PEMF was worn at night. Group 2: Placebo PEMF	NRS (pain score 0-10), Pain during and after sports activity after 3, 6, 12 and 24 weeks. Global perceived effect, measured on a 6-point Likert scale after 3, 6, 12 and 24 weeks: completely recovered(1); much improved (2); somewhat improved (3); same (4); worse (5); much worse (6). Completely recovered and much improved were considered a treatment success, option 3-6 a treatment failure. The Likert scale was obtained for each leg.	The following data is presented by a median and range. NRS pain during and after sports activity: After 3 weeks: Group 1: 4 (1-7), Group 2: 4 (0-9); After 6 weeks: Group 1: 2 (0-7), Group 2: 2 (0-10); After 12 weeks: Group 1: 1(0-8), Group 2: 3.5 (0-8); After 24 weeks: Group 1: 1 (0-6), Group 2: 1 (0-9) Global perceived effect: amount of patients with treatment 'success': After 3 weeks: Group 1: 0, Group 2: 4; After 6 weeks: Group1: 6, Group2: 4;	**3**

	neurovascular disorders.					After 12 weeks: Group 1: 9, Group 2: 4; After 24 weeks: Group 1:5, Group 2: 3. Differences between groups were not tested.	
Rompe et al. (2011)[8] **Non-RCT** **Radial ESWT**	Subjects > 18 years, with complaints > 6 months who had been treated with at least 3 nonoperative treatments without effect were included. Pain on the medial border of the tibia and pain on palpation of the medial border not localized to one spot. Exclusion: CS, pregnancy, subjects with bleeding disorders, rheumatoid arthritis, generalized polyarthritis, local infection, tumors, end stage ipsilateral knee and ankle osteoarthritis and subjects with prior knee or ankle surgery.	Sports athletes population; 78 subjects. Group 1: 47, Group 2: 47.	All data is presented by a mean and range. Group 1: Age (years): 41.4 (18-56); Sex: 19 males, 28 females. Height/Weight/BMI: ?; Duration of complaints (months): 15.4 (8-24). Group 2: Age (years): 42.6 (18-54); Sex: 21 males, 26 females. Height/Weight/BMI: ?; Duration of complaints (months): 13.7 (6-30)	Group 1: 12-week home training program, relative rest, ice and radial shockwave therapy. Radial shockwave therapy in week 2, 3, 4 weeks after the start of 12-week home training program. Each subject received 3 low-energy treatments. At each session: 2000 shocks, with a pressure of 2.5bars. Frequency: 8 shocks p/s. The total energy flux density per treatment was approx. 200mJ/mm^2. Group 2: 12-week home training program, relative rest and ice. Pain killers (paracetemol) were provided to all subjects when requested; 2000-4000 mg/day.	Primary outcome: Degree of recovery after 4 months, on a 6-point Likert scale: completely recovered(1), much improved (2), somewhat improved (3), same (4), worse (5), much worse(6). Completely recovered and much improved were considered a treatment success, option 3-6 a treatment failure. Secondary outcome: Degree of recovery after 1 and 15 months. Severity of pain in the last week after 1, 4 and 15 months on 1-10 scale, 1= no pain, 10=very severe pain.	Success rates after 4 months: Group 1: 63.8%, Group 2: 29.8%. Success rates after 1 month: Group 1: 29.8%, Group 2: 12.8%. Success rates after 15 months: Group 1: 29.8%, Group 2: 12.8%. All: P < 0.001. . Severity of pain scale: 1 month (Mean ± SD): Group 1: 5.8 ± 0.9 Group 2: 7.3 ± 2.9 4 months: Group 1: 3.8 ± 1.1, Group 2: 6.9 ± 0.8, 15 months: Group 1: 2.7 ± 0.9, Group 2: 5.3 ± 2.6 All: P < 0.001.	**4**
Moen et al. (2012) [9]	Subject > 21 days of complaints,	Sports athletes population; 42	All data is presented by a mean and SD, except for sex.	Group 1: 6-phase graded running program. Group 2: 6-phase graded running program +	Days from inclusion to completing phase 6 of the running program (ability of	Time to completion of the running program in days (Mean ± SD):	**4**

Non-RCT **Focused ESWT**	exercise induced pain on the posteromedial border of the tibia with pain on palpation for ≥ 5cm on the posteromedial border of the tibia. Exclusion: History of paraesthesia or other symptoms indicative of other causes of exercise induced leg pain. History of tibial fracture and previous treatment with shockwave therapy for MTSS.	subjects. Group 1: 22, Group 2: 20 subjects	Group 1: Age (years): 22.7 ± 7.2; Sex (%male) 35%; Height (cm): 175.1 ± 6.5; Weight (kg): 68.5 ± 8.6; BMI: 22.2 ± 1.9; Duration of complaints (days): 189.3 ± 339.8. Group 2: Age (years): 30.0 ± 12.5, Sex (%male) 73%; Height (cm) 178.5 ± 10.3; Weight (kg): 74.2 ± 10.1; BMI: 23.2 ± 2.2; Duration of complaints (days): 629.2 ± 761.1.	extracorporeal focused shockwave therapy, without local anaesthesia. 5 treatment sessions in week 1, 2, 3, 5 and 9. Session 1: 1000 shocks with an energy flux density of 0.10mJ/mm^2, 2.5 shocks per second. Session 2: 1500-0.15mJ/mm^2-2.5 shocks p/s, Session 3:1500-0.20mJ/mm^2-2.5 shocks p/s. Session 4:1500-0.25mJ/mm^2-2.5 shocks p/s. Session 5: 1500-0.30mJ/mm^2-2.5 shocks p/s	running 18 consecutive minutes at a pace at which speech becomes difficult).	Group 1: 59.7 ± 25.8 Group 2: 91.6 ± 43.0 P=0.008. Multivariate risk factor analysis: Treatment explained 17.5% of the total variance in the number of days to full recovery. Sex (P= 0.039) explain a significant % of the variance (adjusted R^2)in the number of days to full recovery. Woman needed more days to complete phase 6 of the running program: Group 1: 63.6 ± 35.1, Group 2: 88.8 ± 38.4.	

that it is unlikely that publication bias is present in this study (see appendix 4)

4.4.2. QUALITY ASSESSMENT

All RCTs revealed a high risk of bias; Fig. 2 provides a detailed overview of biases per study. Our justification for assigning a '?', '-' or '?' to each domain of bias is provided in appendix 5.

Generally, in most studies masking of participants and personnel was impossible due to the intervention under investigation. High risk of attrition bias was present in four studies due to high loss to follow-up or dropout rates. All but two studies exhibited a high risk of other biases, mainly due to statistical flaws or performance bias. Many studies had imbalances in the amount of treatments given between groups. Three studies were substantially deficient in their reporting of methodological details. As a result, many of their domains of bias were scored as 'unclear risk of bias'.

Table 2 provides details of the quality assessment for each non-randomized study. Authors' justification for awarding stars to each item per study is provided in appendix 6. Both non-randomized clinical trials assessed were of poor quality.

All studies were downgraded for quality reasons. All RCTs were graded as Level 3 evidence whereas both nonrandomized clinical trials were judged to be Level 4 evidence.[14]

4.4.3. EFFECT OF INTERVENTIONS

The included trials assessed the effect of iontophoresis, phonophoresis, ice massage, ultrasound, low-energy laser treatment, periosteal pecking, stretching and strengthening exercises, a sports compression stocking, lower leg braces, extracorporeal shockwave therapy (ESWT) and pulsed electromagnetic field. A brief summary of their effects is provided in Table 3.

4.4.4. DATA ANALYSIS

Fixed effects models were used to estimate the effect of lower leg braces versus no braces and iontophoresis versus phonophoresis (Figs. 3, 4). No statistical heterogeneity was present in both models.

Data could not be pooled in the two shockwave studies due to clinical heterogeneity.8, 9 One study assessed the effect of radial ESWT whereas the other studied focused ESWT. Furthermore, one study included subjects that had complaints for ≥6 months whereas in the other study subjects with complaints for ≥3 weeks were eligible for inclusion.8, 9 When pooled, considerable statistical heterogeneity was present (Tau^2 = 2.56, I^2 = 96 %). Clinical and methodological heterogeneity could not be tested in a meta-regression or subgroup analysis because only two studies assessed the effect of ESWT.

Domain/item	Rompe et al.[8]	Moen et al. [9]
	Star awarded?	*Star awarded?*
Selection		
Inclusion criteria	Yes	Yes
Intervention group	Yes	Yes
Control group	No	No
Comparability (1)	Yes	Yes
Comparability (2)	No	Yes
Performance		
Treating sessions	No	No
Follow-up sessions	Yes	No
Outcome		
Blinded Outcome assessment	Yes	No
Follow-up	No	Yes
Intention-to-treat-analysis?	No	No
Total stars	**5/10**	**5/10**

Table 2. Quality assessment of nonrandomized clinical trials

4.4.5. DESCRIPTIVE METHODS

4.4.5.1. IONTOPHORESIS, ICE MASSAGE, PHONOPHORESIS AND ULTRASOUND VERSUS CONTROL

One RCT studied the effect of iontophoresis, ice massage, phonophoresis and ultrasound versus no treatment in a military population.[23] Group 1 received iontophoresis via a Phoresor iontophoretic delivery system. 2 mL of dexamethasone (4 mg/mL) and 1 mL of 4 % of lidocaine was used. The constant current average dosage was 2.5–5 mA, for 20 minutes. Group 2 applied 10 minutes of ice massage in a circular motion on the pain site. Group 3 received phonophoresis using a mixture of 33 mg of dexamethasone and 16 mL of lidocaine gel of 2 % in 60 mg of a water-soluble base. Continuous ultrasound was set on an average of 1.5 W/cm^2. Group 4 received ultrasound therapy only, as described above. Group 5 did not receive any modality. All groups performed heel stretching exercises and were placed on limited duty. Subjects in all treatment groups reduced their perceived pain significantly more than the untreated subjects in the control group. However, no treatment was found to be superior to another treatment.[23] Another RCT confirmed that iontophoresis is not superior to phonophoresis.[24]

4.4.5.2. LOW-ENERGY LASER TREATMENT VERSUS SHAM LASER TREATMENT

One RCT studied the effect of low-energy laser treatment versus sham laser treat-

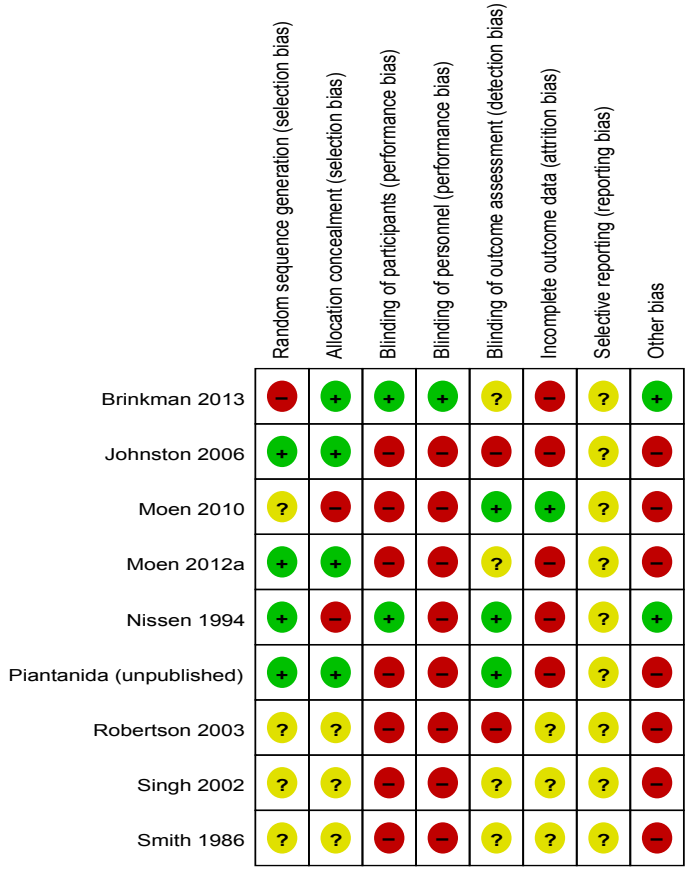

Figure 2. Risk of bias for each domain for each randomized clinical trial. - signifies high risk of bias; + signifies low risk of bias; ? signifies unclear risk of bias. a Reference[10]

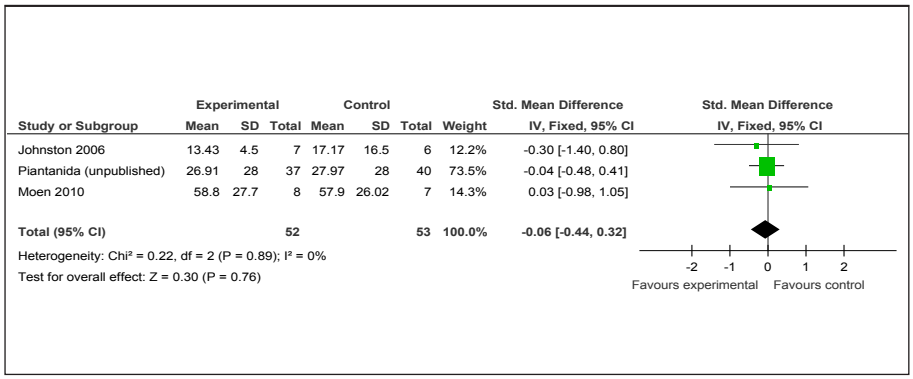

Figure 3. Data analysis of the effect of lower leg braces versus control. CI confidence interval, IV inverse variance, SD standard deviation, Std. standardized, square size indicates the size of the population investigated in each study; diamond estimated pooled effect: width indicates the 95 % confidence interval.

ment in a military population.[25] Group 1 received low-energy laser treatment. Laser rays of 840 nm wavelength were administered. At each treatment, 40 mW for 60 s/cm along the medial tibial border was performed. The aim of the study was to perform six sessions in 2 weeks, with a 1- to 2-day interval. Group 2 received sham low-energy laser treatment. No difference between groups was found on the ability to return to duty after two weeks and time to reach one third and two thirds of the initial visual analog scale (VAS) value.

4.4.5.3. PERIOSTEAL PECKING

One RCT studied the effect of periosteal pecking, a kind of acupuncture, in combination with ultrasound therapy versus ultrasound therapy only, in a sports athlete population.[26] Group 1 received both modalities. Needles were inserted into the tender spots at the medial border of the tibia. Ultrasound therapy was applied with a 1 MHz applicator head set and set on 0.5 W/ cm^2 and pulsed at 2 ms on and 8 s off. Four treatments were provided over 2 weeks. Group 2 received ultrasound therapy only, as described above. Although the periosteal pecking group reached a significant lower pain score than the control group with regard to the pain disability index, no differences were found on the two secondary pain scales.

4.4.5.4. GRADED RUNNING PROGRAM, STRETCHING/STRENGTHENING AND SPORTS COMPRESSION STOCKINGS

One RCT studied the effect of a six-phase graded running program versus a six-phase graded running program in combination with stretching and strengthening exercises for the calf muscles versus a six-phase graded running program in combination with wearing sports compression stockings while running and walking.[10] This study

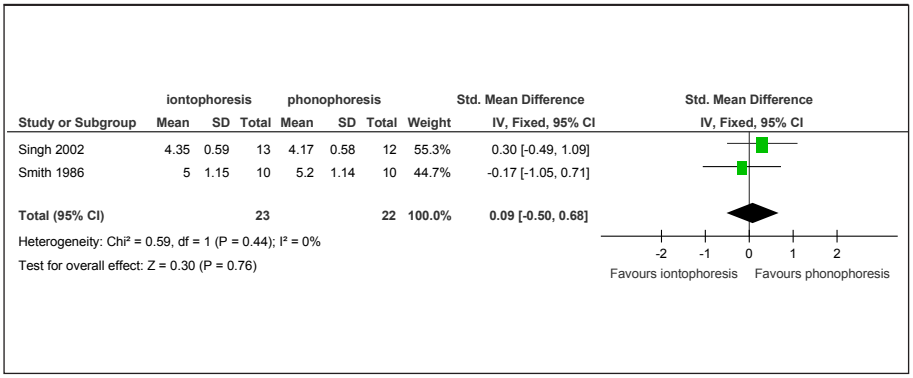

Figure 4. Data analysis of the effect of iontophoresis versus phonophoresis. CI confidence interval, IV inverse variance, SD standard deviation, Std. standardized, square size indicates the size of the population investigated in each study; diamond estimated pooled effect: width indicates the 95% confidence interval

was performed in an athletic population. The first four phases of the graded running program consisted of interval training in which duration was increased from 16 to 20 minutes and intensity increased from light jogging to a running speed where speaking became difficult. In phases 5 and 6, continuous running was performed for 16 and 18 minutes, respectively, and the intensity was increased from light jogging to running at a speed where speaking became difficult. A new phase of the running program was commenced when a phase was finished without a pain score of 4 or higher on the 1–10 VAS. Training was performed three times a week, on non-consecutive days. No differences were found between the groups for the time to completion of the graded running program.

4.4.5.5. LOWER LEG BRACE VERSUS NO LEG BRACE

Three RCTs studied the effect of a lower leg brace versus no leg brace in addition to a graded rehabilitation or running program.[7, 27, 28] In all studies, the program was gradually intensified based on perceived pain. All studies were carried out in military populations. No difference between groups was found for the time to completion of a graded running program or time to being able to run a 0.5 mile without ten consecutive steps of pain, perceived pain, ability to return to duty and global perceived effect.

4.4.5.6. PULSED ELECTROMAGNETIC FIELD VERSUS PLACEBO

One RCT assessed the effect of pulsed electromagnetic field (PEMF) versus placebo in an athletic population.[29] In the intervention group a PEMF was activated by a flat coil in a portable PEMF device. The pulse width was 5 microseconds, pulse frequency was set at 100 kHz, the burst width was 5 ms and the burst frequency was set at 15 Hz. The PEMF was worn for 7 days a week for 6 weeks for 8 hours a night. The control group received a placebo PEMF. No differences were found between groups on pain

Table 3. Summary of intervention effects

Interventions/outcome	*Time to recovery*	*Global Perceived Effect*	*Pain*
Iontophoresis, Phonophoresis, Ultrasound therapy or Ice massage versus control	*NA*	*NA*	+
Iontophoresis versus phonophoresis, ice massage and ultrasound therapy	*NA*	*NA*	+/-
Periosteal pecking versus ultrasound therapy	*NA*	*NA*	+ or +/-
Low-energy laser versus sham laser	*NA*	+/-	+/-
Brace versus no brace	+/-	+/-	+/-
Pulsed electromagnetic field versus placebo	*NA*	+/-	+/-
ESWT* versus control treatment	+	+	+

? Indicates a positive effect, - indicates a negative effect, ?/- indicates no effect, ESWT extracorporeal shockwave therapy, NA not applicable

Table 3. Summary of intervention effects

and global perceived effect after 3, 6, 12 and 24 weeks.

4.4.5.7. EXTRACORPOREAL SHOCKWAVE THERAPY COMPARED WITH CONTROL TREATMENT

One non-randomized clinical trial studied the effect of radial ESWT in addition to a 12-week home training program, relative rest and ice appliance compared with a 12-week home training program, relative rest and ice appliance only.[8] This study was performed in a sports athlete population. Radial shockwave therapy was provided in weeks 2, 3 and 4 after the start of the 12-week home training program. Each subject received three low-energy treatments (Swiss DolorCast, Electro Medical Systems Nyon, Switzerland). At each session, 2,000 shocks, with a pressure of 2.5 bars were provided. The frequency was set at 8 shocks p/s. The total energy flux density per treatment was approximately 200 mJ/mm^2. Paracetamol was provided as needed at a dose of 2000–4000 mg/day. The radial ESWT in addition to an exercise home training program was found to improve global perceived effect and severity of pain when compared with a home training program only.

One non-randomized clinical trial studied the effect of a six-phase graded running program compared with the same running program with the addition of focused ESWT.[9] This study was performed in an athletic population. The focused ESWT was provided without local anesthesia. Five treatment sessions in weeks 1, 2, 3, 5 and 9 were

given. The shocks and energy flux density increased throughout the weeks: Session 1: 1,000 shocks with an energy flux density of 0.10 mJ/mm^2, 2.5 shocks p/s; Session 2: 1,500 shocks, 0.15 mJ/mm^2, 2.5 shocks p/s; Session 3: 1,500 shocks, 0.20 mJ/mm^2, 2.5 shocks p/s; Session 4:1,500 shocks, 0.25 mJ/mm^2, 2.5 shocks p/s; Session 5: 1,500 shocks, 0.30 mJ/mm^2, 2.5 shocks p/s. It was found that focused ESWT in addition to a graded running program reduced time to completion of a graded running program significantly more than a graded running program alone.

4.5. DISCUSSION

This is the first systematic review that assessed the effect of treatments for MTSS, studied in RCTs and non-randomized clinical trials. All studies included assessed conservative interventions. There is no high quality evidence for the effect of any intervention in treating MTSS.

4.5.1. METHODOLOGICAL QUALITY OF THE STUDIES

The study quality is an important aspect to consider when interpreting these results. All RCTs revealed a high risk of bias and the two non-randomized clinical trials were found to be of poor quality.

All RCTs, except for the studies by Brinkman et al. and Nissen et al.,[25, 29] exhibited performance bias due to the impossibility to blind personnel and participants. Nissen et al. aimed to blind both personnel and participants, however during the study the nurse that performed the laser treatments identified the active probe.[25] The studies by Smith et al. and Singh et al. were seriously deficient in their reporting of methodological details.[23, 24] It is unclear to what degree the results obtained were influenced by systematic errors. Therefore, no conclusion can be drawn regarding the observed effects.

Other studies that exhibited serious shortcomings in terms of reporting were those by Moen et al. and Robertson.[7, 26] In these studies, randomization procedures were not described or the study reported that it was randomized but no explanation was provided as to how randomization procedures were carried out. This lack of information makes for difficulties in the assessment of study quality and the replication of experiments. Furthermore, no study protocols were registered prior to commencement in trial registries. Therefore, it was impossible to assess whether selective reporting of results had occurred.

The two non-randomized controlled trials that assessed the effect of ESWT had many systematic errors including selection, performance, attrition and detection bias.[8, 9] More specifically, in both studies no randomization was performed and no sham shockwave treatment was provided, to avoid performance biases. Apart from blinding, this led to inequality of the amount of attention patients received because the treatment group received additional treatment to the single intervention that was received by the control group. Additionally, the study by Rompe et al. could have introduced substantial

selection bias by assigning patients to the shockwave or control group based on the willingness and/or ability to pay $200 for the shockwave treatment regimen.[8] Attrition bias may have been present in this study; the number of subjects in the control group lost to follow up was not described.

In the study by Moen et al.,[9] additional selection bias could have been introduced due to allocating patients to the treatment or control treatment group based on the hospital (academic or local) that they were referred to. The study did not describe to which treatment the groups were assigned. Academic referrals tend to be the more 'severe patients'. As there is no valid standard for the severity of MTSS, it is impossible to verify whether this inequality may have been present or not. A final limitation of the study's report is that it remains unclear whether the outcome assessor was blinded, leading to possible detection bias.

All the biases described above may have led to the effects found in the studies examining ESWT. Therefore, it cannot yet be concluded that ESWT is effective in treating MTSS.

4.5.2. OTHER LIMITATIONS

Other limitations of the studies included concern the duration of follow-up and statistical analysis. Except for the study by Rompe et al.,[8] none of the studies assessed the effect of the treatments in the long term or on possible recurrences. The studies by Smith et al., Singh et al., Nissen et al., Johnson et al. and Robertson had very short follow-up periods.[23-27] For example, the study by Nissen et al. hypothesized that 55 % of the conscripts in the placebo group would return to duty within 2 weeks.[25] Return to duty was defined as ''being able to fully function as a conscript'' which was not specified further but could be considered as being able to do prolonged marching and running activities. In several studies it is noticed that full recovery is not likely to be achieved within 2 weeks.[7-10]

Statistical procedures are another concern that deserves attention. Many studies do not assess their results for possible confounding factors and are frequently analyzed per protocol instead of using the intention-to-treat principle.

4.5.3. RECOMMENDATIONS FOR RESEARCH

No interventions have been proven to be effective in treating MTSS. The studies included vary in their explanations of the theoretical basis for the chosen intervention. The studies describe the underlying pathology of MTSS as musculoskeletal, bony and/or periosteal.

It might be important to understand the underlying histology and etiological factors that may contribute to prolonged complaints in MTSS before proper interventions can be further assessed in research.

A couple of possible interventions for MTSS have not been studied. The effect of weight

bearing, such as the commonly used graded running program, should be assessed. Plyometric exercises, that may enhance bone formation, have been identified as a potential treatment option and could be effective in MTSS patients.[30]

Although two ESWT studies have shown large effects in the treatment of MTSS, no conclusions can be made due to the presence of biases.[8,9] A good quality RCT is warranted to clarify the effect of ESWT. To control for biases a well performed randomization procedure and a sham control group would enhance estimating the effect of ESWT. Furthermore, authors should report according to the Consolidated Standards of Reporting Trials (CONSORT) statement and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[31, 32]

4.5.4. IMPLICATIONS FOR PRACTICE

No intervention has been proven to be effective for MTSS. As MTSS is most likely a bony overload injury, rehabilitation programs that focus on bone recovery seem most appropriate. One might consider several days of nonweight bearing after which weight bearing is gradually increased until full function level has been achieved.

4.5.5. LIMITATIONS OF THIS SYSTEMATIC REVIEW

One of the key limitations of our review is that the Newcastle–Ottawa Scale, used to assess non-randomized controlled trials, is not widely accepted for this task. There is, however, no widely accepted tool for the assessment of non-randomized controlled trials and this tool is one of the recommended tools according to Deeks et al.[33]

A second limitation is that all studies use different outcome measures, which impaired our ability to compare results across studies. No validated specific outcome measure currently exists for MTSS. A specific patient-reported outcome measure for MTSS is needed to validly measure treatment effects and to enable comparison of effects across studies. An outcome measure that incorporates dimensions of pain, limitations of activities of daily living and limitations of sports activities would be best.

4.6. CONCLUSION

There is no evidence for the effect of any intervention in treating MTSS. Studies examining low-energy laser treatment, stretching and strengthening exercises, sports compression stockings, leg braces and pulsed electromagnetic fields showed no treatment effect. There are studies suggesting that iontophoresis, phonophoresis, ice massage, ultrasound, periosteal pecking and extracorporeal shockwave therapy are effective (Level 3 to 4 of evidence). None of the studies are sufficiently free from meth-

odological bias to recommend any of the treatments investigated. Of those examined, ESWT appears to have the most promise.

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Appendix 1. Search strategy

Search terminology

The following mesh terms and key words were used in order to construct the most sensitive search strategy possible:

- medial tibial stress syndrome
- tibial stress syndrome
- medial tibial syndrome
- shin splints syndrome
- shin splint
- shin splints
- shin soreness

Search strategy for MEDLINE:

"Medial Tibial Stress Syndrome"[Mesh] OR Tibial Stress Syndrome*[tiab] OR shin splint*[tiab] OR shin soreness*[tiab] OR tibial Stress injur*[tiab] OR shinsplint*[tiab] OR shin splint syndrome* [tiab] OR medial tibial syndrome* [tiab]

Appendix 1. Search strategy

Domain of bias	*Qualification*	*Criteria for assigning risk of bias*
Selection bias		*Sequence generation*
	+	Computer based random number generators, a table with random numbers or similar methods
	-	Quasi randomization procedures e.g. allocation based on date of birth or on day of the week
	?	None described sequence generation
Selection bias		*Allocation concealment*
	+	Computer based sequence generation method or numbered opaque envelopes, or similar
	-	Envelopes (non-opaque) or any quasi randomization procedure
	?	None described allocation concealment
Performance bias		*Blinding of participants and personnel*
	+	Blinded participants and personnel
	-	Non blinded participants and personnel
	?	None described or unclear blinding of participants and personnel
Detection bias		*Blinding of outcome assessment*
	+	Blinded outcome assessor or outcome obtained by a patient reported outcome measure (PROM)
	-	Non blinded outcome assessment and no PROM was used
	?	Methods of (blinding) the outcome assessment were not described
Attrition bias		*Incomplete outcome data*
	+	Random lost to follow up of participants was present when ≤ 10% was lost to follow up
	-	Selective lost to follow up of participants was present when > 10% was lost to follow up
	?	Unclear lost to follow up
Reporting bias		*Selective reporting* (www.controlled-trials.com, ClinicalTrials.gov, http://apps.who.int/trialsearch/ were searched for protocols)
	+	Articles that reported all a priori described outcomes
	-	Articles that did not report all a priori described outcomes
	?	The protocol was not found.
Other biases		
	+	Any other systematic errors that could lead to bias
	-	No other systematic errors were present

Selection procedure and comparability of groups was assessed based on five items:

Inclusion criteria: One star was awarded when in- and exclusion criteria were described and methods of making the MTSS diagnosis were provided.

Recruitment procedure intervention group: Studies describing how and where subjects in the intervention group were recruited, were awarded a star.

Recruitment procedure of control group: Studies that selected subjects from the same population as the intervention group were awarded a star.

Comparability of groups (1): One star was awarded when possible confounders were obtained and reported.

Comparability of groups (2): One star was awarded when presence of confounder factors were assessed in univariate and - when applicable -multivariate risk factor analysis.

Performance bias was assessed based on two items

Amount of treatment sessions: One star was awarded when all groups received equal amount of treatment sessions.

Amount of follow-up sessions: One star was awarded when an equal amount of follow-up sessions were planned for all groups.

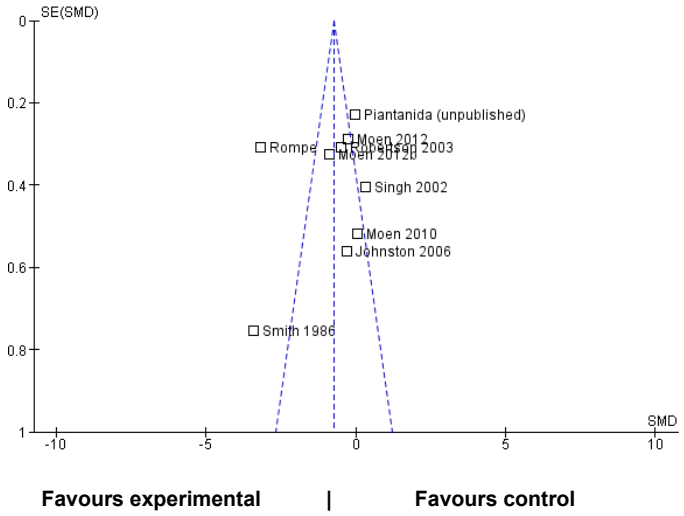
Outcome (detection and attrition bias) was assessed based on the next three items.

Blinded Outcome assessment: One star was awarded when a blinded investigator assessed the outcome, or when the outcome was patient-reported.

Follow-up adequacy: One star was awarded when ≤ 10% of the subjects were lost to follow-up.

Intention-to-treat analysis: Studies analyzing their data based on the intention-to-treat principle were awarded a star.

Appendix 3. Modified Newcastle Ottawa Scale[13]



Appendix 4. Funnel plot; assessment of publication bias. SE = standard error, SMD = Standardized mean difference. Nissen (1994) [25] and Brinkman (2013) [29] could not be included in the plot.

Brinkman (2013)[29]

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	High risk of bias	Subjects were assigned to the intervention or placebo group based on the order of inclusion in the study. There were two boxes, one with the working PEMF's and one with the placebo PEMF's. Subjects received a PEMF from the box with the most PEMF's left.
Allocation concealment (selection bias)	Low risk of bias	Allocation was blinded: the researchers did not know which box contained the active PEMF's and which box contained the sham PEMF's.
Blinding of participants (performance bias)	Low risk of bias	Participants were blinded
Blinding of personnel (performance bias)	Low risk of bias	Personnel was blinded
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Unclear is whether the outcome assessor was blinded
Incomplete outcome data (attrition bias)	High risk of bias	3/17 subjects (17,6%) were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk of bias	No protocol could be found.
Other bias	Low risk of bias	No other biases were noted.

Appendix 5. Risk of bias assessment summary per study (N=9)

Appendix 5. continued

Johnston (2006)[27]		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk of bias	"All subjects … were randomized by using a random-number generator and were blocked in groups of four to either a shin orthosis (experimental) group or a traditional treatment (control) group."
Allocation concealment (selection bias)	Low risk of bias	As described above
Blinding of participants (performance bias)	High risk of bias	Participants could not be blinded
Blinding of personnel (performance bias)	High risk of bias	Personnel could not be blinded
Blinding of outcome assessment (detection bias)	High risk of bias	Outcome assessment was performed at each walk-to-run program session and was not blinded
Incomplete outcome data (attrition bias)	High risk of bias	"Six experimental group subjects (46%) and six control group subjects (50%) did not complete the study."
Selective reporting (reporting bias)	Unclear risk of bias	No protocol could be found.
Other bias	High risk of bias	No intention-to-treat analysis was performed

Appendix 5. continued

Moen et al. (2010)[7]		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk of bias	Sequence generation was not described
Allocation concealment (selection bias)	High risk of bias	'Subjects were randomly assigned by sealed envelope selection'
Blinding of participants (performance bias)	High risk of bias	Participants could not be blinded in this study
Blinding of personnel (performance bias)	High risk of bias	Personnel could not be blinded. Unclear is whether the military instructor that instructed the exercise program, was blinded.
Blinding of outcome assessment (detection bias)	Low risk of bias	"The recruits were assessed every two weeks by a blinded investigator"
Incomplete outcome data (attrition bias)	Low risk of bias	≤10 % lost to follow up.
Selective reporting (reporting bias)	Unclear risk of bias	No protocol could be found
Other bias	High risk of bias	Performance bias: imbalance between groups, the control group did not receive the same amount of interventions as the control group. No intention-to-treat analysis was performed.

Moen et al. (2012)[10]

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk of bias	"For the randomization at each location there were three identical opaque blank envelopes in a box each containing a letter, explaining to which of the three groups the athlete had been allocated. After the athlete had been allocated the letter was returned to the envelope and into the box to be used again by the next envelope"
Allocation concealment (selection bias)	Low risk of bias	"Three identical opaque envelopes in a box with each containing a letter, explaining to which the three groups the athlete had been allocated."
Blinding of participants (performance bias)	High risk of bias	Participants could not be blinded
Blinding of personnel (performance bias)	High risk of bias	Personnel could not be blinded
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Whether the outcome was self-reported or the outcome assessor was blinded to the allocation is unclear.
Incomplete outcome data (attrition bias)	High risk of bias	>10% lost to follow up
Selective reporting (reporting bias)	Unclear risk of bias	No protocol could be found.
Other bias	High risk of bias	Performance bias: imbalance between groups, one group did not receive the same amount of interventions as the other two groups.

Nissen et al. (1994)[25]

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk of bias	Participants were assigned to the intervention or control group based on a 'random mixed envelop system'
Allocation concealment (selection bias)	High risk of bias	Envelopes were used to conceal allocation
Blinding of participants (performance bias)	Low risk of bias	Participants were blinded to whether they received the active laser probe or the sham laser probe
Blinding of personnel (performance bias)	High risk of bias	The nurse that performed treatment found out which probe was the active one
Blinding of outcome assessment (detection bias)	Low risk of bias	VAS was self-reported; functionality was assessed by a blinded medical physician
Incomplete outcome data (attrition bias)	High risk of bias	23/72 (29.1%) participants were excluded during the study.
Selective reporting (reporting bias)	Unclear risk of bias	No protocol could be found.
Other bias	Low risk of bias	No other biases were detected.

Appendix 5. continued

Piantanida et al. (unpublished)[28]		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk of bias	"Subjects were randomly assigned to control versus pneumatic brace group based on a computer based generated random number table"
Allocation concealment (selection bias)	Low risk of bias	As above
Blinding of participants (performance bias)	High risk of bias	Participants could not be blinded
Blinding of personnel (performance bias)	High risk of bias	The primary investigator was blinded but the personnel in the brace shop was not blinded to the allocation.
Blinding of outcome assessment (detection bias)	Low risk of bias	The outcome assessor was blinded
Incomplete outcome data (attrition bias)	High risk of bias	28/77=36.4% of the participants were lost to follow up.
Selective reporting (reporting bias)	Unclear risk of bias	No protocol could be found
Other bias	High risk of bias	The pneumatic leg braces were provided by Air Cast Corporation, Summit, New Jersey, USA. Performance bias: imbalance between groups, the control group did not receive the same amount of interventions as the control group. No intention-to-treat analysis was performed.

Appendix 5, continued

Robertson et al. (2003)[26]		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk of bias	Sequence generation was not described
Allocation concealment (selection bias)	Unclear risk of bias	Allocation concealment was not described
Blinding of participants (performance bias)	High risk of bias	Participants were not blinded
Blinding of personnel (performance bias)	High risk of bias	Personnel could not be blinded
Blinding of outcome assessment (detection bias)	High risk of bias	The outcome assessor was not blinded
Incomplete outcome data (attrition bias)	Unclear risk of bias	Unclear is how many participants dropped out during the study.
Selective reporting (reporting bias)	Unclear risk of bias	No protocol could be found
Other bias	High risk of bias	Participants with adverse events in the intervention group were excluded. Non-parametric tests were used whereas parametric tests might have been more appropriate. Intention-to-treat analysis?

Singh et al. (2002)[24]		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk of bias	Unclear sequence generation: "They were randomly divided into two groups..."
Allocation concealment (selection bias)	Unclear risk of bias	Allocation concealment is not described
Blinding of participants (performance bias)	High risk of bias	Participants could not be blinded
Blinding of personnel (performance bias)	High risk of bias	Personnel could not be blinded
Blinding of outcome assessment (detection bias)	Unclear risk of bias	It was not described whether the outcome assessor was blinded.
Incomplete outcome data (attrition bias)	Unclear risk of bias	It is not reported how many participants completed the study
Selective reporting (reporting bias)	Unclear risk of bias	No protocol could be found
Other bias	High risk of bias	Change scores were analysed; It is unclear whether data was analysed according to the intention-to-treat principle.

Smith et al. (1986)[23]		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk of bias	Method of sequence generation was not specified
Allocation concealment (selection bias)	Unclear risk of bias	Unclear method of randomization and how allocation procedure was concealed
Blinding of participants (performance bias)	High risk of bias	Participants could not be blinded
Blinding of personnel (performance bias)	High risk of bias	Personnel could not be blinded
Blinding of outcome assessment (detection bias)	Unclear risk of bias	VAS was probably self-reported but this not specified.
Incomplete outcome data (attrition bias)	Unclear risk of bias	It is unclear how many participants were lost to follow up or dropped out of the study.
Selective reporting (reporting bias)	Unclear risk of bias	Trial registries did not reveal a priori registered protocols of this study
Other bias	High risk of bias	Change score were analyzed; It is unclear whether data was handled according to the intention-to-treat principle.

Appendix 5. continued

Rompe et al. 2011[8]

Item	Star awarded?	Support for judgment
Selection		
1	Yes	Inclusion/exclusion criteria and methods of making the MTSS diagnosis were described
2	Yes	"Consecutive subjects referred to the outpatient clinic for persisting MTSS were evaluated on the basis of a history and a physical examination, and checked for the study inclusion and exclusion criteria."
3	No	Whether subjects chose the treatment or control treatment depended on the willingness and ability to pay a fee of $200,- for the shockwave program.
4	Yes	Possible confounding factors were obtained
5	No	Imbalances between groups were not described and no multivariate risk factor analysis was performed.
Performance		
6	No	The amount of treatment session was not the same for both groups
7	Yes	Subjects in both groups were seen after 1, 4 and 15 months.
Outcome		
8	Yes	The nurse that collected the outcome data was blinded to treatment allocation
9	No	In the treatment group lost to follow-up was below 10% however in the control group drop out percentages are not described.
10	No	One patient in the treatment group was excluded due to missing follow up data; 78 subjects in the control group were excluded based on not matching sex and age of the subjects in the intervention group.
Total	**5/10**	**Poor quality**

Appendix 5. continued

Moen et al. 2012[9]

Item	Star awarded?	Support for judgment
Selection		
1	Yes	Inclusion and exclusion criteria were described. Methods of making the MTSS diagnosis are described
2	Yes	Recruitment procedure was described
3	No	Patients were allocated to the treatment or control treatment group based on the hospital (academic or local) that they were referred to. Unclear is to which treatment the groups were assigned. Academic referrals tend to be the more 'severe patients'.
4	Yes	Possible confounding factors were obtained
5	Yes	Univariate and multivariate analyses were performed
Performance		
6	No	Subjects in the intervention group had additional treatments for shockwave and the control group had no comparative treatment or placebo
7	No	Unclear is how follow-up was carried out, and how many times both groups were seen for follow-up.
Outcome		
8	No	Unclear is how the outcome was assessed, by interview or self-reported. Was the interviewer blinded?
9	Yes	The lost to follow-up percentages was below 10%
10	No	Unclear is whether data was handled in accordance with the intention to treat principle.
Total	**5/10**	**Poor quality**

Appendix 5. continued

Chapter 05

Atrophy and depigmentation after pretibial corticosteroid injection for medial tibial stress syndrome: two case reports

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M. Winters

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J Sport Rehabil. 2016;25(4):380-381

5.1. ABSTRACT

5.1.1. INTRODUCTION

No reports have been published on the results of corticosteroid injections for medial tibial stress syndrome (MTSS).

5.1.2. CASE PRESENTATION

We present two cases of women with MTSS who showed atrophy and depigmentation of the skin after pretibial corticosteroid injections. Case 1 is an 18-year-old woman presenting with pain in her lower leg for twelve months. No improvement was noticed after conservative treatment. Therefore she received local injections with corticosteroids. Five months later physical examination showed tissue atrophy and depigmentation around the injection sites. Case 2 is a 22-year-old woman, who presented with pain in both lower legs for twenty-four months. Several conservative treatment options failed therefore she received local injections with corticosteroids. Physical examination revealed tissue atrophy and depigmentation around the injection sites.

5.1.3. CONCLUSION

We found no positive effect of injections with corticosteroids in two cases of MTSS. Furthermore, considerable tissue atrophy and depigmentation of the skin was observed.

5.2. INTRODUCTION

Medial tibal stress syndrome (MTSS) is defined as "pain along the posteromedial border of the tibia that occurs during exercise, excluding pain from ischemic origin or signs of stress fractures".[1] In the eighties the traction theory proposed that traction of the foot flexors and foot invertors caused periostitis.[2] More recent studies concluded that MTSS is most probably bone overload of the medial tibia,[2] whereby inflammation of the periosteum could play a role.[3,4] Despite the low level of evidence the best treatment options seem to be; extracorporeal shockwave therapy, inlays and a graded exercise plan.[5] If complaints persists despite these options, sometimes corticosteroid injections are advised.[2] No studies have been published that investigated the effect of corticosteroid injections in the treatment of MTSS. However, a few anecdotal reports show that these injections are being used in clinical practice, especially when complaints are severe.[2,6] Complications after these corticosteroid injections for MTSS have never been described.

5.3. CASE REPORTS

Case 1 is a 18-year-old Caucasian woman presenting with MTSS. Her medical history reported a well healed spiral fracture of the left tibia due to a trauma at the age of 12. One year ago, she noticed pain in her left lower leg during and after a working day as a waitress. Physical examination showed recognizable pain along the posteromedial border of the tibia, confirming the diagnosis.[1,2] A splint was constructed in the hospital visited prior to the visit to our clinic, with the aim to provide rest for the leg. In addition, previous treatments included a graded running program, focused shockwave therapy and a sports compression stocking. No improvement was noticed after any of these interventions. Then, she received three local injections near the periosteum with corticosteroids (in total 1ml Kenacort 40 mg/ml and 3ml Lidocaïne 2%). Injection fluids were equally distributed over the three injection sites. Injections were performed on the three most painful sites along the posteromedial border of the tibia. The post-injection restriction was to avoid heavy loaded activities and the pain had to be less than 4 on the visual analogue scale at or after activity. In the first two weeks some pain relief was noticed, but the complaints returned. Five months after injection the patient returned and the following conditions were noted; considerable atrophy of the fat tissue and depigmentation of the skin around the injection sites (figure 1), and palpation pain along the tibial border. The X-ray of her lower leg showed no abnormalities except for the consolidated tibial fracture.

The magnetic resonance imaging (MRI) showed subcutaneous edema and a decrease in the amount of subcutaneous fat tissue at the injection sites (figure 2). Due to cosmetic complaints, she was referred to a plastic surgeon for lipofilling which was performed with a good result according to the patient. Unfortunately, the complaints of pain had not been resolved and she was referred to an orthopaedic surgeon to discuss surgical options for MTSS (fasciotomy and release of the tibialis posterior muscle). Several months after the surgery, she was not pain free during heavy activities, but activities

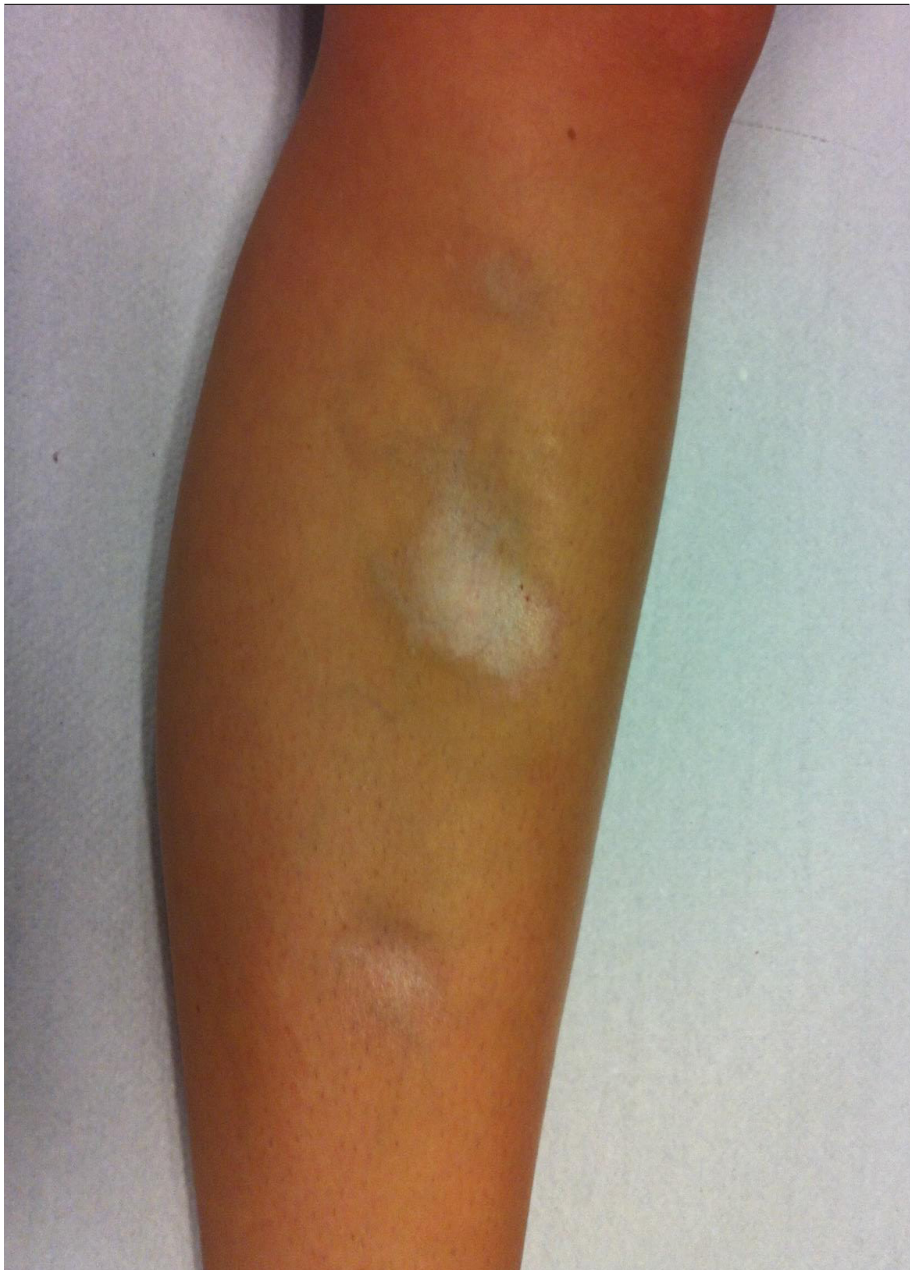

Figure 1: Atrophy and depigmentation around the injection sites five months after pretibial corticosteroid injection.

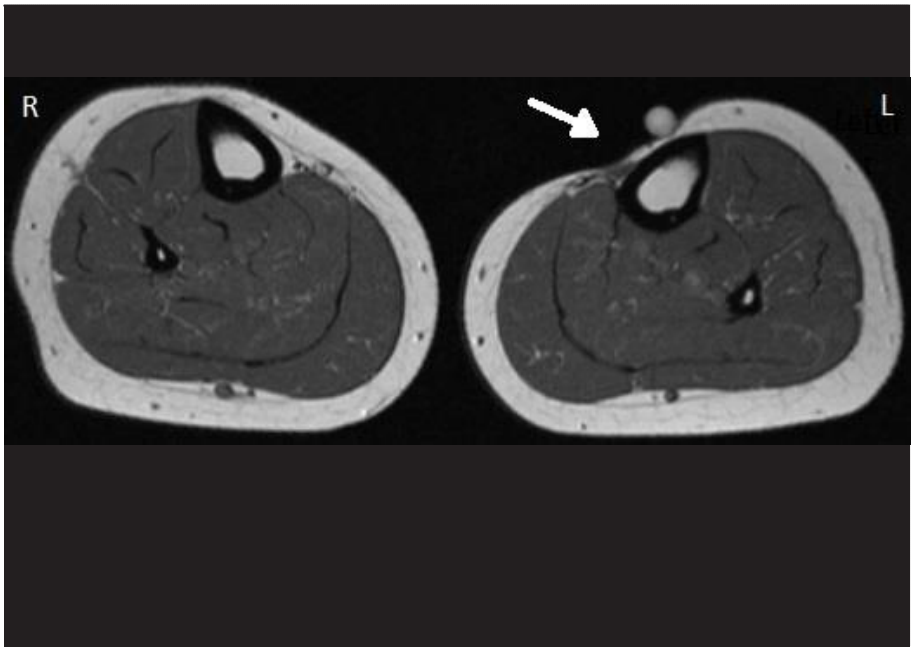

Figure 2: MRI of both mid shaft tibia shows on the left tibia subcutaneous edema with a decrease in the amount of subcutaneous fat tissue atthe injection sites (arrow).

in daily life could be performed without problems.

Case 2 is a 22-year-old Caucasian woman presenting with complaints of MTSS. Complaints developed two years ago and were now present especially during soccer playing and at night. Physical examination showed recognizable palpation pain along the posteromedial border of the tibia of both legs. The patient started with focused shockwave therapy of the tibia, a graded running program, shoe inserts with a raised medial arch to support pes planus and sports compression stockings, but no improvement occurred. The MRI showed normal bone, periosteum and musculature, which is a common finding in MTSS.[2] The patient then received two local injections near the periosteum with corticosteroids (in total 1ml Kenacort 40 mg/ml and 3ml Lidocaïne 2%) on each lower leg along the portion of the tibia that was painful on palpation. During the first two weeks some pain relief was noticed, but then the patient complained of the reoccurrence of pain symptoms. Physical examination showed considerable atrophy of the fat tissue and depigmentation of the skin around the injection sites and pain with palpation along the tibial border. This patient was also referred to a plastic surgeon who advised lipofilling of the lesions. After several months the leg looked better according to the patient. Complaints of MTSS were still present, but were deemed less than before.

5.4. DISCUSSION

MTSS is a common diagnosis in sports medicine.[2] When complaints persist after several conservative treatment options sometimes local injections with corticosteroids are provided.[2] The aim of these injections is a temporary improvement in pain and function and therefore the ability to train and to improve the load capacity. So far, no side effects of these injections in the MTSS population have been described. In the treatment of tendinopathy a low frequency of serious adverse events after corticosteroid injections have been reported, suggesting an acceptable risk according to a recent review in the Lancet.7 However, complications such as post injection pain (8%), subcutaneous atrophy (9%) and skin depigmentation (<1%) are commonly reported.[7]

This case report shows that no evidence for corticosteroid injections in the treatment of MTSS is available. In addition this report shows the possibility of considerable side effects of these injections; atrophy of the fat tissue and depigmentation of the skin.

Even when multiple conservative treatment options failed to relieve MTSS complaints, we still advise against treatment with corticosteroid injections. This is due to the lack of efficacy and the possible considerable side effects such as atrophy of the fat tissue en depigmentation of the skin.

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Chapter 06

The medial tibial stress syndrome score: item generation for a new patient reported outcome measure

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6.1. ABSTRACT

6.1.1. BACKGROUND

There is no valid and reliable instrument that evaluates injury severity and treatment effects for medial tibial stress syndrome (MTSS) patients.

6.1.1. OBJECTIVE

The aim was to generate items for the MTSS score, a new patient-reported outcome measure for patients with MTSS.

6.1.2. METHODS

The authors consulted experts in the field of MTSS to generate items that measure the severity of MTSS and to reach consensus on the relevance of items for the MTSS score. This research consisted of a pilot study and two Delphi rounds. The Delphi approach entails the consultation of experts about a topic for which no evidence is available during which consensus is sought on this topic. Additionally, 20 MTSS patients appraised the MTSS score on readability and comprehension.

6.1.3. RESULTS

Nineteen experts consented to participate, 13 of whom reached consensus. Generated items address the following domains: 'limitation in sporting activities', 'pain while performing sporting activities', 'pain while performing activities of daily living' and 'pain at rest'. Patients with MTSS confirmed the good readability and comprehension of the items.

6.1.4. CONCLUSION

This study supports the importance of items in the aforementioned domains while evaluating treatment effects in patients with MTSS.

6.2. INTRODUCTION

Medial tibial stress syndrome (MTSS) is one of the most common lower leg injuries in athletes and military personnel.[1,2] It is an overuse injury with pain along the distal medial border of the tibia that is thought to be due to overloading of the bone.[3]

A recent systematic review highlighted a lack of good studies on the treatment of MTSS.[4] One commonly used definition for MTSS is provided by Yates and White: 'the presence of exercise-induced pain along the posteromedial border of the tibia over five or more consecutive centimetres that is elicited by palpation'.[5] In previous research, numerous outcome variables have been used to assess treatment effects on MTSS patients; e.g. visual analogue scales, global perceived effect scales, and time to recovery.[4] Over the past two decades, the opinion of the patient has received increasing attention when determining treatment effects in clinical trials and practice. Hence, the use of Patient Reported Outcome Measures (PROMs) has been recommended to quantify the effect of interventions in randomised controlled trials and clinical settings.[6]

A recent systematic review on MTSS showed there is a need for a standardised outcome measure as no validated outcome measures have yet been developed.[4] Item generation is the first step in creating a new PROM. Therefore the aim of this study was to generate items for a new PROM for MTSS patients and have these items' relevance and comprehension subsequently appraised by patients with MTSS. This PROM should evaluate severity and treatment effects, and also incorporate the perception of the patient.

6.3.1. METHODS AND MATERIALS

The authors used a Delphi consensus study to combine expert opinions and reach consensus. A Delphi approach entails the consultation of experts about a topic for which no evidence is available. These experts are blind to the other experts involved in the study; thus their opinion are not influenced by other expert opinions. In a Delphi study a consensus of opinion is sought from those regarded as experts in their fields. These expert opinions are solicited "blind".[7-9] For this study the authors received permission from the local medical ethics committees of the provinces of Utrecht (12-542/C) and Zuid-Holland (12-092).

6.3.2. IDENTIFYING AND INVITING MTSS EXPERTS

The authors aimed to include experts in the field of MTSS who were currently actively involved in MTSS research and who also had clinical experience with MTSS patients. Therefore they firstly identified experts in the field of MTSS by contacting national sports medicine associations, (the American College of Sports Medicine, the American Orthopaedic Society for Sports Medicine, the Australasian College of Sports Physicians, the British Association of Sport and Exercise Medicine, the Canadian Academy of Sport and Exercise Medicine, the Danish Association of Sports Medicine, German Federation

for Sports Medicine and Prevention, and the Swedish Society of Exercise and Sports Medicine) and requested they provide the contact information of their key experts in the field of MTSS. In addition, those who had published studies in the field of MTSS were contacted. Based on their network of clinical experts, the authors also approached a number of people in the Netherlands. All experts were invited to participate by email.

6.3.3. DELPHI STUDY

A pilot study among the experts in the authors' own network (N = 9) was conducted prior to starting the study in order to generate preliminary items. This network consisted of sports physicians and sports physiotherapists in the field of MTSS with whom collaboration had taken place in previous research projects in The Netherlands. In the first round of the Delphi study, all experts were requested to comment on the preliminary items and asked to suggest new items.

In consecutive rounds, these new items were included. These experts were asked to indicate their level of agreement with regard to the inclusion of the preliminary items in the MTSS score on a five-point scale: strongly disagree, disagree, no opinion, agree, strongly agree. They were also requested to suggest additional items. Consensus was reached upon an item when 67% of the experts voted for its inclusion or exclusion.[6] The Delphi study was completed when consensus was reached upon all items and no further items were proposed. No maximum number of rounds was set. After consensus was reached, all items were translated into Dutch by a native Dutch speaker with a medical background who was also proficient in English.

6.3.4. APPRAISAL BY PATIENTS

A sports medicine physician diagnosed MTSS if exercise-induced pain along the posteromedial border of the tibia was elicited by palpation on the posteromedial border of the tibia over a length of five or more consecutive centimeters.[5] Patients were eligible for participation when they were ≥ 16 years of age and had had symptoms for ≥ three weeks. When focal tibial pain, indicative of a stress fracture, or a medical history with a cruris fracture was present, subjects were excluded.[10] After item generation, the patients appraised the items in two rounds. In the first round, the authors asked 15 MTSS patients to provide feedback on readability and comprehension using a semi-structured interview. They subsequently modified the items according to their feedback. In the second round, an additional five patients with MTSS were requested to appraise the items.

6.3.5. CROSS-CULTURAL TRANSLATION

All the generated items for the MTSS score were translated from Dutch to English. Steps One to Four from the cross-cultural validation process, as described by Sousa and Rojjanasrirat[11] and Beaton et al.[12] were performed. The translation contained forward

and back-translations. A steering committee, in which the translators and all authors (except MF), were represented, reviewed both the forward and back-translations and decided on the final English version. The decision making process was based on consensus, which was reached when 67% of the committee members present agreed. In case consensus could not be reached for all items, the authors planned to have them translated again using different translators.[11, 12]

6.4. RESULTS

Twenty-one international and eleven Dutch experts were invited to participate, 19 of whom consented to participate: four Americans, four Australians, one Canadian, nine Dutch and one from England. There were eight sports physiotherapists, six sports physicians, one podiatrist, one surgeon in sports medicine, one podiatric surgeon, one exercise and sports specialist and one biomedical engineer. Figure 1 is the study's flow diagram. One expert withdrew his participation during the pilot study and five were lost to follow-up during the second round of the Delphi study. Those experts (N = 13: 8 Dutch, 3 Australian, 2 American) with whom consensus was reached are named in the Acknowledgements section, except for one expert (MF) who co-wrote this manuscript. The supplementary online material presents all the items generated.

6.4.1. PILOT STUDY

The pilot study included 16 items on the limitations of activities in daily life (ADL) (N = 10) and sporting activities (N = 6). These items were scored from 0 to 4, with 0 indicating 'no problem' to 4 indicating an 'extreme problem'. The remaining items: 3, 5, 9, 10, 11, 13 and 15 were developed during the pilot study.

6.4.2. ROUND 1

In Round 1, the main feedback provided was that there were too many items related specifically to running and sporting activities. Furthermore, participants proposed that each outcome should have a descriptor, which was accordingly included for all items. Items on sprinting, uphill running, and sudden accelerations and decelerations when running were removed as suggested by the majority of the experts, as these items were irrelevant to MTSS patients that do not usually run. Items 1, 2, 7, 8, 12 and 14 were produced in Round 1 (see Appendices 1 and 2 for items in Dutch and English).

6.4.3. ROUND 2

In this round, consensus was reached on all but two items. One item was proposed in the second round but did not reach the pre-validation stage. This item looked at provoking pain during hopping. This item was considered irrelevant for the study's objective as most patients do not usually hop. Two items (4 and 6) were suggested in Round 2; however, these items were not included in the additional round of the Delphi study. Items 4 and 6 both cover pain during sporting activities. Table 1 provides an overview

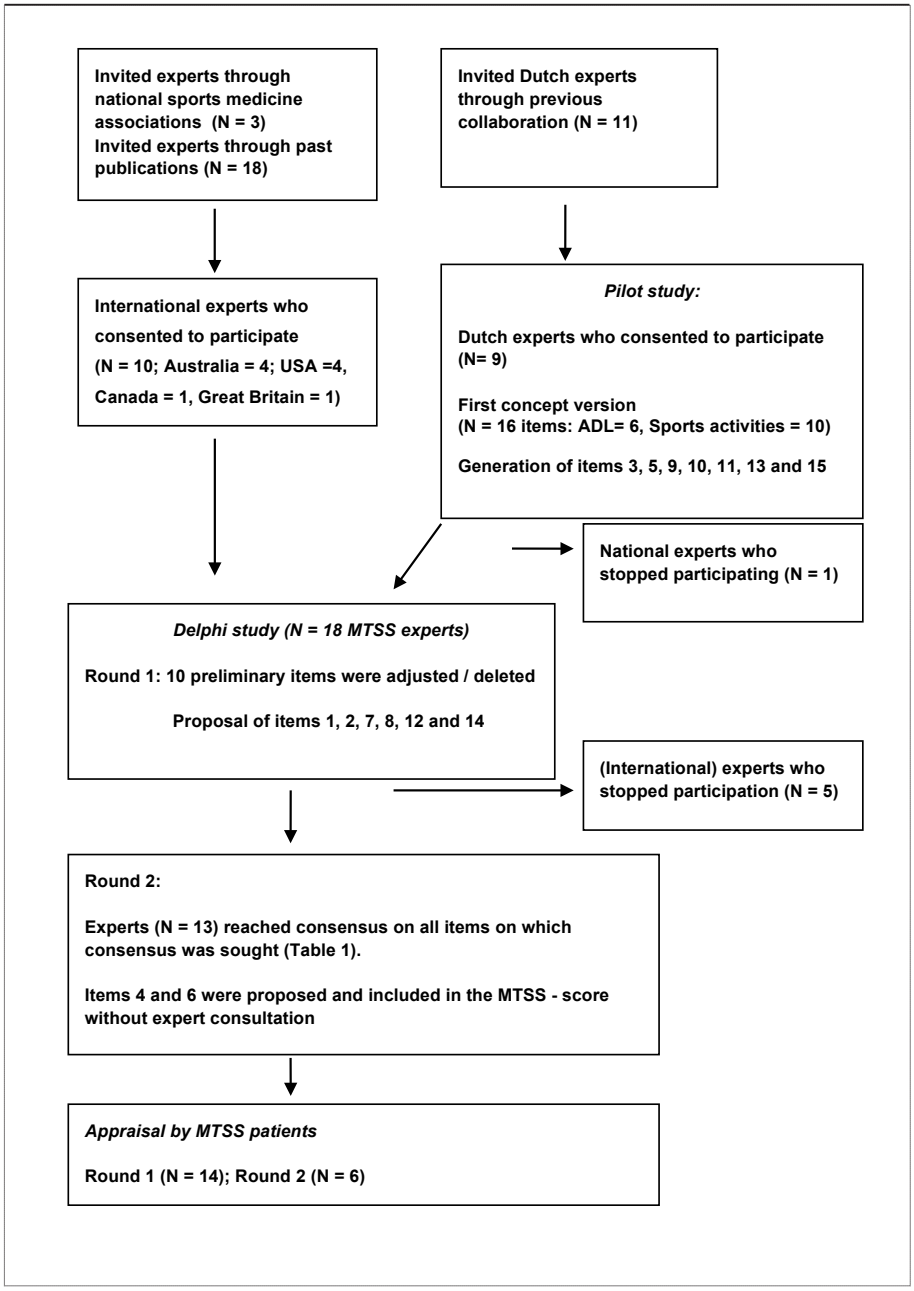

Figure 1: Flow diagram and patients' appraisal of the MTSS-score

of the final level of consensus reached for each item. Consensus was reached on all items formulated in English.

6.4.4. CONTRIBUTION OF EXPERTS WHO STOPPED PARTICIPATING

During the study, five of the 19 experts did not respond to the authors' attempts to seek contact and contributions from the project. The expert who stopped participating during the pilot study suggested, together with other experts, to use an item on the current content of sporting activity (Item 3). In the second round of the Delphi study, five experts discontinued responding to the authors' emails. The first of these experts stated that the questionnaire was complete in the first round and therefore did not respond to the authors' further emails. The second expert suggested including items on the current content of sporting activities (Item 3) and current sporting activity (Item 1). One expert suggested including an item on night pain (Item 14), and on pain experienced after sporting activities (Item 8). The importance of the latter was supported by one of the other experts who also withdrew their participation. The fifth expert suggested including an item that differentiated between the various types of pathophysiology (e.g. stress fracture, compartment syndrome, MTSS) of shin pain. However, it was decided not to include this item in the Delphi study as it discriminates between types of lower leg pain instead of the severity of perceived complaints.

6.4.5. APPRAISAL BY PATIENTS (FIGURE 1)

Fourteen patients (seven women and seven men) commented on the newly developed MTSS score. They completed the questionnaire and provided feedback on the questionnaire's readability, comprehension and ease of use. The first concept of the questionnaire was shaped according to the example of the VISA-A questionnaire with a guide to continue or skip to the next item. To continue or to skip an item depended on whether the patient was still involved in their usual sporting activity, was involved in alternative sporting activities only, or was not involved in any sporting activity at all.[13] However, some of the patients did not understand this structure. Therefore the preliminary MTSS score was modified so that every patient had to complete all the items. Item 15 was not well understood. This item was aimed at the measurement of pain on touch. It started with descriptors for three different degrees of touch followed by statements of when pain was induced at touch. This was changed by using the various degrees of touch (e.g. bumping, pressing, rubbing) in the response options. Other patients' suggestions concerned alternative words for pain. Changes were made based on the feedback provided. In addition, six patients (three women and three men) provided comments on the updated MTSS score. No further comments were made and the MTSS score was considered ready for validation.

6.4.6. THE MTSS SCORE

The MTSS score consists of 15 items: current sporting activities, current amount of

Table 1: Number of experts (N = 13) that agree/disagree with inclusion of an item in the MTSS-score

Table 1: Number of experts (N=13) that agree/disagree with inclusion of an item in the MTSS-score

Item	Strongly disagree	Disagree	No opinion	Agree	Strongly agree	% of experts that agree with inclusion
1. Current sporting activities		1		2	10	92.3%
2. Current amount of sporting activities		1		3	9	92.3%
3. Current content of sporting activities				5	8	100%
4. Pain while performing sporting activities						Not assessed in Delphi study
5. Time to onset of pain during sporting activities			1	4	8	92.3%
6. Pain throughout sporting activities 1						Not assessed in Delphi study
7. Pain throughout sporting activities 2		1		3	9	92.3%
8. Pain after sporting activities				4	9	100%
9 Pain while standing		2	1	6	4	76.9%
10. Pain while walking				4	9	100%
11. Pain while walking up- or downstairs				6	7	100%
12. Pain while performing common daily activities		1	1	4	7	84.6%
13. Pain at rest				4	9	100%
14. Pain at night		2	2	5	4	69.2%
15. Pain to touch		1	1	4	7	84.6%

sporting activities, current content of sporting activities, pain while performing sporting activities, time to onset of pain during sporting activities, pain throughout sporting activities (Item 6 of the total set, see Appendices 1 and 2), pain throughout sporting activities (Item 7 of the total set, see Appendices 1 and 2), pain after sporting activities, pain while standing, pain while walking, pain while walking up or down stairs, pain while performing common daily activities, pain at rest, pain at night and pain to touch (Table 1).

6.4.7. CROSS-CULTURAL TRANSLATION

The MTSS score was translated from Dutch to English according to the appropriate guidelines.[11, 12] All minor discrepancies between translators of the forward and back-translations were resolved at consensus meetings. The forward and back-translations of the MTSS score were critically reviewed by a steering committee comprising of all authors and translators. The back-translation highlighted a few minor discrepancies between the forward translation and the original version: "I feel ..." instead of "I have ..." (Items 9, 10 and 11). Other discrepancies were seen in Item 5 where 'sporting activities' was included in the response options. All discrepancies were resolved so that the English version was a correct cross-cultural translation of the original Dutch version.

6.5. DISCUSSION

This study provides expert-generated and patient-appraised items for a new patient reported outcome measure for MTSS. Consensus was reached on all generated items that were included during the Delphi study. Items generated relate to limitation in sporting activities, pain while performing sporting activities, pain while performing activities of daily living and pain at rest. Patients appraised the generated items as to their ease of understanding and relevance to the injury. In previous research, a great variety of pain scales were used and definitions of when patients have recovered differ greatly between studies. This hampers comparison of results across studies. This present study aimed to generate items for a new standardised instrument to evaluate treatment effects in MTSS patients. Furthermore, the MTSS score meets the need for an instrument that evaluates effects and incorporates the perceptions of the patient.

The MTSS score was developed using the Delphi technique, a widely used method to reach consensus among experts in fields for which no evidence is available. One of the most important advantages is that experts are unaware as to who their co-participants are. Therefore the experts opinions are free from the influence of other panel members.[7-9] The strong aspects in this Delphi study include the size of the expert panel and the wide variety of experts with different backgrounds. In addition, the items have been appraised by a total of 20 patients with MTSS, in two rounds. Although five experts stopped participating during course of the Delphi study, all experts contributed to the development of the MTSS score's items. Furthermore, the quality of the contributions were considered as more important than the quantity of the contributions.

There were also some limitations in the current study. Consensus was not sought on

two items (Items 4 and 6). These items were proposed in Round 2. As five experts did not respond to the authors' emails after Round 1, there was concern that more experts may drop out in additional rounds, thus leaving little or no consensus on the items. These two items were appraised by the authors' group and were found to be useful. The content validity for Items 4 and 6 is acknowledged and therefore less supported by expert consultation. The authors are confident that their decision to not seek consensus on these two items enabled a broad consensus on all other items. In the Delphi method, there is no widely accepted threshold for when consensus among experts is met. Previous reports suggested using thresholds between 50% and 70%.[8,9] In this research project, it was decided to set the threshold at 67%; however, there was >75% agreement for all but one item.[7] A report on the validation study, in which items for the MTSS score were selected and its reliability, validity and responsiveness is assessed elsewhere.[14]

6.6. CONCLUSION

This study reports on the item generation process for the MTSS score, a new patient-reported outcome measure for patients with MTSS. The results support the importance of items in the domains of pain, limitations in activities of daily living and sporting activities while measuring the severity of MTSS from the patient's perspective. The items generated in this study cover all these domains.

ACKNOWLEDGEMENTS

The authors are very grateful for the valuable contributions of the expert panel members. The experts that participated in the final round of the Delphi study were: Carl Barten, BPt; Steef Bredeweg, MD, PhD; Fred Hartgens, MD, PhD; Shannon Munteanu, PhD; Carol Otis, PhD; Rodney Pope, BPt, PhD; Steven Rayer, MSPT; Michiel Schipper, MSPT; Victor Steeneken, MSc; Jack Taunton, MD, PhD; Joost Vollaard, MSPT; Wessel Zimmermann, MD. We thank Sophia Stone and Jesse Tjebbes (forward-) and Elmar Kal, PhD, and Jacintha Kal (back-) for their valuable cross-cultural translations.

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Appendix 1: Item set in Dutch as generated by the Delphi Study

Sportactiviteiten

Voor militairen: marsen en marcheren zijn sportactiviteiten.

1) Momenteel:

Beoefen ik al mijn gebruikelijke sportactiviteiten ☐

Kan ik, door mijn scheenbeenklachten, minder dan mijn gebruikelijke sportactiviteiten doen ☐

Kan ik, door mijn scheenbeenklachten, alleen alternatieve sportactiviteiten doen ☐

Kan ik, door mijn scheenbeenklachten, geen enkele sportactiviteit doen ☐

2) Deze vraag gaat over de hoeveelheid van uw sportactiviteiten

Ik heb het aantal keer dat ik sport per week niet aangepast ☐

Ik heb het aantal keer dat ik sport per week teruggebracht met 1-25% ☐

Ik heb het aantal keer dat ik sport per week teruggebracht met 26 - 50% ☐

Ik heb het aantal keer dat ik sport per week teruggebracht met 51 - 75% ☐

Ik heb het aantal keer dat ik sport per week teruggebracht met 76-100% ☐

3) Deze vraag gaat over de inhoud van uw sportactiviteiten

Ik heb mijn sportactiviteiten niet aangepast ☐

Ik heb mijn sportactiviteiten een beetje aangepast (+/-25%), bijvoorbeeld een beetje minder sprintwerk/sprongwerk, een beetje minder lang sporten ☐

Ik heb mijn sportactiviteiten behoorlijk (+/-50%) aangepast, ik sport minder intensief; bijvoorbeeld veel minder sprintwerk/sprongwerk, minder lang achter elkaar hardlopen ☐

Ik heb het merendeel (75%) van mijn training aangepast, ik sport veel minder intensief; bijvoorbeeld geen sprintwerk/sprongwerk, niet lang achter elkaar hardlopen, alleen kort durende lichte belasting ☐

Ik kan geen enkele sportactiviteit doen vanwege mijn scheenbeenklachten ☐

Appendix 1: Item set in Dutch as generated by the Delphi study

4) Tijdens het sporten:

Heb ik geen pijn in mijn scheenbeen ☐

Heb ik enige pijn in mijn scheenbeen ☐

Heb ik veel pijn in mijn scheenbeen ☐

Ik kan niet sporten vanwege de pijn in mijn scheenbeen ☐

5) Hoe lang, nadat u gestart bent met sporten, voelt u pijn aan het scheenbeen?

Ik heb geen pijn tijdens het sporten ☐

Langer dan 15 minuten nadat ik gestart ben ☐

Binnen 15 minuten nadat ik gestart ben ☐

Direct nadat ik gestart ben ☐

Ik kan niet sporten vanwege de pijn aan mijn scheenbeen ☐

6) Als u pijn heeft tijdens het sporten, en u gaat door met sporten, wat gebeurt er dan met de pijn?

Ik heb geen pijn tijdens het sporten ☐

De pijn neemt af ☐

De pijn blijft hetzelfde ☐

De pijn neemt toe ☐

Ik kan niet sporten vanwege de pijn aan mijn scheenbeen ☐

7) Als de pijn aanwezig is wanneer u begint met sporten, en u gaat door met sporten, wat gebeurt er dan met de pijn?

Ik heb geen pijn tijdens het sporten ☐

De pijn verdwijnt binnen 10 minuten ☐

De pijn verdwijnt na 10 minuten ☐

De pijn verdwijnt niet ☐

Ik kan niet sporten vanwege de pijn aan mijn scheenbeen ☐

8) Na het sporten:

Heb ik geen pijn ☐

Verdwijnt de pijn binnen 12 uur ☐

Verdwijnt de pijn tussen de 12 uur en 2 dagen ☐

Blijft de pijn langer dan 2 dagen aanwezig ☐

Ik kan niet sporten vanwege de pijn aan mijn scheenbeen ☐

9) Tijdens staan:

Heb ik geen pijn in mijn scheenbeen ☐

Heb ik enige pijn in mijn scheenbeen ☐

Heb ik veel pijn in mijn scheenbeen ☐

Ik kan niet staan vanwege de pijn in mijn scheenbeen ☐

10) Tijdens lopen:

Heb ik geen pijn in mijn scheenbeen ☐

Heb ik enige pijn in mijn scheenbeen ☐

Heb ik veel pijn in mijn scheenbeen ☐

Ik kan niet lopen vanwege de pijn in mijn scheenbeen ☐

11) Tijdens trap op- of aflopen:

Heb ik geen pijn in mijn scheenbeen ☐

Heb ik enige pijn in mijn scheenbeen ☐

Heb ik veel pijn in mijn scheenbeen ☐

Ik kan niet traplopen vanwege de pijn in mijn scheenbeen ☐

Gewone dagelijkse activiteiten

Bijvoorbeeld: staan, wandelen, lopen, traplopen of fietsen.

12) Tijdens gewone dagelijkse activiteiten:

Heb ik geen pijn in mijn scheenbeen ☐

Heb ik enige pijn in mijn scheenbeen ☐

Heb ik veel pijn in mijn scheenbeen ☐

Ik kan geen gewone dagelijkse activiteiten doen vanwege de pijn in mijn scheenbeen ☐

Pijn in rust

Bijvoorbeeld zitten of liggen.

13) In rust is mijn scheenbeen:

Niet pijnlijk ☐

Gevoelig ☐

Pijnlijk ☐

Heel pijnlijk ☐

14) 's Nachts:

Heb ik geen pijn ☐

Is mijn scheenbeen soms gevoelig ☐

Word ik wakker van de pijn in mijn scheenbeen maar ik val snel weer in slaap ☐

Kan ik door de pijn in mijn scheenbeen delen van de nacht niet slapen ☐

15) Pijn bij aanraking

Ik heb geen pijn bij aanraking van mijn scheen ☐

Ik heb alleen pijn wanneer ik de scheen stoot ☐

Ik heb pijn wanneer ik op de scheen druk én wanneer ik de scheen stoot ☐

Ik heb pijn wanneer ik over de scheen wrijf, er op druk én de scheen stoot ☐

Appendix 2: English cross-cultural translated item set as generated by the Delphi study

Sporting activities

For military: Marching is considered to be a sporting activity.

1) Presently:

I perform all of my usual sporting activities ☐

I am forced to do less of my usual sporting activities due to pain in my shin ☐

I am forced to do alternative sporting activities only due to pain in my shin ☐

I cannot do any sporting activity due to pain in my shin ☐

2) This question concerns the frequency of your sporting activities

I have not reduced the frequency of my sporting activities ☐

I have reduced the frequency of my sporting activities by 1 - 25% a week ☐

I have reduced the frequency of my sporting activities by 26 - 50% a week ☐

I have reduced the frequency of my sporting activities by 51 - 75% a week ☐

I have reduced the frequency of my sporting activities by 76 - 100% a week ☐

3) This question concerns the content of your sporting activities

I have not adjusted my sporting activities ☐

I have adjusted my sporting activities slightly (+/-25%)
e.g. slightly less sprinting and jumping, slightly decreasing the duration of my sporting activities ☐

I have adjusted my sporting activities substantially (+/-50%), my sporting activities are less intense.
e.g. substantially less sprinting and jumping, decreasing the duration of running ☐

I have adjusted the majority (+/-75%) of my sporting activities, my sporting activities are substantially less intense.
e.g. avoiding sprinting and jumping altogether, running for short periods of time, only short and light loads ☐

I cannot do any sporting activity due to my shinbone pain ☐

Appendix 2: English cross-cultural translated Item set as generated by the Delphi study

4) While performing sporting activities:

I have no pain in my shin ☐

I have some pain in my shin ☐

I have a lot of pain in my shin ☐

I cannot do any sporting activity due to my shin pain ☐

5) How long, after you have started a sporting activity, do you feel the pain in your shin?

I have no pain during sporting activities ☐

After 15 minutes, after I have started ☐

Within the first 15 minutes after I have started ☐

Immediately after I have started ☐

I cannot do any sporting activity due to my shinbone pain ☐

6) In the case of pain being present during your sporting activity, and you continue the activity, what happens to your pain?

I have no pain during sporting activities ☐

The pain decreases ☐

The pain remains unchanged ☐

The pain increases ☐

I cannot do any sporting activity due to my shinbone pain ☐

7) If you feel pain in your shin when starting your sporting activity, and you continue the activity, what happens to your pain?

I have no pain during sporting activities ☐

The pain disappears within 10 minutes ☐

The pain disappears after 10 minutes ☐

The pain does not disappear ☐

I cannot do any sporting activity due to my shinbone pain ☐

8) After sporting activities:

I have no pain ☐

The pain disappears within 12 hours ☐

The pain disappears between 12 hours to 2 days ☐

The pain remains present for longer than 2 days ☐

I cannot do any sporting activity due to my shinbone pain ☐

9) While standing:

I have no pain while standing ☐

I have some pain while standing ☐

I have a lot of pain while standing ☐

I cannot stand due to the pain ☐

10) While walking:

I have no pain in my shin ☐

I have some pain in my shin ☐

I have a lot of pain in my shin ☐

I cannot walk due to pain in my shin ☐

11) While going up or down stairs:

I have no pain in my shin ☐

I have some pain in my shin ☐

I have a lot of pain in my shin ☐

I am unable to walk up or down stairs due to the pain in my shin ☐

Usual daily activities

e.g.: standing, walking (up - or downstairs) or cycling

12) While performing common daily activities:

I have no pain in my shin ☐

I have some pain in my shin ☐

I have a lot of pain in my shin ☐

I cannot do any common daily activity due to pain in my shin ☐

Pain at rest
e.g. sitting or laying down

13) At rest, my shin is:

Not painful ☐

Sensitive ☐

Painful ☐

Very painful ☐

14) At night:

I have no pain ☐

My shin is sometimes sensitive ☐

I wake up sometimes because of the pain in my shin, but I can fall back asleep soon ☐

I cannot sleep due to the pain in my shin for parts of the night ☐

15) Pain while touching

I have no pain when touching my shin ☐

I have pain when I bump my shin ☐

I have pain when I press and when I bump my shin ☐

I have pain when I rub, press on and when I bump my shin ☐

Chapter 07

The medial tibial stress syndrome score: a new patient-reported outcome measure

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7.1. ABSTRACT

7.1.1. BACKGROUND

At present, there is no validated patient-reported outcome measure (PROM) for patients with medial tibial stress syndrome (MTSS).

7.1.2. AIM

Our aim was to select and validate previously generated items and create a valid, reliable and responsive PROM for patients with MTSS: the MTSS score.

7.1.3. METHODS

A prospective cohort study was performed in multiple sports medicine, physiotherapy and military facilities in the Netherlands. Participants with MTSS filled out the previously generated items for the MTSS score on 3 occasions. From previously generated items, we selected the best items. We assessed the MTSS score for its validity, reliability and responsiveness.

7.1.4. RESULTS

The MTSS score was filled out by 133 participants with MTSS. Factor analysis showed the MTSS score to exhibit a single-factor structure with acceptable internal consistency (α=0.58.) and good test–retest reliability (intraclass correlation coefficient=0.81). The MTSS score ranges from 0 to 10 points. The smallest detectable change in our sample was 0.69 at the group level and 4.80 at the individual level. Construct validity analysis showed significant moderate to large correlations (r=0.34–0.52, p<0.01). Responsiveness of the MTSS score was confirmed by a significant relation with the global perceived effect scale (=–0.288, R^2=0.21, p<0.001).

7.1.5. CONCLUSION

The MTSS score is a valid, reliable and responsive PROM to measure the severity of MTSS. It is designed to evaluate treatment outcomes in clinical studies.

7.2. INTRODUCTION

The medial tibial stress syndrome (MTSS) is one of the most common exercise-induced leg injuries among running and jumping athletes and military personnel.[1] It is defined as exercise-induced pain along the posteromedial border of the tibia, and when pain is additionally provoked by palpation over five or more consecutive centimetres.[2]

A recent systematic review showed that there is no conclusive evidence for any effective intervention in the management of MTSS.[3] The absence of a specific outcome measure for patients with MTSS disables a valid measurement of injury severity and intervention effects. Studies investigating the effects of interventions in participants with MTSS have used a wide range of outcome measures to quantify their results, for example, time to recovery, visual analogue scales, Likert scale and numeric rating scale.[4–6] Differing definitions for the same outcome measure such as 'time to recovery' are often used.[6, 7]

A standardised assessment instrument that enables a valid and reliable assessment of treatment effects in patients with MTSS is needed.[3] The patient's perspective has become increasingly important in the context of determining treatment effects.[8]

Patient-reported outcome measures (PROMs) are recommended to evaluate effectiveness in clinical settings and randomised controlled trials.[9] Recently, items for a new PROM for patients with MTSS were generated using a Delphi procedure.[10] The objective of this study was to test the methodological properties of these items, select the best ones to form the MTSS score, and assess the MTSS score's validity, reliability and responsiveness.

7.3. METHODS

7.3.1. DESIGN AND OBJECTIVE

A prospective cohort design was used to select the best items for the MTSS score and to assess its validity, reliability and responsiveness. We followed the consensus-based standards for selection of health measurement instruments (COSMIN) guidelines while validating the MTSS score.[11]

7.3.2. PARTICIPANTS

Between 1 January 2013 and 1 January 2015, 13 healthcare centres (including 5 sports medicine facilities, 1 military medical centre, 5 sports physiotherapy practices and 2 military physiotherapy centres) in The Netherlands assessed possible eligible participants for study participation. Sports physicians and sports physiotherapists working in the participating facilities assessed potential candidates by applying our inclusion and exclusion criteria. Participants (≥16 year) with MTSS for at least 3 weeks were considered eligible for inclusion. MTSS was defined as activity-related pain along the posteromedial tibial border and tenderness on the same site over a length of at least

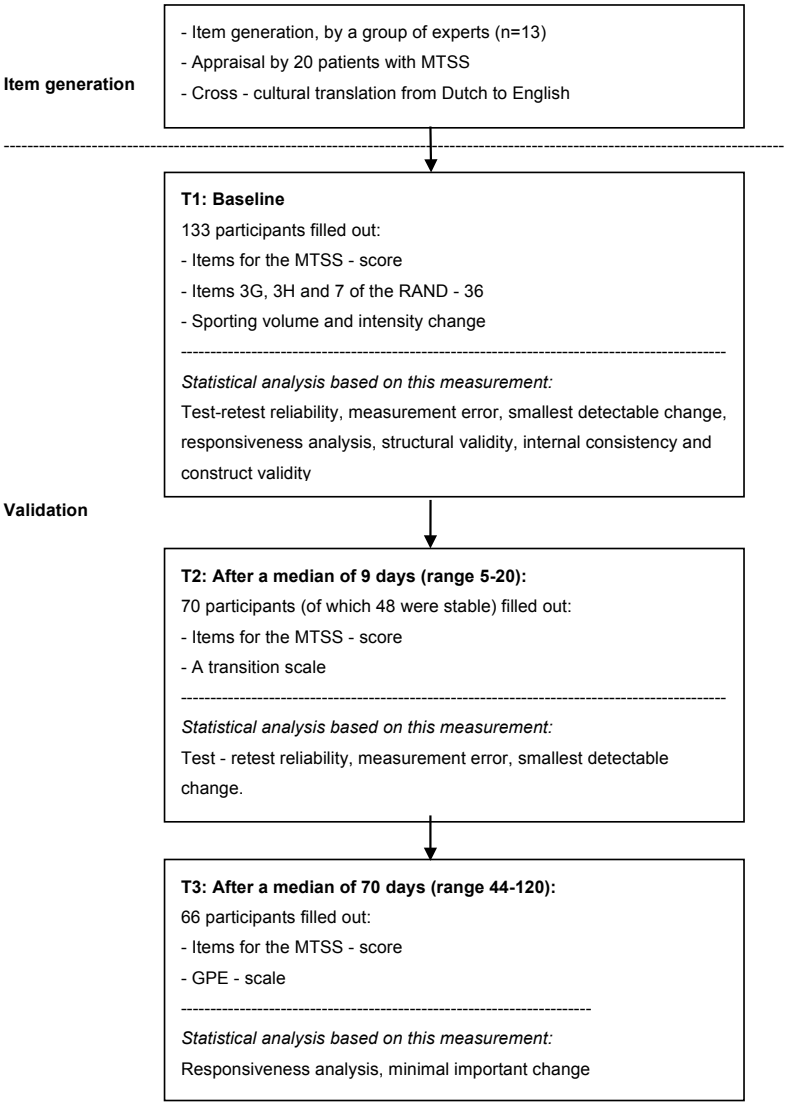

Figure 1. Flow diagram (GPE, global perceived effect; MTSS, medial tibial stress syndrome).

five or more consecutive centimetres.[2] Participants were excluded when a history of tibial fracture, clinical suspicion of chronic compartment syndrome or stress fracture was present, or when coexisting injuries were present.[12] Participants with concurrent lower extremity symptoms and participants with spoken or written Dutch language comprehension difficulty were excluded. Participants who met the inclusion criteria were informed about the study purpose and participated after signing informed consent. The medical ethics committees of Zuid-West Holland (12–092) and Utrecht (12–542/C), The Netherlands, provided approval before the study's initiation.

7.3.3. PROCEDURE

Participants were asked to fill out questionnaires on three occasions. At baseline (T1), participants were asked to fill out a form relating demographic information, preliminary items of the MTSS score, the RAND 36-item Health Survey and to answer questions relating to their sports activities. After 1 week (T2), the primary investigator (MW) contacted participants by telephone and requested them to fill out the preliminary items of the MTSS score again in an online environment. The final measurement was administered at 3 months (T3). Participants were approached by telephone to fill out the MTSS score's preliminary items, a global perceived effect (GPE) scale and to answer questions relating to their weekly sports activities in an online environment. During the study, participants continued standard medical care at their facility. Figure 1 shows the study flow and the administered measures for each occasion.

7.3.4. MEASURES

7.3.4.1. ITEMS FOR THE MTSS SCORE

Experts developed items for the MTSS score by means of a Delphi study. These items were then appraised by a total of 20 patients with MTSS who did not participate in the validation study. We reported on the item generation process elsewhere.[10] All items were generated in Dutch. In total, 15 items were generated, assessing limitations in sporting activities, pain while performing sporting activities, pain while performing activities of daily living (ADL) and pain at rest. Items have four response options with descriptors for each response category. Higher item scores indicate a more severe pain or limitation and hence more severe MTSS symptoms. Participants were asked to fill out the MTSS score with their most painful shin in mind, in case of bilateral symptoms.

7.3.4.2. ITEMS OF THE RAND 36-ITEM HEALTH SURVEY

We used items of the Dutch version of the RAND 36-item Health Survey for assessment of construct validity.[13] The RAND-36 is widely used to measure a variety of domains, including pain and limitations while performing ADL, and also in musculoskeletal and sports medicine-related research.[14–16] Of specific interest to this study were items 3G,

3H and 7. Item 3G measures the limitation while walking >1 km. Item 3H measures the limitation while walking 0.5 km. Low non-standardised scores indicate that the activity is more limited for both items. Item 7 of the RAND-36 evaluates the degree of pain in the past week, with higher non-standardised scores indicating less pain.

7.3.4.3. TRANSITION SCALE

At T2, the transition scale assesses the perceived change since T1. Participants could indicate if their condition had improved, worsened or remained unchanged.[11] Those participants whose condition had remained unchanged were considered 'stable' participants.

7.3.4.4. GPE SCALE

The GPE scale assesses the participant's perceived condition at follow-up (T3) compared with T1; 'completely recovered', 'much improved', 'slightly improved', 'not changed', 'slightly worsened', 'much worsened' or 'worse than ever'.[17]

7.3.4.5. CHANGE IN INTENSITY AND VOLUME OF SPORTING ACTIVITIES

At baseline, participants indicated the number of hours they were able to perform sporting activities, and how much they had reduced their training volume since the onset of their MTSS symptoms. We labelled the difference as 'volume change in sporting activities in hours'. In addition, we asked to what degree the intensity of their exercise had changed since the onset of their symptoms ('severely diminished', 'diminished', 'my exercise intensity has remained unchanged', 'my exercise intensity increased', 'I am unable to perform any type of exercise due to my shin pain'). We labelled this as 'intensity change in sporting activities'.

7.3.5. DATA ANALYSIS AND STATISTICS

All data were analysed with SPSS (V.20.0, IBM SPSS Inc, Chicago, USA) by one author (MW). Missing data were handled by imputing item medians of the sample investigated for all analyses. Demographic data were presented with appropriate measures of central tendency and dispersion.

7.3.5.1. PRELIMINARY DATA ANALYSIS AND ITEM REDUCTION

We planned to reduce the item set to have one item for all relevant domains (limitations in sporting activities, pain while performing sporting activities, pain while performing ADL and pain at rest). We used the reliability and responsiveness analysis to identify the best items for the final version of the MTSS score.

We selected the best item for each domain:

- For limitation in sporting activities: item 'current sporting activities', 'current amount of sporting activities' or 'current content of sporting activities';
- For pain while performing sporting activities: item 'pain while performing sporting activities', 'time to onset of pain during sporting activities', pain throughout sporting activities [1], 'pain throughout sporting activities [2] or 'pain after sporting activities';
- For pain while performing ADL: item 'pain while standing', 'pain while walking', 'pain while walking up or downstairs' or 'pain while performing common daily activities';
- For pain at rest: item 'pain at rest', 'pain at night' or 'pain to touch'.

We used the following analyses to select the best items:

- Test–retest reliability as calculated with intraclass correlation coefficients (ICCs);
- Association between item change scores and the GPE scale.

7.3.6. TEST–RETEST RELIABILITY

We used the data of stable participants, collected at T1 and T2, for evaluation of the MTSS score's items and subscale reliability. Test–retest reliability was assessed with a two-way random effects, consistency, single measures ICC for all items. ICCs were presented with their 95% CIs.[18] ICC values of <0.50 were regarded as insufficient, ICCs between 0.50 and 0.75 were considered acceptable, and ICCs>0.75 were labelled as good.[19]

7.3.7. ITEM RESPONSIVENESS

We used the data collected at T1 (MTSS score) and T3 (MTSS score and GPE scale) for this analysis. We assessed the relation between each item change score (independent variable) and the GPE scale (dependent variable) in a linear regression analysis. We calculated change scores for each item subtracting T3 from T1 for each item of the MTSS score. The -coefficient and the R^2 expressed the direction and magnitude of the relation between each item and the GPE scale. These measures were used to select the best items for the MTSS score. We considered a p value <0.1 as a significant relation. We hypothesised a greater change to be negatively correlated with GPE (the lower the GPE score, the greater the improvement).

All items were discussed for relevancy and importance by four authors (MW, AW, MHM and EWPB) until consensus was reached on which items should be selected for the final MTSS score. However, when consensus could not be met, we voted for selection of an item. Items were selected when a majority of the authors (3/4) favoured selection. When no majority was reached, a fifth author (FJGB) made the decision.

7.3.8. FURTHER METHODOLOGICAL TESTING OF THE FINAL MTSS SCORE AND STATISTICS

- We further assessed the remaining item set for its:
- Structural validity and internal consistency;
- Construct validity;
- Responsiveness of the total score;
- Test–retest reliability of the total score.

In addition, we calculated:

- Measurement error and smallest detectable change (SDC);
- Minimal important change.

We present a summary of item variation at T1 and T3 to further address the interpretability of the MTSS score.

7.3.9. STRUCTURAL VALIDITY AND INTERNAL CONSISTENCY

To investigate the structural validity of the MTSS score, we ran a factor analysis on the MTSS score data collected at T1. We estimated the amount of common variance by estimating communality values for all variables using the maximum-likelihood method (MLM) with direct oblique rotation. MLM enables generalisation of the results beyond the study's population. Direct oblique rotation assumes that underlying (latent) factors of the MTSS score are related.[20] Kaiser's criterion (eigenvalues ≥1) and a scree plot (point of inflexion) assisted in identifying relevant factors.[21, 22] Items with factor loadings of >0.4 were thought to be important for the factor being studied.[23] We checked the item-rest correlations for the items that were maintained in the MTSS score at T1. Item-rest correlations >0.3 were considered to measure the same construct. We addressed the internal consistency of the item set by calculating Cronbach's α (CA). We considered CA around 0.6 as acceptable, and above 0.75 as good.[24, 25]

7.3.10. CONSTRUCT VALIDITY

We assessed the relationships between items of the MTSS score with three items of the RAND-36, and volume and intensity change in sporting activities, collected at T1. After the item selection process, we formulated a hypothesis for each item of the MTSS score. Spearman's Rank tests were used to assess correlations between items. We regarded correlation coefficients around 0.1 as small, around 0.3 as moderate and those around or above 0.5 as large.[26] We recoded item scores of items 3G and 3H (recoded: higher scores indicate more limitation) for this analysis.

7.3.11. RESPONSIVENESS OF THE MTSS SCORE

To determine item responsiveness, we calculated the change in MTSS scores between T1 and T3 (i.e., T1–T3). We performed a linear regression analysis with these change scores as the independent variable and the GPE as the dependent variable. The β-coefficient and the R^2 expressed the direction and magnitudeof the relationship between the MTSS score and the GPE scale.

We considered a p value <0.05 as a significant relationship. We hypothesised a greater change to be negatively correlated with GPE (the lower the GPE score, the greater the improvement).

7.3.12. TEST–RETEST RELIABILITY, MEASUREMENT ERROR AND SDC OF THE MTSS SCORE.

We used the data of 'stable' participants, collected at T1 and T2, for evaluation of the MTSS score's reliability. Test–retest reliability of the total MTSS score was assessed in the same way as individual items. We expressed measurement error by the standard error of measurement (SEM). The SEM was calculated as SEM = SDmeasurement1+2√1-ICC.[18] The SDC was calculated on both individual (SEM x 1.96 x √2) and group level (SEM x 1.96 x √2/√n).[18, 27]

7.3.13. MINIMAL IMPORTANT CHANGE

We used the data of those participants who indicated that their condition had 'slightly improved' or 'slightly worsened' on the GPE scale at T3. The same change scores were used here as in the responsiveness analysis. We considered the mean change score of those participants who indicated 'slightly improved' or 'slightly worsened' to be the minimal important change.

7.3.14. INTERPRETABILITY

To enhance the interpretability of the MTSS score, we present the means, SDs and distributions of the MTSS score at T1 and T3. Floor or ceiling effects were considered to be present when 15% or more of the participants scored the lowest or highest possible MTSS score.[11, 28]

7.3.15. CROSS-CULTURAL TRANSLATION

We translated all items of the preliminary MTSS score into English. This translation process contained a forward and backward translation. As for item generation, we report on the cross-cultural translation process elsewhere.[10] We present here the final (Dutch) MTSS score and its English cross-cultural translation.

Table 1. Demographic information

Demographic variable	**Participants (N=133)**	
Male/female, *n*	73 (55%) / 60 (45%)	
Age, *mean ± SD*	24.2 ± 7.9	
Length in cm, *mean ± SD*	177 ± 10	
Weight in kg, *mean ± SD*	74 ± 13	
BMI, *mean ± SD*	23 ± 3	
Sports athletes / Military, *n (%)*	87 (65%) / 46 (35%)	
Sports category *n (%)*	Running Fitness Hockey Soccer Athletics (non-distance running) Volleyball Cycling Other	35 (26%) 21 (16%) 14 (11%) 14 (11%) 7 (5%) 6 (4%) 5 (4%) 31 (23%)
Hours of exercise a week at T1, *median with range (min-max)*	4.0 (0 - 30)	
Duration of complaints in months, *median with range (min-max)*	18 (0.75 - 144)	
Side of complaints, *n (%)*	Both legs: Only left leg: Only right leg:	109 (82%) 11 (8%) 13 (10%)

Table 1: BMI, body mass index; T1, baseline.

7.3.16. SAMPLE SIZE

We calculated the required sample size for test–retest reliability analysis and exploratory factor analysis, before the study's start. For test–retest reliability, a sample size of 51 stable participants was required, as well as constructing a two-sided 95% CI and assuming an ICC of 0.80 with a lower limit of 0.70.[29] For exploratory factor analysis, a minimum of 100 participants is advised; however, others suggest including 10 participants for each item tested in the analysis.[30]

7.4. RESULTS

7.4.1. PROSPECTIVE COHORT STUDY

A total of 133 participants met the inclusion criteria and agreed to participate in this prospective cohort study. The study comprised 73 men and 60 women, the mean age was 24.2 (SD=7.9), and the mean body mass index was 23.0 (SD=3.0). Forty-six participants (35%) were military personnel and 87 (65%) were athletes. Eighty-two per cent of the participants had bilateral MTSS, and 18% had unilateral MTSS. Table 1 provides further demographic information on our participants.

All 133 participants completed the MTSS score, the RAND-36 and questions concerning their exercise volume and intensity at T1. Seventy participants completed the MTSS score at T2 (the median number of days post T1 was 9 (range 5–20)), of whom 48 were 'stable'. At T3, the MTSS score was completed by 66 individuals, whereas the GPE was completed by 63 participants (median number of days post T1 was 70 (range 44–120)).

7.4.2. MISSING ITEMS

For items of the MTSS score, few data were missing: at T1 2%, at T2 1.25%, while at T3 no data were missing. At T1, 7.25% of the data of the three items of the RAND-36 were missing. A minority of the participants did not provide information on sports volume (5.6%) and sports intensity change (6.8%) at T1. No data were missing for the transition scale at T2 or the GPE scale at T3.

7.4.3. PRELIMINARY DATA ANALYSIS AND ITEM SELECTION

7.4.3.1. TEST–RETEST RELIABILITY ON ITEM LEVEL

Forty-eight participants indicated that their symptoms had remained 'unchanged' at T2. We used their data, collected at T1 and T2, to estimate the two-way random effects, consistency, single measures ICCs for all items of the MTSS score. Table 2 provides ICC values for all preliminary items of the MTSS score. All ICCs were acceptable or good, except for items 'pain to touch', 'pain while performing common daily activities', 'pain throughout sporting activities 1' and 'pain throughout sporting activities 2'. These items exhibited low test–retest reliability (ICC<0.50).

Table 2

Table 2. Item selection for the MTSS-score

		Test-retest reliability	Responsiveness analysis*		
Theoretical Domain	**Item**	**ICC (95% CI)**	**B-coefficient**	**R-square**	**P-value**
Limitation in sporting activities					
	Current sporting activities	*0.80 (0.67 - 0.88)*	*-0.43*	*0.065*	*0.04*
	Current amount of sporting activities	0.76 (0.61 - 0.86)	-0.03	0.001	0.78
	Current content of sporting activities	0.84 (0.73 - 0.91)	-0.38	0.114	< 0.01
Pain while performing sporting activities					
	Pain while performing sporting activities	*0.63 (0.43 - 0.78)*	*-0.45*	*0.129*	*<0.01*
	Time to onset of pain during sporting activities	0.72 (0.56 - 0.84)	-0.44	0.201	< 0.01
	Pain throughout sporting activities 1	0.44 (0.19 - 0.65)	-0.11	0.018	0.31
	Pain throughout sporting activities 2	0.34 (0.07 - 0.57)	-0.15	0.031	0.18
	Pain after sporting activities	0.74 (0.58 - 0.85)	-0.20	0.048	0.085
Pain while performing activities of daily life					
	Pain while standing	0.72 (0.55 - 0.84)	-0.55	0.098	0.01
	Pain while walking	*0.82 (0.70 - 0.90)*	*-0.50*	*0.089*	*0.02*
	Pain while walking up- or downstairs	0.86 (0.76 - 0.92)	-0.18	0.008	0.48
	Pain while performing common daily activities	0.48 (0.23 - 0.67)	-0.52	0.107	<0.01
Pain at rest					
	Pain at rest	*0.60 (0.39 - 0.76)*	*-0.21*	*0.019*	*0.28*
	Pain at night	0.91 (0.85 - 0.95)	0.22	0.023	0.22
	Pain to touch	0.50 (0.26 - 0.69)	-0.19	0.059	0.06

Items in italics were selected for use in the MTSS-score. ICC = intraclass correlation coefficient, 95% CI = 95% confidence interval, ADL = activities of daily living, * as assessed with linear regression analysis. B indicates how the GPE - scale changes for each extra unit of the item, R square represents the magnitude of the relation between the global perceived effect scale and each item.

7.4.3.2. ITEM RESPONSIVENESS ON ITEM LEVEL

Change scores between T1 and T3 were calculated for all items of the MTSS score. The change score item 'pain at night' showed an inverse relation with the GPE scale at T3 and was therefore considered invalid. All other change score items showed a relation with the GPE scale at T3; however, this relationship was only significant for items 'pain while standing', 'pain while walking', 'current sporting activities', 'current content of sporting activities', 'pain while performing sporting activities', 'time to onset of pain during sporting activities' and 'pain after sporting activities'.

7.4.4. ITEM SELECTION

7.4.4.1. LIMITATION IN SPORTING ACTIVITIES

The item 'current sporting activities' was selected for 'limitation in sporting activities'. The item 'current content of sporting activities' showed comparable test–retest reliability (ICC=0.80 vs. 0.84) and association with the GPE scale (=−0.43 vs. −0.38); however, we considered the first to reflect this domain best.

7.4.4.2. PAIN WHILE PERFORMING SPORTING ACTIVITIES

The item 'pain while performing sporting activities' showed the best relation with the GPE scale and exhibited the best test–retest reliability (see table 2) and was therefore selected.

7.4.4.3. PAIN WHILE PERFORMING ADL

The item 'pain while walking' was selected for 'pain while performing ADL'. Although the items 'pain while standing' and 'pain while walking up or downstairs' were equally reliable and related to the GPE scale (see table 2), we considered walking more relevant and feasible than standing and walking up or downstairs. More specifically, standing and walking up or downstairs are activities that not all possible participants with MTSS would engage in on a daily basis. 'Pain while performing common daily activities' exhibited a low test–retest reliability (ICC=0.48), but one author considered this item the most relevant to measure this domain. Therefore, the steering committee further discussed item selection for this domain (see Steering committee section).

7.4.4.5. PAIN AT REST

The item 'pain at rest' was considered the best item for 'pain at rest''. 'Pain at night' exhibited an inverse relation with the GPE scale (=0.22) and was therefore considered invalid. The item 'pain to touch' exhibited a low test–retest reliability (ICC=0.50).

Table 3

Table 3. Factor analysis and internal consistency analysis

		Factor analysis	Internal consistency analysis	
Items		**Factor loadings**	**Item rest correlations**	**Cronbach's Alpha**
MTSS - score				**0.58**
Item 1	**Current sporting activities**	**0.40**	**0.3**	
Item 2	**Pain while performing sporting activities**	**0.52**	**0.4**	
Item 3	**Pain while walking**	**0.64**	**0.4**	
Item 4	**Pain at rest**	**0.48**	**0.3**	

factor analysis and internal consistency analysis of definitive items in the MTSS-score. MTSS, medial tibial stress syndrome

7.4.4.6. STEERING COMMITTEE

Selection was made on the basis of consensus for all items, except for 'pain while performing activities of daily life'. On this domain, no consensus was reached; we voted for the item 'pain while performing common daily activities' or 'pain while walking'. A majority (3/4 authors) voted for pain while walking.

7.4.5. METHODOLOGICAL TESTING OF THE FINAL MTSS SCORE

7.4.5.1. STRUCTURAL VALIDITY AND INTERNAL CONSISTENCY ANALYSIS

Data collected at T1 from all 133 participants were used to assess the structural validity of the item set. One factor yielded an eigenvalue of ≥1, explaining 44.4% of the variance in the item set. The scree plot confirmed the unidimensionality of the item set. All items loaded on this factor satisfactorily (>0.4). We checked the item-rest correlation for each subscale. Item-rest correlations were adequate, r≥0.3. CA showed acceptable internal consistency, α=0.58. Table 3 depicts all results of the factor and the internal consistency analyses.

7.4.5.2. CONSTRUCT VALIDITY

We checked whether the remaining items of the MTSS score at T1 were associated with items of the RAND-36 and sports volume and intensity change.

We hypothesised that:

1. Item 'current sporting activities' would show a moderate-to-large positive correlation (r=0.3–0.5) with volume change in sporting activities. A positive correlation of r=0.34 (95% CI 0.17 to 0.50, p<0.01) was found.

1. Item 'pain while performing sporting activities' would exhibit a moderate to large positive correlation with intensity change in sporting activities (r=0.3–0.5). We found a positive correlation of r=0.34 (95% CI 0.17 to 0.50, p<0.01).

2. Item 'pain while walking' would show a moderate-to-large positive correlation (r=0.3–0.5) with items 3G and 3H (degree of limitation while walking >1 km and walking around 0.5 km, respectively). A large positive correlation was found with items 3G (r=0.58, 95% CI 0.43 to 0.70, p<0.01) and 3H (r=0.48, 95% CI 0.32 to 0.63, p<0.01).

3. Item 'pain at rest' would show a moderate-to-large correlation (r=0.3–0.5) with item 7 (degree of pain in the past week) of the RAND. Item 1 showed a large positive correlation (r=0.53, 95% CI 0.39 to 0.64, p<0.01).

7.4.5.3. RESPONSIVENESS OF THE MTSS SCORE

A significant negative relation confirmed the responsiveness of the total MTSS score: β=−0.288, R^2=0.21, t=−3.962,p<0.001.

Table 4. Interpretability; item variation of the MTSS-score at T1 (N=133)

Item nr.	Item name	Answer option 1, *n (%)*	Answer option 2, *n (%)*	Answer option 3, *n (%)*	Answer option 4, *n (%)*	Mean	Median	Missing values
1	**Current sporting activities**	16 (12.0%)	48 (36.1%)	57 (42.9%)	8 (6.0%)	1.44	2	4 (3.0%)
2	**Pain while performing sporting activities**	4 (3.0%)	65 (48.9%)	52 (39.1%)	8 (6.0%)	1.50	1	4 (3.0%)
3	**Pain while walking**	41 (30.8%)	71 (53.4%)	20 (15.0%)	1 (0.8%)	0.86	1	0 (0.0%)
4	**Pain at rest**	48 (36.1%)	69 (51.9%)	14 (10.5%)	2 (1.5%)	0.77	1	0 (0.0%)

table 4. nr . = number

Table 5. Interpretability; item variation of the MTSS-score at T3 (N=66)

Item nr.	Item name	Answer option 1, *n (%)*	Answer option 2, *n (%)*	Answer option 3, *n (%)*	Answer option 4, *n (%)*	Mean	Median	Missing values
1	**Current sporting activities**	13 (19.7%)	25 (37.9%)	24 (36.4%)	4 (6.0%)	1.29	1	0 (0.0%)
2	**Pain during sporting activities**	9 (13.6%)	37 (56.1%)	15 (22.7%)	5 (7.6%)	1.24	1	0 (0.0%)
3	**Pain while walking**	31 (47.0%)	30 (45.4%)	5 (7.6%)	0 (0.0%)	0.61	1	0 (0.0%)
4	**Pain at rest**	31 (47.0%)	31 (47%)	4 (6.0%)	0 (0.0%)	0.59	1	0 (0.0%)

table 5. nr. = number

Table 6. Interpretability; MTSS-score at T1 (n=133), T3 (n=66) and MTSS change - score (T1 - T3, n=66)

	Mean	SD	95% CI	Median	Range	Absolute min	Absolute max	Floor effects *n (%)*	Ceiling effects *n (%)*
MTSS - score at T1	4.58	1.88	4.26 - 4.90	5	1 - 10	0	10	2 (1.5%)	1 (0.8%)
MTSS - score at T3	3.72	2.08	3.22 - 4.24	4	0 - 9	0	10	3 (2.3%)	0 (0.0%)
Change MTSS - score T1 - T3	1.00	1.56	0.62 - 1.38	1	-2 to 5	-10	10	0 (0.0%)	0 (0.0%)

table 6. Interpretability. SD = standard deviation, CI = confidence interval, n = number

7.4.5.4. TEST–RETEST RELIABILITY OF THE TOTAL MTSS SCORE

The total MTSS score showed good test–retest reliability: ICC=0.81 (95% CI 0.70 to 0.89, F=9.95, p<0.001).

7.4.5.5. MEASUREMENT ERROR, SDC AND MINIMAL IMPORTANT CHANGE

We assessed the measurement error by calculation of the SEM and the SDC at the group and individual patient level. The SEM was 1.73. The SDC on the individual level was 4.80. The SDC and the minimal important change at the group level were both 0.69. This means that the MTSS score can measure the minimal important change.

7.4.5.6. INTERPRETABILITY

The MTSS score is provided in Dutch and English (crossculturally translated version) and available online as supplementary material (appendices 1 and 2). In addition, tables 4–6 provide information on scoring distributions, means and medians of the MTSS score at T1 and T3. We conclude that floor or ceiling effects are not present for the MTSS score at T1 and T3.

The lowest possible MTSS score is 0, indicating that no MTSS symptoms are present, whereas 10 is the maximum score. This indicates the highest severity of MTSS symptoms. In our study, the mean MTSS scores were 4.58 (±1.88) and 3.72 (±2.08) at T1 and T3, respectively.

7.5. DISCUSSION

This is the first study to assess a PROM for patients with MTSS for reliability, validity and responsiveness. We selected the best items from an item pool generated by a group of experts to be used in the final MTSS score. This new MTSS score is a simple four-item scale that addresses pain at rest, pain while performing ADL, limitations in sporting activities and pain while performing sporting activities. The MTSS score specifically measures pain experienced along the shin and limitations due to shin pain. Its items exhibit four response options with descriptors for the degree of shin pain and limitations. The variation in items, from low-demand activities (resting/walking) to high-demand activities (sports activities), also contributes to the specificity of this new instrument.

7.5.1. RIGOROUS CLINIMETRIC EVALUATION

A previously performed Delphi study supports the content validity of the MTSS score, as shown by consensus among a group of experts in the field of MTSS. In addition, those items were appraised by a patient panel and were found to be valid, readable and comprehensive.[10] Structural analysis confirmed the unidimensionality of the MTSS score. In addition, the MTSS score showed good construct validity when compared with items of the RAND-36 and the participants' volume and intensity change in sporting

activities. The MTSS score's overall scale reliability and responsiveness confirmed the suitability for its use in scientific research.

Taken together, this study shows that the MTSS score is a valid, reliable and responsive PROM for the evaluation of the injury severity in patients with MTSS.

In addition to reliability, validity and responsiveness, low measurement error is important for the MTSS score's utility. We found quite a large SDC (4.8, almost 50% of the possible score range) at the individual level. However, analysis at the group level showed that the SDC was equal to the minimal important change (both 0.69 points). This suggests that the MTSS score is an appropriate measure to compare tendencies across different groups, such as in RCTs into the effectiveness of different interventions in the treatment of MTSS.

Another outcome measure for exercise-induced lower leg pain has been validated recently. This outcome measure aims to measure 'functional impairment and limitation in sports ability' in runners.[31] In our opinion, the MTSS score is more valid and feasible for patients with MTSS. Most of the activities that can be scored in the outcome measure developed by Nauck et al.[31] may not be relevant to all patients (such as taking off and landing while jumping). In addition, our study suggests that pain at rest and ADL are important limitations to patients with MTSS and should therefore be part of an outcome assessment tool.

7.5.2. CLINICAL UTILITY OF THE NEW MTSS SCORE

Many of the patients in our study had a long duration of symptoms prior to enrolling in our study. This suggests that current interventions and routine care for MTSS are not very effective. The MTSS scores at T1 and T3, and GPE scale at T3, showed that little improvement was made after participants sought medical care in centres with a large clinical experience. This highlights the necessity for new approaches to treating MTSS.

The MTSS score can be used in several ways to enhance better treatment outcomes. First, the MTSS score allows for determination of treatment effects as reported by the patient in contrast to determination of treatment effects by the assessor or by physical parameters. Second, the MTSS score is able to reliably and validly track changes in groups. This is predominantly important in randomised clinical trials. Finally, a possible future application could be if the MTSS score was able to predict a window for time to recovery (prognosis). We note that in a 2015 systematic review of risk factors for MTSS, there was no mention of certainty of the clinical diagnosis or any variation in severity of the condition.[32] If adopted, our instrument will allow the broad condition of 'MTSS' to be subcategorised according to level of severity of the condition. This instrument may be limited for monitoring individual patients with MTSS.

7.5.3. STRENGTHS AND LIMITATIONS

A strength of the present study is the inclusion of a broad variety of participants with

MTSS, athletes and military personnel with short-standing and long-standing symptoms. This strengthens the study's external validity. The MTSS score is a practical outcome measure; the patient can fill out the MTSS score without any help from a physician or physiotherapist, and it takes little time for the patient to do so.

Our study also has limitations. First, we followed the classical test theory for all analyses, whereas the item response theory would have been more appropriate. Item response theory analyses, however, require large sample sizes, up to 200–500 participants, depending on the type of analysis.[28] This was not possible within our network of healthcare providers and budget.

Another limitation is the sample size in relation to the number of statistical tests performed. We acknowledge that 18 tests is a large amount. Statistically, this may have introduced one significant result due to chance. Our methods were, however, in accordance with the COSMIN guidelines, a methods criterion in this field of research.[11]

The MTSS score exhibits one factor (it is unidimensional) which explained 44% of the variance in the item set. Some would regard this as moderate or low. However, to the best of our knowledge, no hard cut-off values for when this value is sufficient exist in the field of clinimetrics. The MTSS score yielded a value similar to those of other PROMs successfully validated in the field of musculoskeletal pain.[33–35]

We used the CA statistic to assess for internal consistency. The MTSS score's CA was 0.58 and we considered this as acceptable. Other classification systems may rate this as moderate or poor.[28] Cortina[36] showed that a high number of items may inflate CA and a low number of items may deflate CA. Given the relatively low number of items in the MTSS score (N=4), we are confident that the internal consistency is acceptable, also given the sufficient item-rest correlations (all ≥0.3). With regard to test–retest reliability, there are some methodological issues to address: first, 70 of the 133 participants filled out the MTSS score at T1 and T2. Although we attempted to contact all participants for the second measurement, we have not succeeded in reaching them all. It is unclear how this may have affected the test–retest reliability results exactly. However, we were still able to find sufficient test–retest reliability levels for all items of the MTSS score as well as for the overall MTSS score. Second, we used ICCs for categorical data instead of weighted. Among the many advantages of ICC over weighted, the most important ones are that ICC is able to deal with (the presence or absence of) various sources of error and with missing values.[37] Therefore, it is most likely that the MTSS score's test–retest reliability is estimated more precisely with ICCs, and consequently, conclusions can be drawn more robustly. The direction and magnitude of the -coefficient and R2 of the linear regression analysis were used to select the most responsive items. In view of the moderate sample size used in this analysis (N=66), we set the threshold for significance to <0.1 to avoid missing true significant relations between the GPE and 'MTSS change score'.[38] Finally, the cross-cultural English translation should be validated in English-speaking MTSS populations.

We conclude that the MTSS score is a valid, reliable and responsive PROM to evaluate injury severity in patients with MTSS. We recommend its use in studies of MTSS treatment.

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Appendix 1: **Mediaal Tibiaal Stress Syndroom Score**

Naam: **Datum:**

Ik heb klachten aan mijn:

Beide scheenbenen	☐
Alleen het linker scheenbeen	☐
Alleen het rechter scheenbeen	☐

Indien klachten aan beide scheenbenen:

Ik heb het meeste last van:

Mijn linker scheenbeen	☐
Mijn rechter scheenbeen	☐

Instructies:

- Denk bij het invullen van deze vragenlijst aan de pijn zoals u die in de afgelopen dagen maximaal hebt ervaren/gehad, kruis het antwoord aan dat het **beste** past bij die pijn in het scheenbeen.
- Houd bij het invullen van deze vragenlijst **het scheenbeen** in gedachte waar u het **meeste last** van hebt.
- Lees **alle** antwoordopties zorgvuldig door voordat u een antwoord aankruist.
- **Kies steeds één antwoord, bij alle vragen.**

Sportactiviteiten

Voor militairen: marsen en marcheren zijn sportactiviteiten.

1) Momenteel:		**P**
Beoefen ik al mijn gebruikelijke sportactiviteiten	☐	0
Kan ik, door mijn scheenbeenklachten, minder dan mijn gebruikelijke sportactiviteiten doen	☐	1
Kan ik, door mijn scheenbeenklachten, alleen alternatieve sportactiviteiten doen	☐	2
Kan ik, door mijn scheenbeenklachten, geen enkele sportactiviteit doen	☐	3

2) Tijdens het sporten:

Heb ik geen pijn aan mijn scheenbeen	☐	0
Heb ik enige pijn aan mijn scheenbeen	☐	1
Heb ik veel pijn aan mijn scheenbeen	☐	2

Ik kan niet sporten vanwege de pijn aan mijn scheenbeen ☐ 3

Lopen

3) Tijdens lopen: **P**

Heb ik geen pijn aan mijn scheenbeen ☐ 0

Heb ik enige pijn aan mijn scheenbeen ☐ 1

Heb ik veel pijn aan mijn scheenbeen ☐ 2

Ik kan niet lopen vanwege de pijn aan mijn scheenbeen ☐ 2

Pijn in rust
Bijvoorbeeld zitten of liggen.

4) In rust is mijn scheenbeen:

Niet pijnlijk ☐ 0

Gevoelig ☐ 1

Pijnlijk ☐ 2

Heel pijnlijk ☐ 2

Interpretatie:

Per vraag zijn er 4 antwoordcategorieën.

De eerste antwoordcategorie (0 punten) geeft geen beperkingen aan, de laatste categorie (2 of 3 punten) betekent de meeste beperking.

De totaalscore is de som van de 4 vragen. De eindscore varieert van 0 (geen beperking) tot 10 (volledige beperking)

Kleinst meetbaar verschil op individueel niveau = 4.80

Kleinst meetbaar verschil voor een groep = 0.69

Minimaal belangrijke verandering (groep) = 0.69

Appendix 2: **Medial Tibial Stress Syndrome Score**
Name: **Date:**

I have complaints in:

Both shins	☐
Only the left shin	☐
Only the right shin	☐

In case of complaints in both shins:

I have most complaints in:

My left shin	☐
My right shin	☐

Instructions:

- While completing this questionnaire, keep in mind the pain as you have experienced maximally over the past days, and check the answer that fits **best** this shin pain
- While completing this questionnaire, keep in mind your **shin with most** complaints.
- Please read **all** options before you select a checkbox.
- **For all questions, choose one answer per question only.**

Sporting activities

For military: Marching is considered to be a sporting activity.

1) Presently:		**P**
I perform all of my usual sporting activities	☐	0
I am forced to do less of my usual sporting activities due to pain in my shin	☐	1
I am forced to do alternative sporting activities only due to pain in my shin	☐	2
I cannot do any sporting activity due to painin my shin	☐	3

2) While performing sporting activities:

I have no pain in my shin	☐	0
I have some pain in my shin	☐	1
I have a lot of pain in my shin	☐	2
I cannot do any sporting activity due to my shin pain	☐	3

Walking

3) While walking:		**P**
I have no pain in my shin	☐	0
I have some pain in my shin	☐	1
I have a lot of pain in my shin	☐	2
I cannot walk due to pain in my shin	☐	2

Pain at rest
e.g. sitting or laying down

4) At rest, my shin is:		
Not painful	☐	0
Sensitive	☐	1
Painful	☐	2
Very painful	☐	2

Interpretation:

There are four checkboxes for each item.

The first checkbox (0 points) indicates no limitation, the final checkbox (2 or 3 points) indicates a full limitation.

The sum score is the sum of the four items. The final score ranges from 0 (no limitation) to 10 (full limitation)

Smallest detectable change, individual level = 4.80

Smallest detectable change, group = 0.69

Minimal important change, group = 0.69

Chapter 08

General discussion

Medial tibial stress syndrome (MTSS) is a common exercise-related injury yet little evidence exists to guide treatment decisions. In this thesis we aimed to address some of the gaps in the knowledge regarding MTSS. In this chapter, we will discuss the following topics:

1. Pathogenesis
2. Pain
3. Diagnosis
4. Prognosis
5. Treatment
6. Outcome assessment
7. Return-to-sport

In each section we will discuss our most important findings, the limitations of our studies and the implications for future research and clinical practice.

8.1. PATHOGENESIS

Since MTSS was first described in 1958, many studies have looked into the involvement of several structures in athletes with MTSS.[1-13] Their findings suggest that MTSS is either a bony overload injury, a traction-induced periostitis, a fasciitis or a combination of two or three of these pathogenic entities.

As outlined in Chapter 1, the soleus muscle, tibialis posterior, flexor digitorum longus and flexor hallucis longus were thought to induce traction onto the posteromedial periosteum leading to a periostitis for years. However, anatomic studies in cadavers showed that it is unlikely that the origins of these muscles are in the MTSS area. These studies also showed that the crural fascia is attached in the MTSS area, showing that it could induce traction onto the posteromedial tibial periosteum.

In Chapter 2 we scanned structures along the posteromedial border with musculoskeletal ultrasonography, and we assessed if these were affected. We evaluated the presence of periosteal abnormalities (thickening, oedema and vascularisation), posteromedial tibial cortical bone abnormalities (oedema, irregular bone contours (i.e. erosions and spurs)) and tendinous abnormalities (thickening, intratendinous hypoechoic areas, oedema and hypoechoic areas in the tendon sheath) of the tibialis posterior, flexor hallucis longus and flexor digitorum longus in a dance population. In this case-control study we included dancers with MTSS and asymptomatic controls from the same dance population.

One medical imaging specialist scanned the medial aspects of the lower leg and was blinded to the injury status of participants. In addition, we evaluated the inter-examiner reliability of our procedures in an adjacent study. We found that musculoskeletal ultra-

sonography has moderate reliability for periosteal and tendinous oedema. Reliability for other abnormalities could not be calculated or not be considered good estimations due to low prevalence values.

We found that periosteal and tendinous abnormalities are as common in athletes with as without MTSS. No bony abnormalities were seen in athletes with MTSS. This specific finding should be interpreted with caution. Musculoskeletal ultrasonography may not be able to detect intra-cortical changes.[14] It cannot be ruled out that bone changes important to MTSS were present but were not detectable by musculoskeletal ultrasonography. We concluded that it seems that periosteal and tendinous 'abnormalities' are actually normal findings in a highly active population, and do not explain the presence of MTSS. None of the 42 athletes had the concurrent presence of periosteal oedema, thickening and vascularisation, fitting the text-book description of a periostitis. It seems unlikely that a traction-induced periostitis is the underlying pathology of MTSS.

We were not able to investigate abnormalities in the crural fascia as it can be poorly evaluated upon musculoskeletal ultrasound assessment. Johnell et al. found inflammatory findings in 39% of the crural fascia biopsies taken from athletes with MTSS.[4] The crural fascia as the structure affected in MTSS is therefore a possibility. To what extent inflammation of the crural fascia is present in healthy active controls and depict normal physiological properties is unknown. Repeating this study with a non-injured control group could elucidate on the relationship between these 'abnormalities' in the fascia and MTSS. Ultrasonographic tissue characterization (UTC) is a relatively new type of ultrasonographic imaging that could also be used for this purpose.[15] It may be a feasible device to evaluate degenerative changes in the crural fascia. It can measure structures as thin as the Achilles' paratenon. Therefore, it may also be able to visualise changes within the crural fascia (personal communication dr. Hans van Schie, Scientific Director at UTC Imaging). A case-control study in a population with athletes with and without MTSS that also includes a reliability study could elucidate on its validity and reliability in the evaluation of changes in the crural fascia.

There is a need for new studies that investigate the bony overload theory. As outlined in Chapter 1, section 1, paragraph 1.3.2., the aggregated findings from two studies suggest that the local tibial bone is only affected in a measurable way in patients with a long duration of pain. If MTSS is an injury that occurs because of a failing bone remodelling process, leading to locally decreased tibial BMD, it may be important to know when this decrease occurs. It should be investigated if athletes with lowered BMD values have a worse prognosis.

8.1.1. CURRENT UNDERSTANDING:

- There is no evidence for a relation between the origin of the deep ankle plantar flexors and the MTSS area.
- We did not find any evidence for MTSS being a posteromedial tibial periostitis (Chapter 2).

- Initial preliminary studies suggest that fascia may also play a role in the pathogenesis of MTSS.
- There is very limited evidence for a local tibial bone overload injury as the pathogenic process in MTSS.
- Available studies suggest that there are no local tibial bone changes in athletes with a short period of pain, but there is a reduced bone mineral density in athletes with a long-standing MTSS.

8.1.2. IMPLICATIONS FOR CLINICAL PRACTICE:

- The pathogenesis of MTSS remains unclear; MTSS should still be considered a clinical condition/syndrome.

8.1.3. RECOMMENDATIONS FOR FUTURE RESEARCH:

- Ultrasonographic tissue characterisation should be explored as an option for the evaluation of changes in the crural fascia. A case-control study in athletes with and without MTSS and an adjacent reliability study could provide preliminary information on its validity and reliability before its use in prospective studies.
- There is a need for longitudinal studies that follow athletes (at risk for MTSS) prior to MTSS onset, during MTSS and while MTSS is recovering. During the entire follow-up bone strength measurements should be made, preferably with high-quality peripheral qualitative computed tomography scans or dual-energy X-ray absorptiometry.

8.2. PAIN

Understanding shin pain is important for athletes, clinicians and researchers alike. Studies in other musculoskeletal injuries show that patients who understand their injuries correctly have better outcomes than those patients that do not.[e.g.16] Understanding what causes the shins to hurt may be vital for managing MTSS in a sensible way, and may improve outcomes over time.

In the absence of strong evidence for these two theories, we can only speculate on the possible underlying tissues affected and pain mechanisms involved in MTSS.

A typical onset of pain in MTSS is insidious; initially athletes feel some stiffness and discomfort along the posteromedial tibial border. Upon continuation of sporting activities the shin becomes painful, often after exercise has finished in the initial stages. Pain becomes present during sporting activities as the injury progresses. Even light weight-bearing activities, like walking or standing, may provoke pain afterwards. In the MTSS score study (chapter 7) we found that 52% of the athletes had sensitive shins at rest, and 12% reported to even have pain at rest. Clinical observations suggest that pain is usually load dependent; i.e. the pain is provoked or worsens with exercise and

subsides upon cessation of the pain-provoking activity.

Pain is a complex phenomenon and a full appreciation of pain science is beyond the scope of this section. Instead, we will focus on peripheral mechanisms of pain; how nociception; "the molecular, cellular and systemic mechanism that deals with the processing of pain-related information"[19, 20] may occur in sensory nerve endings in the bone and fascia. We will discuss the peripheral neural anatomy in bone and fascia, the mechanisms through which a nociceptive signal may occur and how pain mechanisms may relate to clinically observed pain in MTSS.

8.2.1. NOCICEPTIVE INNERVATION IN THE TIBIAL BONE AND THE CRURAL FASCIA

Peripheral sensory afferent nerves can be differentiated according to their size and conduction velocity. In the musculoskeletal system low-threshold fibres (Aβ) are able to sense temperature (thermoreceptors) and mechanical forces (mechanoreceptors). These are large diameter myelinated axons enabling action potentials to reach high conduction velocities. High-threshold fibres respond to noxious stimuli and are called nociceptors. The Aδ fibres have small diameter myelinated axons with moderate conduction velocities, whereas the C- fibres are small diameter non-myelinated axons, with low conduction velocities.[20]

Aβ, Aδ and C-fibres have consistently been found in the periosteum, mineralised bone and bone marrow.[21-23] The periosteum is the most densely innervated structure of bone. However, the bone marrow has the highest number of sensory nerve endings, then the mineralised bone and then the periosteum.[22]

Stecco et al. investigated the histological characteristics and neural innervation of fasciae.[24, 25] The crural fascia as a multi-layered structure with adipose and connective tissue separating the layers, to enable the sliding of one layer relative to another.[24-26] Aβ, Aδ and C-fibres have been found in the crural fascia, and in many other fasciae in the human body, which supports nociceptive innervation of the crural fascia.[26-29]

Signals in nociceptors travel to the dorsal horn of laminae I and II of the spinal cord. In the spinal cord the nociceptor synapses with a second order neuron. This spinal nociceptor projects to the cerebral cortex, via a relay in the thalamus, producing a pain sensation. Nociceptive input increases arousal and sets of emotional, autonomic and neurohumeral responses concurrent to pain sensation.[30]

8.2.2. NOCICEPTION IN MTSS

Nociception is "the molecular, cellular and systemic mechanism that deals with the processing of pain-related information". Nociception is regarded as a physiologic response to (a threat to) tissue damage and is thought to protect homeostasis.[31-33] There are several ways through which nociception may occur in MTSS.

8.2.2.1. BONE

Bone remodelling is dependent on hormones, cytokines and mechanical stimulation.[21] Altered volume or intensity of loading may trigger bone remodelling.[34] Osteocytes signal the necessity for bone remodelling and initiate osteoclast formation to resorb mineralised bone cells.[35, 36] Osteoclasts form a highly acidic compartment between themselves and mineralised bone.[21, 22] This acidic environment can be sensed by afferent nociceptors. In normal physiogenic circumstances this acidic environment may contribute to mechanoreception and aid in maintaining homeostasis.[23, 31] However, under mechanical stimulation or when the acidic environment depolarises a nociceptor, a nociceptive potential may occur.[36, 37] This mechanism could explain the initial shin soreness after exercise. It does not seem to explain the loading-dependent pain, i.e. pain due to loading.

Overloading the bone during a window of bone adaptation may escalate osteoclast activity which could potentially increase the acidic environment to more easily exceed a nociceptor's depolarisation threshold.[38]

In the theoretical model of bone overload in MTSS and stress fractures, it is assumed that bone resorption outpaces bone formation. Theoretically, if osteoclast activity is matched by osteoblast activity no pain would occur. Yet, the possible role of osteoblasts in mediating the osteoclast activity-induced acidic environment, or inhibiting depolarisation of the nociceptor by this acid environment, remains unclear.

Bone microcracks may also set off bone nociceptors. Repetitive strains may compromise the architectural bone structure leading to microcracks in the cortical bone.[39] Microcracks may disrupt the nerve endings which leads to nociceptive pain from sensory nerve fibres.[40]

8.2.2.2. FASCIA

Pain through nociceptor activity in the crural fascia cannot be excluded as an explanation for initial pain in MTSS. However, there are fewer studies available that investigate nociception in fasciae. Johnell et al. took [33] fascia biopsies from athletes with MTSS and examined them for the presence of inflammation[4] They found focal aggregates of leukocytes, histocytes and mast cells surrounding and infiltrating small arteries' walls in 39% of the investigated cases with MTSS, which suggests an inflammatory process in the crural fascia.[4] Clinical observations suggest that no inflammation is present in MTSS. The cardinal clinical signs of inflammation are rubor, calor, dolor, tumor and functio laesa. To the best of our knowledge, there are no studies reporting calor or rubor in athletes with MTSS. We also have not observed these signs in our studies concerning athletes with MTSS. The "inflammatory cells" reported by Johnell et al. could depict collagen degeneration, which would fit with findings in other fasciae in the human body, and with tendons.[41-44]

Cytokine cells like tumor necrosis factor-alpha (TNF-α), interleukine-1 beta (IL-1β)

and interleukine-6 (IL-6) stimulate pro-inflammatory and anti-inflammatory cells like leukocytes and mast cells. TNF-α, IL-1β and IL-6 cells could form a noxious stimulus for nociceptors in the fascia. This may have a similar mechanism as reported in tendinopathy.[45] In brief, these cells may facilitate synaptic transmission in nociceptors; they have been associated with increased Aδ and C-fibre firing.[46] This process could explain the initial shin soreness/pain after exercise. It does not explain the loading dependent pain; i.e. pain getting worse with loading.

8.2.3. MECHANICAL ALLODYNIA

Many athletes experience an onset, or increase, of pain while performing sporting activities and activities of daily living (chapter 5). Pain during loading is suggestive of mechanical allodynia. Allodynia is defined as "pain in response to a non-noxious stimulus".[19,20] This means that usual painless loading activities become painful. There are several mechanisms through which non-noxious stimuli can induce nociception in a state of mechanical allodynia. Initially, this may work through pain modulation; e.g. the central nervous system allows stimuli from certain nociceptors to register more easily by increasing the excitability of the nociceptor terminal membrane.[30] Over time this may lead to modification of the pain system; e.g. phenotype-switch of Aβ fibres; instead of delivering proprioceptive information, mechanoreceptors change to nociceptive-like fibres. Other examples through which mechanical allodynia may occur are "wind-up of action potential firing in Aδ or C-fibers" and sprouting of Aβ fibers to spinal areas designated for nociceptive input.[20] It has been suggested that this mechanism is physiogenic in order to protect homeostasis,[32] however, they may become maladaptive if nociceptors keep firing action potentials where there is no actual threat of tissue damage.

There are multiple ways through which bone mechanosensation (and nociception in a state of mechanical allodynia) may work. Low-threshold sensory nerve endings sense mechanical distortion in the cellular environment. Mechanical forces deform the mineralised cellular environment leading "to strain across the cell's substrate, pressure in the intra-medullary cavity and within the cortices with transient pressure waves, shear forces through cannaliculi which cause drag over cells, and dynamic electric fields as interstitial fluid flows past charged bone crystals".[38] Mechanical sensing in the periosteum and bone marrow may also contribute to nociception in this model. The periosteum is densely innervated with sensory nerve endings and is particularly susceptible to mechanical distortion. Intra-cortical pressure may be sensed by mechanosensors in the periosteum and bone marrow.[47] Periosteal oedema may cause mechanical distortion in the periosteum and set of Aβ fibers and contribute to mechanical sensation.

Mechanosensation in the crural fascia occurs through Pacini and Ruffini corpuscles and free mechanoreceptors. They signal fascia stretch and cause Aβ fibers to start firing action potentials.[27]

Taken together, loading would give proprioceptive input in normal circumstances. How-

ever, these mechanosensors may contribute to nociception in a state of allodynia.[20, 30]

Pain to touch is another clinical pain phenomenon in MTSS worth mentioning. Forty-four percent of the athletes with MTSS reported to have pain to rubbing the shin (unpublished data from chapter 7). This could be regarded as allodynia in the periosteum and/or referred allodynia in the skin.[20]

8.2.4. CENTRAL PAIN MECHANISMS AND PATHOGENIC ADAPTATIONS IN MTSS

There are no studies that investigated pain mechanisms in MTSS. A recently published report in Achilles tendinopathy suggests that an altered endogenous central pain modulation may play a role in long-standing sports injuries.[48] This study showed that pain was inhibited to a lesser extent by the central neural system. Whether central pain modulation is altered in athletes with MTSS remains to be investigated.

This is a brief summary of how nociception and clinically expressed pain symptoms in MTSS could be explained. There is a need for a comprehensive literature study into pain mechanisms in MTSS. Future studies should investigate which pain mechanisms play a role in MTSS. If there proves to be a variety in pain profiles in athletes with MTSS, it may be worthwhile to investigate the relationship between 'pain profiles' and outcomes over time.

8.2.5. CURRENT UNDERSTANDING:

- There is little understanding about pain mechanisms in athletes with MTSS.
- Osteoclasts and microcracks may contribute to initial nociception in nociceptors in the tibia.
- Collagen degeneration may cause cytokines to trigger signals in nociceptors in the cural fascia.
- Mechanical allodynia could explain load-depended pain in MTSS.
- To what extent an altered central pain modulation plays a role in MTSS is presently unclear.

8.2.6. RECOMMENDATIONS FOR RESEARCH

- There is a need for a comprehensive review on possible pain mechanisms in MTSS.
- Central pain modulation should be investigated in MTSS. Measuring pain pressure threshold in the MTSS area, while performing the cold pressor test, could elucidate on (altered) central pain modulation.

8.3. DIAGNOSIS

Previous studies into the diagnostics of MTSS used the clinical diagnosis as the gold standard while investigating the accuracy of imaging techniques.[49, 50] In this approach

the diagnostic accuracy will always be lower than the clinical diagnosis. For conditions with an unknown or equivocal pathology, such as MTSS, this seems not to be a logical approach. Rather than clarifying the patient's condition, imaging seems to contribute to uncertainty - i.e. when 'abnormalities' are falsely related to the condition. There is a need for a paradigm shift in diagnostic research for conditions where the pathology is unclear.[51] Clinical conditions for which the pathogenesis is unclear, such as MTSS, should be diagnosed clinically. Imaging may be used to rule out other entities with a known pathogenesis (e.g. stress fractures, or suspicion of another rare condition like osteosarcoma, i.e. if there is doubt in the source of lower leg pain).[52]

To the best of our knowledge, we are the first to have investigated the reliability of making the diagnosis of an overuse sports injury clinically. In Chapter 3 we investigated the inter-rater reliability of making the diagnosis of MTSS, based on history and physical examination (fig 1).[53, 54] In addition, we examined if clinicians were able to reliably identify concurrent lower-leg injuries, as this may be important for clinical trials in which multiple clinicians assess candidates for the presence of MTSS. We found an almost perfect reliability of making the diagnosis MTSS clinically. We also demonstrated that multiple clinicians are able to reliably identify concurrent lower leg injuries, which supports the use of multiple clinicians in assessing candidates with lower leg pain for MTSS trials.

In our study there were no athletes with lower leg pain in which the presence of a tibial stress fracture was suspected. We are aware that in other populations (e.g. military), or in other geographical areas (e.g. Australia, Great Britain, Israel and the USA) tibial stress fractures are more common.[55-58] Future studies should investigate to what extent this may affect the reliability of making the diagnosis of MTSS clinically.

Making the diagnosis MTSS clinically may fall short once the pathogenesis of MTSS is known. Imaging may then be more appropriate to confirm the diagnosis of MTSS in clinical practice. There are three requirements for this approach to be feasible:

- the known pathogenesis can be detected upon non-invasive imaging of the affected area;
- correct classification of the affected tissue should lead to a clinically, patient-relevant, improvement of the treatment pathway when compared to a misclassification of the condition;
- benefits should weigh-up to adverse outcomes and costs associated with imaging.

8.3.1. CURRENT UNDERSTANDING:

- The diagnosis MTSS is made clinically, based on history and physical examination
- We found almost perfect reliability for making the diagnosis MTSS clinically (Chapter 3)
- There is a limited place for imaging; when a known pathology is suspected, e.g. a tibial stress fracture or a tibial osteosarcoma
- Implications for clinical practice:
- MTSS should be diagnosed based on history and physical examination.

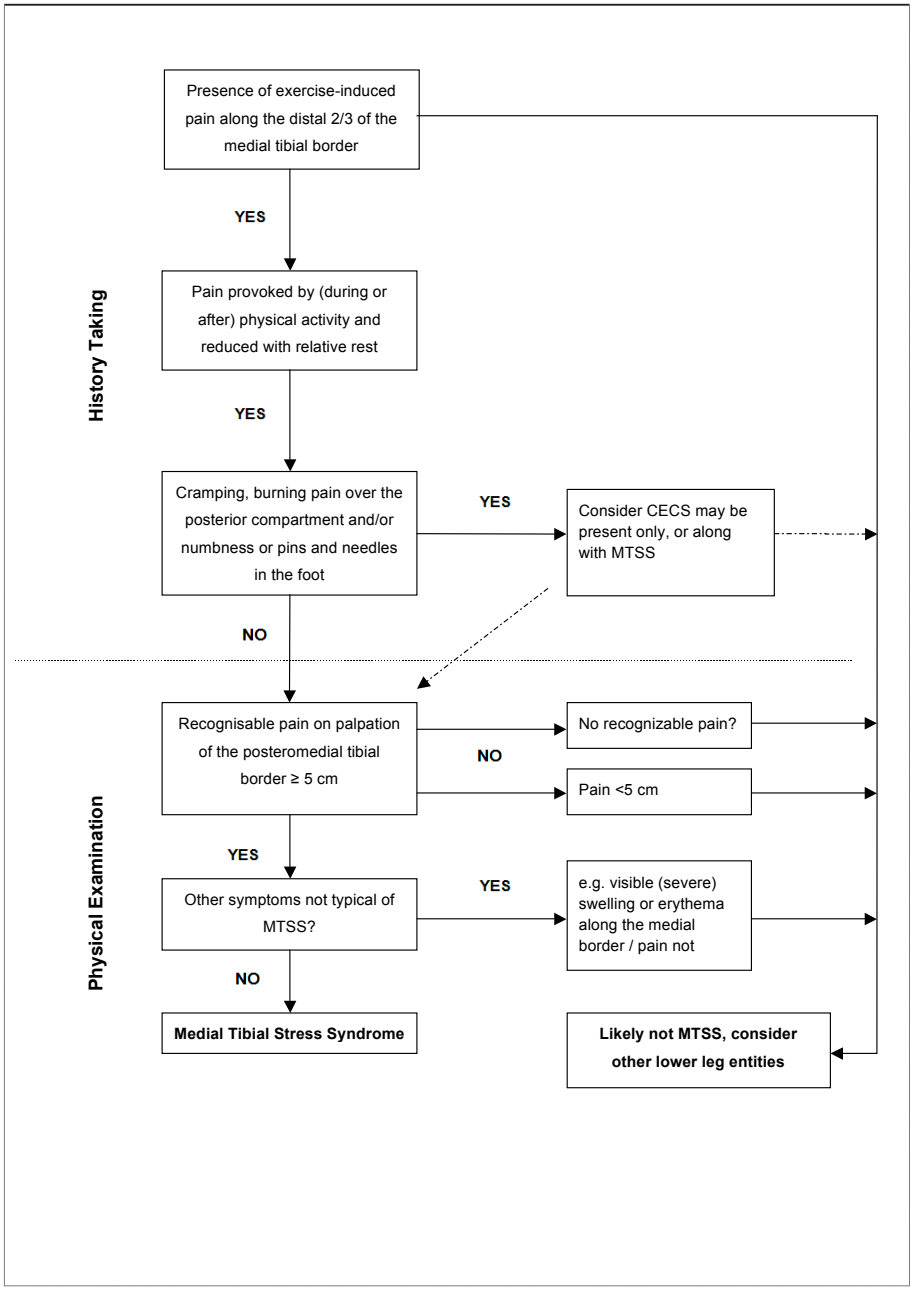

Figure 1. History taking and physical examination tool for lower leg pain in clinical practice.

MTSS = medial tibial stress syndrome, CECS = chronic exertional compartment syndrome

8.3.2. RECOMMENDATIONS FOR FUTURE RESEARCH:

- Clinical trials on MTSS should use the clinical diagnosis as their inclusion criterion.
- Future studies should investigate if the clinical diagnosis MTSS can be made reliably in military populations, and in other geographical areas where tibial stress fractures are more common than in The Netherlands.

8.4. PROGNOSIS

Prognostic factors are of importance in the management of MTSS. Few studies have looked into prognostic factors for MTSS. One controlled study suggests that females need a longer time to recover from MTSS; a mean of 89 days to recovery (defined as being able to run for 18 consecutive minutes) versus 64 days for men.[59] In the same study, age and duration of symptoms were not associated with time to recovery. The second study looked at the relationship between the presence of periosteal and bone marrow oedema, upon magnetic resonance imaging, and time to recovery. If bone marrow oedema was present, the mean recovery time was 52 days whereas it was 78 days for when no bone marrow oedema was present. Similarly, the presence of periosteal oedema was associated with a quicker recovery: 44 days with periosteal oedema versus 78 days for those without.[60] It could be that bone marrow and periosteal oedema represent a bone remodelling process, which may explain the faster recovery.[61, 62] It has not been reported how much of the variance in time to recovery is explained by these variables, and no data on the accuracy of this prediction are provided. This makes it difficult to interpret how clinically useful MRI's are in providing the patient with a prognosis. Therefore, it cannot be recommended to make MRI's in order to provide patients a prognosis yet. New studies should evaluate if MRI's are of prognostic value or could predict treatment response. MRI's should be studied alongside clinical variables when assessing its prognostic value, as shown by a recent study of acute hamstrings.[63]

Moen et al. studied the prognostic value of the Sports Activity Rating Scale (SARS) and the Lower Extremity Function Scale (LEFS), two measures to evaluate activity levels.[60] Combined they explained 54% of the variance in time to recovery (defined as being able to run 18 consecutive minutes on a pace that speaking becomes difficult, with a maximum pain of 4 on a 1-10 pain scale). Although this is a relatively high percentage for two measures it leaves much uncertainty for an accurate estimation of time to recovery in clinical practice.

Meters run on a treadmill, another measure to evaluate activity levels in athletes with MTSS, was not associated with time to recovery.[59] Presently, we do not fully understand the contradiction between the SARS and LEFS on the one hand, and the treadmill test on the other. One would expect that the meters run without pain represents the capacity of the tissue to tolerate load. The fact that no association was found questions the importance of tissue capacity as an individual variable in the prognosis of MTSS. However, how well athletes are capable to match loading to loading capacity may be important in the prognosis of MTSS. This could be regarded as a behavioural factor.

Studies in other long-standing musculoskeletal injuries, such as low back pain, shoulder pain and patellofemoral pain syndrome have shown that psychosocial and behavioural factors are important in the prognosis of injuries.[64-66] To the best of our knowledge, no studies investigating psychosocial and behavioural factors exist in the field of MTSS. It's our experience that many athletes seem to ignore their symptoms causing them to get worse, likely affecting their prognosis negatively. There is a need for explorative studies that investigate the most common beliefs among athletes with MTSS, and how this may affect the way they deal with their injury. Psychosocial factors, e.g. the influence of trainers/coaches/parents, should also be considered while exploring how athletes cope with MTSS. Then, these factors' prognostic value could be investigated alongside biomedical factors.

8.4.1. CURRENT UNDERSTANDING:

- Athletes with periosteal and bone marrow oedema upon MRI assessment recover faster than those without.
- Available studies suggest it will take 40 - 120 days, to run 18 consecutive minutes with less than 4 on a 1-10 pain scale. However, it seems likely that the duration of return-to-sport is much beyond this definition of recovery for most athletes.
- Women may need more time to get better than men.
- Studies suggest that there is no association between age, duration of symptoms, meters run on a treadmill and time to recovery.

8.4.2. IMPLICATIONS FOR CLINICAL PRACTICE:

- Presently, it is not possible to provide patients with an accurate prognosis of how long it will take to return-to-sport without pain and discomfort.
- Clinicians should be aware that women may need more time to get better than men.

8.4.3. RECOMMENDATIONS FOR RESEARCH:

- Explorative qualitative studies should investigate common beliefs among athletes with MTSS, and how these beliefs may affect the way they deal with their injury.
- Biomedical, psychosocial and behavioural factors should be investigated jointly to identify the most important prognostic factors for MTSS.
- The prognostic value of MRI could be further investigated, jointly with clinical parameters to assess its additive value to the measurement of clinical parameters.

8.5. TREATMENT

Previous to this thesis' start there was no clarity regarding the evidence for any interven-

tion in the treatment of MTSS. As outlined in paragraph 1.5., Chapter 1, there were three RCT's published before 2009 and several new controlled studies emerged between 2009 and 2014. In this thesis, we performed a systematic review into the effects of any intervention in the treatment of MTSS. We found there is no treatment that has proven to be effective (Chapter 4). Studies investigating low-energy laser treatment, stretching and strengthening exercises, sports compression stockings, leg braces and pulsed electromagnetic fields showed no treatment effect compared to other treatments. There were studies that suggested that iontophoresis, phonophoresis, ultrasound therapy, ice massage, periosteal pecking and extracorporeal shockwave therapy (ESWT) were effective when compared to control groups (Level 3 - 4 of Evidence). All studies had a high risk of bias and therefore we were not able to make recommendations regarding their application in clinical practice.

There are two randomised controlled trials that became available only recently. The first investigated the effect of focused ESWT versus sham shockwave in a small trial (N = 28). They found no difference between groups, with regards to pain felt during pressure on muscle and bone, pain while running, participation level and on the global rating of change scale.[67] Given the low power of the study it would have only been able to identify a large clinical difference between the two treatments. This study, as is common in the field of MTSS, had a serious lack of reporting and used non-validated outcome measures. It was stated that the randomisation procedure, patient and outcome assessor were blinded but no description on how blinding was performed was provided (fig 2).

The second study investigated the effect of a gait-retraining running program and corticosteroid injection (20mg of Kenalog (Triamcinolone acetonide) and 1% of 1ml lidocaine) in addition to a 3-phased standardised rehabilitation program, which was compared to a control group that received the 3-phased rehabilitation that gradually increased load from non-weight bearing to return to military duty.

The intervention group (N = 32) received one injection into the most painful site along the diffusely painful posteromedial tibial border, and pain on palpation as measured on a visual analogue scale at 2, 4 and 26 weeks, rehabilitation time and plantar pressure values (non-specified) were obtained. The control group (N = 34) received a 3-phased standardised rehabilitation program only. The intervention group had less pain on all follow-up measurements. In addition rehabilitation time was significantly shorter in the intervention group compared to controls (38 (SD 10) versus 86 days (SD 20)). Concurrently, plantar peak pressure decreased in the intervention group, whereas they remained the same in the control group, suggesting that the running-retraining was effective.[68]

As promising as these findings seem, there are multiple limitations to take in consideration. The study did not evaluate effects in the mid and long term and did not report on adverse effects. Risk of bias should be considered as well (fig 2). Firstly, it was not described if the allocation procedure was concealed (selection bias), if the outcome assessor was blinded (detection bias), and the lost-to follow rates where 12.5% in the intervention group and 47% in the control group (attrition bias). Reporting bias seems

present as the observation of adverse effects was described but no results were reported. To what extent this is true for other outcomes cannot be verified. No protocol, published prior to the commencement of the study, could be found in trial registers.

In this thesis (Chapter 5) we presented two cases that received corticosteroid injections (in total 1ml Kenacort 40 mg/ml and 3ml Lidocaïne 2%) near the posteromedial tibial periosteum. They suffered from atrophy of subcutaneous fat tissue and depigmentation of the skin. In these two patients no satisfactory effects of corticosteroid injections were observed: the first athlete chose to have a fasciotomy and the second athlete still had pain after the injections, although reported the pain to be less than before. Given the risk of bias in the RCT by Sharma et al.,[68] the lack of knowledge where to inject and the possible adverse effects, the use of corticosteroid injections should be practised with caution.

An update for our systematic review (Chapter 4) may be warranted for scientific purposes, however, for clinical purposes little would change. There is a serious need for high quality studies in the field of MTSS, this could be improved by reporting according to guidelines such as CONSORT and by incorporating methodological procedures that allow for an unbiased estimate of treatment effect.[69]

It remains unclear which intervention is most effective for MTSS. One can question whether a RCT would be the most logical step at present. There is still little understanding about the pathogenesis, pain mechanisms and prognostic factors in MTSS. It seems that first prospective cohort studies are warranted, in which patients with MTSS are followed over time. This could help to establish a reference group, elucidate on the pathogenesis, and enable the investigation of prognostic factors in MTSS.

In the absence of a known pathogenesis for MTSS it seems not logical to target structures with a specific intervention, like corticosteroids injections; where would we need to set the injection?

Given that there is no hard evidence for tissue damage in MTSS, and its primary cause seems a mismatch between loading and loading capacity, it seems most logical to comprehensively target the injury with a graded loading program. In this program the balance should be restored and loading should be used to expose the athlete to more loading in a step-by-step fashion. A graded program that incorporates loading and exercises focused on bone and fascia seems to make most sense.

Waldorf et al. suggests that weight-bearing could be beneficial for bone rehabilitation. They investigated the effects of weight-bearing compared to a hind limb suspension group, and compared to a hind limb suspension with intermittent weight-bearing following damage-inducing loading. The authors report that the weight-bearing group showed a significant increase in osteoblast-activity, along with a concurrent reduction of microdamage, when compared to the other groups that showed a lack of osteoblast-activation.[70] This suggests that weight-bearing activities may improve symptoms and limitations for athletes with MTSS. Plyometric exercises have also been suggested to enhance bone formation.[74] These could be considered in a program that aims to

gradually increase tibial bone loading.

It seems logical to stimulate the physiogenic properties of the fascia, in addition to targeting the tibial bone. This could be achieved by applying stretch through contracting the deep ankle plantar flexors, as per the theory of Bouché and Johnson.[3, 72] Strengthening exercises for the plantar flexors have been studied along a gradual running program by Moen et al.[73] There was no positive effect for these exercises when compared to a graded running program alone, or a graded running program and a lower leg stocking on time to running 18 consecutive minutes with minimal pain. It is unclear if the athletes were instructed to reduce their usual loading while following the graded running and exercises program. Hence, the exercises may have contributed to overloading the shin structures even more, and consequently, delayed time to recovery.

8.5.1. MANAGEMENT; HOW TO PREVENT THE RETURN OF SHIN PAIN?

Preventing subsequent episodes of symptoms associated with MTSS is desirable. Secondary prevention is ideally a continuous process of risk assessment and - correction that will be carried out beyond the duration of medical treatment. We will focus on the role of the clinician in targeting modifiable risk factors while treating athletes with MTSS.

MTSS is associated with a number of modifiable and non-modifiable risk factors. Studies investigating risk factors of MTSS have primarily investigated intrinsic, biomedical factors. Newman et al. and Hamstra-Wright et al. recently reviewed the current body of literature regarding the risk factors for MTSS.[74, 75] They report evidence for the association of the female gender, previous history of MTSS, fewer years of running experience, orthotic use, increased body mass index, increased pronation (i.e. increased navicular drop test), increased ankle plantar flexion range of motion, and increased external hip range of motion in males with MTSS.[74, 75] This body of evidence suggests it is important to focus on modification of these factors, when possible. However, most of the findings are derived from case-control studies or from prospective studies with high risk of bias.

New evidence shows that the degree to which load meets load bearing capacity is highly important in the risk assessment of overuse injuries, but this has not been investigated in relation to MTSS. The so-called 'training spikes', acute training load relative to the chronic load is associated with the onset of injuries in basketball, cricket, football, Australian football, and rugby.[e.g. 76-82] Gabbett and co-authors showed that an acute workload (last 7 days) ≥ 1.5 of the chronic workload (last month) increases the risk of an injury by 2-4 times in the subsequent 7 days. In addition, they demonstrated that as long as loads were kept within a moderate zone (i.e. an acute:chronic workload ratio within the range 0.85 - 1.35) high chronic loads were associated with the lowest risk of injury.[83] This suggests that the simple paradigm of high loads leading to injuries is not correct. Rather the recent load relative to the load an athlete is used to performing is relevant. It seems best to keep acute loads within 10% of the chronic workload.[84] Studies should investigate if this phenomenon holds for populations in which MTSS frequently occurs (e.g. runners, sports academies, military personnel). This should be

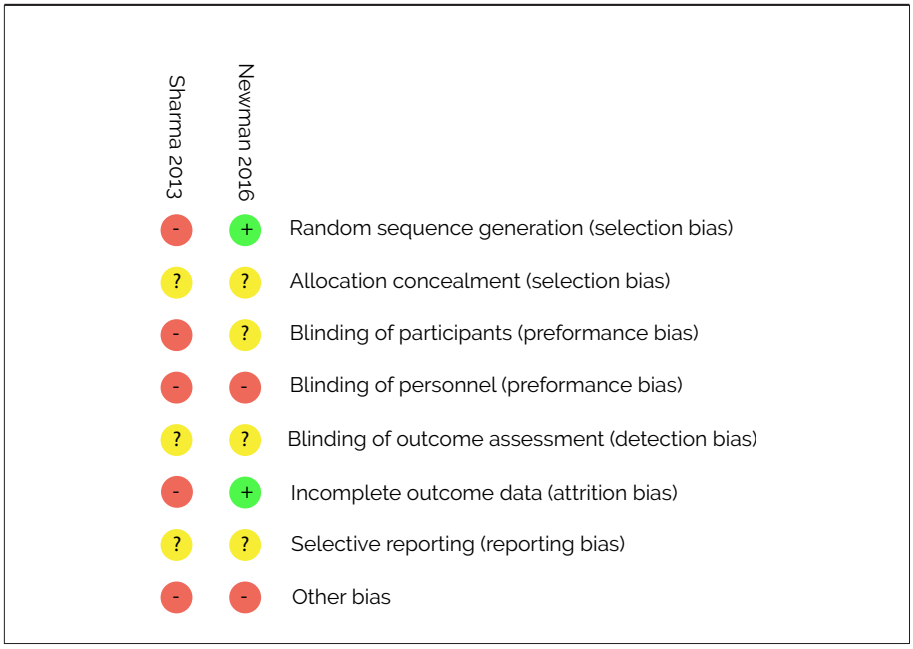

Figure 2. Risk of bias in two newly available RCT's[67, 68]

investigated alongside factors previously identified to explore the most important risk factors for MTSS.

Meanwhile, clinicians could evaluate if these spikes might frequently occur in training situations and educate athletes how to monitor their training load. Workload can be evaluated by measures of internal loads or external loads. Internal loads measure the 'relative physiological and psychological stress imposed' (e.g. blood lactate, recovery/stress/wellbeing perception).[84] External loads 'are the quantified loads performed by the athlete' (e.g. training frequency, time, running distance covered, high speed distance etc.).[83] Athletes could be advised which instruments to self-monitor their training load while returning to their sports activities.

8.5.2. CURRENT UNDERSTANDING:

- Studies investigating extracorporeal shockwave therapy, iontophoresis, phonophoresis, ultrasound therapy, ice massage and periosteal pecking show a positive effect on time to recovery and pain (level 3 - 4 of evidence) (Chapter 4).
- Lower leg braces, calf strengthening and stretching exercises, sports compression stockings in addition to a gradual running program; low-energy laser; pulsed electromagnetic fields seem not to be effective in the treatment of MTSS (level 3 of evidence) (Chapter 4).
- Commonly used interventions, such as insoles, massage therapy, (kinesio) taping, acu-

puncture, or surgery (i.e. periosteal stripping, fasciotomy of the crural fascia) have not been assessed in controlled trials. Hence, there is no evidence to recommend or advise against any of these interventions.

- A recently published RCT suggests that ESWT is not effective in athletes with MTSS in terms of pain and global perceived effect (level 3 of evidence).
- A recent unpublished RCT claims that corticosteroid injections in combination with running gait-retraining is effective compared to a control group that followed a 3-phased rehabilitation program, in terms of pain and rehabilitation time (level 3 of evidence).
- We presented two cases with adverse effects after corticosteroid injections, they sustained fat tissue atrophy and skin depigmentation. (Chapter 5).
- Overall: there is no intervention proven to be an effective treatment for patients with MTSS.

8.5.3. IMPLICATIONS FOR CLINICAL PRACTICE:

- A graded tibial loading program and ankle plantar flexor strengthening exercises seem the most logical intervention, addressing the two possibly affected structures in MTSS: the tibial bone and crural fascia.
- Clinicians should evaluate athlete's workload over time and, when spikes in the athletes' training are frequently present, they should educate the athlete on how to monitor their training workload and advice them keep it within ~ 10% of their chronic workload.

8.5.4. RECOMMENDATIONS FOR FUTURE RESEARCH:

- RCT's may not be the most urgent priority in this research field, given the lack of pathology, pain physiology and factors that enhance or delay recovery.
- Large case series that observe treatment outcomes and prognostic factors over time may a good first step towards the performance of RCT's.
- In the future, interventions should be studied in well-performed RCT's that follow the CONSORT statement when designing the study and reporting the findings.
- RCT's should incorporate long follow-ups, at least 12 months using the MTSS score, to allow for a proper investigation of mid- and long-term effects.

8.6. OUTCOME ASSESSMENT

Patient-reported outcome measures, time to return-to-recovery and the risk of re-injury are considered key outcomes in sports medicine.[85, 86] No standardised, widely-accepted approach for the assessment of outcomes in MTSS patients and research was available previous to this thesis' commencement.

Chapter 6 reports on the development on items for a new patient-reported outcome

measure specifically for patients with MTSS: the medial tibial stress syndrome (MTSS) score. Items were generated by means of the Delphi technique; experts in the field of MTSS were blinded to the other experts' contributions. In the final round of this study we sought consensus upon the items. Fifteen items were generated and consensus was reached on their possible relevance for the MTSS score. Items for the following domains were developed: 'limitations in sporting activities', 'pain while performing sporting activities', 'pain while performing activities of daily living' and 'pain at rest'. A total of 20 athletes with MTSS critiqued and subsequently confirmed the readability and comprehension of the items. In chapter 7 we report on a prospective cohort study in 133 patients with MTSS. Firstly, we reduced the item set based on item reliability and responsiveness. The final version of the MTSS score is a practical 4-item scale, which exhibits good validity, reliability and responsiveness (figure 3). It specifically measures both shin pain and limitations due to shin pain. Our analyses highlighted that the smallest detectable change for an individual was 4.82 on average, and 0.69 for the entire group. The average minimal important change was 0.69. This means that the MTSS score is well equipped to evaluate groups of patients, but may be less suitable to track individual patients. Yet, its (lack of) utility to track individual athletes should be appraised with caution. First, our methods seem to have underestimated the true reliability of the MTSS score. This is mainly due to items 3 and 4 (test-retest reliability (ICC) was 0.60 and 0.72 respectively). We used an overall anchor to determine which patients did not change between the first and second MTSS score administration. We think it is likely that athletes indicated 'unchanged' primarily based on the most important limitation to athletes; to engage in sporting activities. Anchors for each 'domain', i.e. sporting activities, activities of daily living and pain at rest, may have been more appropriate to identify 'stable patients' for each item. Secondly, we should be aware that there are a number of limitations in estimating minimal important changes for individuals. The minimal important change is dependent to both the individual change of the athletes in the sample, as much as on the magnitude of treatment effect.[87] In our study we did not control for the treatment given to patients; yet it seems that only small effects were achieved after around 70 days; 3% of the patients reported to be 'completely recovered' on the global perceived effect scale; 22% 'much improved'; 46% 'slightly improved'; 22% 'no improvement'; 5% 'slightly worse'; and 2% 'worse than ever'. This may have led to an underestimation of the instruments' ability to measure minimal important changes in individuals. Moreover, the minimal important change is based on a small sample of 29 athletes that reported 'slightly improved'. What is minimally important may also vary from athlete to athlete.

Future studies should further investigate the reliability of the items pain at rest, and pain while walking with item-specific anchors. In addition, the minimal important change should be investigated in larger populations of athletes that perceive a slight improvement while receiving treatments with known large effects.[87] Unfortunately, it was not possible to test the MTSS score using item response theory testing procedures. These methods require larger samples than we were able to include within our available time and resources.[87] We cross-culturally translated the original Dutch MTSS

score to English, by means of forward- and backward translation procedures. This language version should be cross-culturally validated before being used in English language populations.

Predictive validity is considered one of the more important types of validity for outcome measures. Predictive validity is the degree to which an instrument is able to predict future outcomes; e.g. recovery from an event/injury, or the presence or absence of a new injury. Whether this bears up for MTSS, and for the MTSS score specifically, is questionable. The MTSS score measures pain and limitations due to pain. Good predictive validity would be based on the premise that the degree of tissue damage is related to pain and limitations on the one hand, and the relationship between the degree of tissue damage and the biological recovery capacity on the other. As mentioned in the prognosis section: It is likely that other than biomedical factors play a role in the prognosis of MTSS[64-66] The possible predictive validity of the MTSS score should be assessed alongside biomechanical, psychological and behavioural factors.

8.6.1. THE MTSS SCORE: MEASUREMENT OF INJURY STATUS AS THE BETTER ALTERNATIVE FOR THE 'INJURY-RECOVERY-RE-INJURY' OUTCOME PARADIGM?

Injury, recovery, and re-injury are important concepts in injury management evaluation. Definitions for these measures have hardly been described in the MTSS literature. There are several definitions for what 'an injury' is. Initial injuries can be defined in light of 'match time loss', 'time loss', 'medical attention' and 'all complaints'.[88] The study purpose is leading when deciding which definition should be chosen. For example, 'all complaints' would be appropriate while studying the pathogenesis of MTSS (chapter 2), or determining if clinicians can reliably diagnose MTSS based on history and physical examination (chapter 3). However, if the impact of MTSS is studied, the 'match time loss' or 'time loss' definitions may be more appropriate. The 'medical attention' definition seems most appropriate while studying treatment effects in MTSS, as this resembles clinical practice best.

'When will I be able to play/run/etc. again?' is a common question asked by the athlete with MTSS. As difficult it seems to define an injury; recovery and re-injury could even be more difficult to define in overuse injuries like MTSS. Sports overuse injuries are often persistent and pain exacerbates in response to an imbalance of loading and loading capacity. Often, pain may be absent but swiftly return upon an increase of loading. This suggests that MTSS can still be latently present after symptoms have subsided. Studies in the field of groin pain and patellofemoral pain syndrome showed that overuse injuries can be very persistent, and swiftly exacerbate upon loading. For example, athletes with previous groin pain filled out the Copenhagen Hip and Groin outcome score (HAGOS) at the beginning of a new season. Upon the season's start they still had low HAGOS scores, suggesting the presence of pain and limitations due to some degree of hip and groin pain.[89] Sixty-five percent of 153 adolescents diagnosed with patellofemoral pain syndrome still suffered from knee pain 2 years after the start of a randomised controlled trial.[90] Chapter 7 suggest that this phenomenon is also

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Medial Tibial Stress Syndrome Score
Name: **Date:**

I have complaints in:

Both shins	☐
Only the left shin	☐
Only the right shin	☐

In case of complaints in both shins:

I have most complaints in:

My left shin	☐
My right shin	☐

Instructions:

- While completing this questionnaire, keep in mind the pain as you have experienced maximally over the past days, and check the answer that fits **best** this shin pain
- While completing this questionnaire, keep in mind your **shin with most** complaints.
- Please read **all** options before you select a checkbox.
- **For all questions, choose one answer per question only.**

Sporting activities

For military: Marching is considered to be a sporting activity.

1) Presently:		**P**
I perform all of my usual sporting activities	☐	0
I am forced to do less of my usual sporting activities due to pain in my shin	☐	1
I am forced to do alternative sporting activities only due to pain in my shin	☐	2
I cannot do any sporting activity due to painin my shin	☐	3

2) While performing sporting activities:

I have no pain in my shin	☐	0
I have some pain in my shin	☐	1
I have a lot of pain in my shin	☐	2
I cannot do any sporting activity due to my shin pain	☐	3

Figure 3: Medial Tibial Stress Syndrome Score, English language version

Walking

3) While walking:		**P**
I have no pain in my shin	☐	0
I have some pain in my shin	☐	1
I have a lot of pain in my shin	☐	2
I cannot walk due to pain in my shin	☐	2

Pain at rest
e.g. sitting or laying down

4) At rest, my shin is:		
Not painful	☐	0
Sensitive	☐	1
Painful	☐	2
Very painful	☐	2

Interpretation:

There are four checkboxes for each item.

The first checkbox (0 points) indicates no limitation, the final checkbox (2 or 3 points) indicates a full limitation.

The sum score is the sum of the four items. The final score ranges from 0 (no limitation) to 10 (full limitation)

Smallest detectable change, individual level = 4.80

Smallest detectable change, group = 0.69

Minimal important change, group = 0.69

Figure 3: Medial Tibial Stress Syndrome Score, English language version

present in athletes with MTSS. The median duration of complaints upon study entry was 18 months (range 0.75 - 144) in this study. These findings challenge the concept of 'recovery'.

Defining subsequent injury does not seem a logical approach in the absence of 're-covery'. A group of authors recently suggested that a subsequent new injury should be recorded when an increase in pain or limitations exceeds the normal fluctuations of chronic conditions, for example after a sudden increase in activity.[91] However, strong fluctuations in pain and limitations could be regarded as a property of the MTSS trait. There seems to be a close relationship between how well the athlete balances loading and loading capacity on one hand, and immediate perceived pain and limitations on the other.

The common 'injury-recovery-re-injury' paradigm does not seem to fit with the natural course of most overuse injuries. MTSS should be considered as a continuum of subtle states that vary between what is traditionally considered 'injured' and 'not injured' instead. Patient-reported outcome measures in general - and the MTSS score for athletes with MTSS specifically - should be used to measure these states. Athletes will still ask 'how long will it take for me to play/run/etc again?' in clinical practice. It seems best to explain the natural course of MTSS and that there is more subtlety to the definition 'recovery' than meets the eye. A practical example is a clinician who explains to a running athlete that running for 30 minutes without pain during and after running is good news, but further progression requires small steps (<10% load change per week) otherwise the pain may return or aggravate if it was still present. This slow progression of loading seems vital to prevent regression of the athlete's MTSS' state.

Studies following athletes with MTSS at multiple time points for many years are need-ed to monitor the normal course of the injury and assess which prognostic factors contribute to improved outcomes for athletes with MTSS. The MTSS score should play a prominent role in evaluation of injury course and prognostic factors. This line of research could enable the delivery of information to patients regarding treatment expectations, and planning of future treatment studies.

8.6.2. CURRENT UNDERSTANDING:

- The MTSS score is a valid, reliable and responsive patient-reported outcome measure and should be used to assess intervention outcomes, instead of traditional outcome measures 'recovery' and 're-injury' (Chapter 6 and 7)
- The MTSS score should be used as an alternative to the 'injury-recovery paradigm'; clini-cians should be aware of the chronic nature of MTSS. The MTSS score is the best available instrument to track athletes with MTSS over time.

8.6.3. IMPLICATIONS FOR CLINICAL PRACTICE:

- The MTSS score can be used in daily practice to measure injury severity. However, changes in individual patients should be interpreted with caution. Individual relevant outcomes in

MTSS patients may not be detected by the MTSS score.

8.6.4. RECOMMENDATIONS FOR FUTURE RESEARCH:

- The MTSS score should be used as a primary outcome measure in clinical studies into MTSS
- The MTSS score should be cross-culturally translated to, and validated in, other languages before it can be used in other geographical areas. The English version of the MTSS score should be validated in English speaking populations.
- Future studies should investigate the predictive validity of the MTSS score alongside bio-mechanical, psychosocial and behavioural factors.

8.7. RETURN-TO-SPORT: A DECISION?

Return-to-sport is traditionally regarded as a decision that is made on a set of criteria.[92] For example, in hamstring injuries athletes can return-to-sport once they are pain-free on a set of physical and functional tests and the athlete feels psychologically ready.[93] Deciding if an athlete can return to sport is presented as a dichotomous yes/no in this paradigm. Recently, experts reached consensus on definitions for return to sport.[86] In their opinion, return-to-sport can be considered in light of success of participation, performance and absence of re-injury. Return-to-sport is considered a "continuum paralleled with recovery and rehabilitation".[86] They emphasised that return-to-sport should follow "a graded, criterion-based progression...".[86] This can be considered a paradigm shift, from a return-to-sport decision to criteria-based load management. This seems a more logical approach to return-to-sport for athletes with an overuse injury like MTSS.

Clinical studies in the field of MTSS have hardly report which criteria are used for athletes to return to sport. Moen et al. describe that athletes were advised to pick up on their sporting activities after finishing the final phase of a graded running program, meaning being able to run 18 consecutive minutes with a visual analogue score ≤ 4, on a 1-10 scale.[59] Nissen et al. report that military participants with MTSS were physically examined after 14 days of treatment. It was evaluated if the patient could return to duty, without further specifying criteria.[94] Other studies did not describe when athletes were able to pick up on their sporting activities.[67, 95-101]

Only a few studies report on the criteria used to have athletes progressing their loading. The studies by Moen used the criterion "4 or less pain on a 1-10 scale" to have athletes progressing to the next phase of a gradual running program.[59, 73] This seems a logical approach in the consideration of return-to-sport. The success of a speedy return to participation and performance in MTSS, and absence of a deterioration of injury status, seems closely related to the extent the athlete is able to balance loading and loading capacity successfully. Balancing loading and loading capacity should be a continuous process of evaluation of pain during and after loading, throughout the

full rehabilitation and return-to-sport process. Which criteria for pain during and after loading could be followed best, is presently unknown. Future studies could focus on testing these criteria: e.g. should we use a 2, 4 or 6 on a 0-10 visual analogue scale to progress loading? Are there any other measures (more) appropriate as a criterion for load progression? These criteria should be evaluated in light of future MTSS scores.

8.7.1. CURRENT UNDERSTANDING:

- Return-to-sport should be a gradual, criteria-based, load progression process in contrast to a hard yes/no decision.

8.7.2. IMPLICATIONS FOR CLINICAL PRACTICE:

- We advise clinicians and athletes to gradually progress loading, based on a 4 or lower on the visual analogue scale. Return-to-sport participation and performance should be gradually, based on the pain-response to loading.

8.7.3. RECOMMENDATIONS FOR FUTURE RESEARCH:

- Future studies should evaluate which criteria are most valid in light of improvement and deterioration of the MTSS score.

8.8. CONCLUSION

The work in this thesis showed that MTSS is probably not a posteromedial tibial periosititis. There is currently no good evidence for tissue damage in MTSS. It should be considered a clinical pain syndrome and diagnosed clinically. We showed that MTSS can be diagnosed reliably based on history and physical examination. We also found that there is no good evidence for any intervention in the treatment of MTSS. Gradually exposing the athlete to loading seems most appropriate. We developed a new patient-reported outcome measure for athletes with MTSS: the MTSS score. We showed that the MTSS score is valid, reliable and responsive.

Although we hope this work has contributed substantially to the field, there is still a long way to go. “One step at a time is good walking” (Chinese Proverbs).

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Summary

Medial tibial stress syndrome (MTSS) is one of the most common leg injuries among jumping and running athletes. Despite that MTSS is being frequently seen in sports medicine and physiotherapy practices, little evidence exists for how to best manage it. In **CHAPTER 1** the current knowledge regarding the pathogenesis, diagnosis, treatment and outcome assessment of MTSS is discussed. The most important gaps in the body of knowledge, and how this thesis strives to address these, are discussed.

CHAPTER 2 reports on a case-control study in dancers with and without MTSS. It was investigated if the presence of periosteal, tendinous and bone abnormalities, observed upon musculoskeletal ultrasonography were associated with MTSS. We did not find any ultrasonographic differences between dance students with and without MTSS. The study showed that periosteal and tendinous 'abnormalities' are very common in dancers and do not differentiate those with and without lower leg pain. None of the participants had the textbook description of a periostitis; the combination of periosteal vascularisation, -thickening and -edema. The conclusions were that ultrasound cannot be used to diagnose MTSS and that the traction-induced periositis theory seems an unlikely explanation of the pathogenesis of MTSS.

The diagnosis MTSS is commonly made clinically. MTSS is a clinical syndrome with unknown underlying pathology, which supports the approach of making the diagnosis based on history and physical examination. In **CHAPTER 3** it was investigated if making the diagnosis MTSS clinically is reliable. In addition, it was examined if the presence of possible co-existing lower-leg injuries could be identified reliably. Two clinicians assessed athletes with non-traumatic lower leg pain. They used a standardised history and physical examination to diagnose MTSS. The results were that making the diagnosis MTSS clinically has almost perfect reliability. In addition, clinicians were also able to reliably identify co-existing lower leg injuries. The conclusion was that the clinical diagnosis of MTSS can be made reliably based on history and physical examination.

Only three trials investigating treatments for athletes with MTSS were reported up to 2009. Between 2009 and 2012 a number of new trials were published. In **CHAPTER 4,** the current evidence regarding the treatment of MTSS was reviewed systematically. Published and unpublished trials investigating treatments in patients with MTSS were searched for. The conclusion was that none of the studies were sufficiently free from bias to choose between the many treatments proposed in clinical practice.

CHAPTER 5 reports on a case series of two athletes treated with corticosteroid injections. The patients in this report experienced adverse effects after corticosteroid injections; depigmentation of the skin and atrophy of the subcutaneous fat tissue. Furthermore, they had little to no beneficial effect of the treatment; months later both cases still experienced shin pain. There seems to be no indication for corticosteroid injections, also given the associated risks of adverse effects.

No patient-reported outcome measure existed to evaluate outcomes in athletes with MTSS, prior to this thesis' commencement. **CHAPTER 6** reports on a Delphi study to

generate items for a new patient-reported outcome measure for athletes with MTSS: the Medial Tibial Stress Syndrome (MTSS) score. In this study experts in the field of MTSS were consulted and consensus upon the relevance of the items was reached. Patients with MTSS were consulted to provide feedback on the initial items of the MTSS score. A total of 15 items were generated.

CHAPTER 7 reports on a prospective cohort study in multiple sports medicine and military centres in The Netherlands. In this study, the items developed in the Delphi study were tested (chapter 6). Firstly, the item set was reduced based on test-retest reliability and the responsiveness analysis. Subsequently, the final MTSS score was validated; it was tested for its validity, reliability and responsiveness. The MTSS score showed good validity, reliability and responsiveness and is particularly suitable for following groups of patients. It may be less appropriate to use the MTSS score to follow individual athletes.

The thesis finishes with a general discussion of our findings in light of the body of knowledge in

CHAPTER 8. The clinical implications and recommendations for research regarding the pathogenesis, pain, diagnosis, prognosis, treatment, outcome assessment and return to sport in athletes with MTSS are discussed.

Nederlandse Samenvatting

Summary in Dutch

Het mediaal tibiaal stress syndroom (MTSS) is een veelvoorkomende blessure bij sporters die veelvuldig springen en rennen. MTSS wordt vaak gezien in sportmedische en sportfysiotherapeutische centra, desondanks is er weinig evidentie voor hoe we sporters met MTSS het beste kunnen behandelen.

In **HOOFDSTUK 1** worden de huidige inzichten omtrent de pathogenese, diagnose, behandeling en uitkomstbepaling van MTSS besproken. De belangrijkste kennisvragen, en hoe dit proefschrift deze vragen probeert te beantwoorden, werden belicht.

In **HOOFDSTUK 2** werd de aanwezigheid van periostale, tendinogene en ossale abnormaliteiten in een danspopulatie onderzocht. In deze studie werden dansers met en zonder MTSS met musculoskeletale echografie onderzocht. Er werden geen verschillen tussen de groepen gevonden. Periostale en tendinogene abnormaliteiten bleken prevalent bij dansers en niet gerelateerd aan MTSS. Bij geen van de deelnemers was een "tekstboek-beschrijving" voor periostitis zichtbaar op echografie: een combinatie van periostale vascularisatie, verdikking en oedeem. Gezien deze bevindingen lijkt een periostitis een onwaarschijnlijke verklaring voor de pathogenese van MTSS.

De diagnose MTSS wordt doorgaans gesteld op basis van anamnese en lichamelijk onderzoek. MTSS is een pijnsyndroom zonder bekend pathogeen substraat; het stellen van de diagnose MTSS op klinische gronden is daarom de meest logische wijze van diagnosticeren. In **HOOFDSTUK 3** werd onderzocht of deze wijze van diagnosticeren betrouwbaar is. Ook werd bekeken of mogelijke co-existente onderbeenblessures betrouwbaar geïndentificeerd konden worden. Twee (para-)medici onderzochten sporters met niet-traumatische onderbeenpijn. Zij gebruikten een gestandaardiseerde anamnese en lichamelijk onderzoek om MTSS te diagnosticeren. Er werd gevonden dat MTSS met bijna perfecte betrouwbaarheid op klinische gronden gediagnosticeerd kan worden. (Para-)medici waren tevens in staat om co-existente onderbeenblessures betrouwbaar te identificeren. Er werd geconcludeerd dat MTSS betrouwbaar kan worden gediagnosticeerd op basis van de anamnese en lichamelijk onderzoek.

Slechts drie gerandomiseerde behandelstudies waren bekend in 2009. Tussen 2009 en 2012 verscheen een meervoud aan nieuwe studies. In **HOOFDSTUK 4** werd een systematische literatuurstudie naar de behandeling van MTSS gerapporteerd. In deze literatuurstudie werd gezocht naar gepubliceerde en ongepubliceerde onderzoeken. De conclusie was dat geen van de onderzoeken in voldoende mate vrij waren van bias om een behandeling aan te bevelen voor de klinische praktijk.

HOOFDSTUK 5 verhaalt over twee patiënten die behandeld werden met pre-tibiale corticosteroïden injecties. De patiënten ondervonden ongewenste effecten in de vorm van depigmentatie van de huid en atrofie van subcutaan vetweefsel. Tevens ervaarden zij geen tot nauwelijks een positief effect in termen van pijn en functioneren. Er lijkt geen behandelindicatie voor corticosteroiden injecties, mede gezien deze bijwerkingen.

Voor aanvang van dit proefschrift bestond er geen patiënt-gerapporteerde uitkomstmaat (PROM) voor sporters met MTSS. In **HOOFDSTUK 6** werd het proces om items voor een nieuwe PROM te ontwikkelen, door middel van een Delphi studie, beschreven. In dit

onderzoek werden experts op het gebied van MTSS geconsulteerd en werd er naar consensus gestreefd over de relevantie van de items. Patiënten met MTSS werden gevraagd om feedback te geven op de items voor de nieuwe PROM. In totaal werden er 15 items gegenereerd voor een nieuwe PROM voor MTSS: de Mediaal Tibiaal Stress Syndroom (MTSS) score.

HOOFDSTUK 7 doet verslag van een prospectieve cohort studie in meerdere sportmedische en militair medische centra in Nederland. In deze cohort studie werden de in de Delphi studie (hoofdstuk 6) ontwikkelde items getest. Eerst reduceerden we de item set op basis van de test-hertest betrouwbaarheid en de responsiviteit van de individuele items. Vervolgens werd de definitieve MTSS score gevalideerd; de validiteit, betrouwbaarheid en responsiviteit werd onderzocht. De MTSS score bleek valide, betrouwbaar en responsief, en vooral geschikt om groepen van patiënten te volgen over tijd. De MTSS score lijkt minder geschikt om individuele patiënten te volgen.

De thesis werd afgesloten met een algemene discussie van de bevindingen in licht van de huidige inzichten, in **HOOFDSTUK 8**. De implicaties voor de klinische praktijk werden bediscussieerd en er werden aanbevelingen voor toekomstig onderzoek gedaan betreffende de pathogenese, pijn, diagnose, prognose, behandeling, uitkomstbepaling en de return-to-sport in sporters met MTSS.

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BAREND, RENS, ELMAR – de fiets- en hardloopmannen, "de Rippers": Wat was het leuk en afzien om met jullie in een huis te wonen. Terug naar 2012: hard gelachen werd er toen jullie al vakantie hadden en ik nog aan de masterthesis zat. Jullie tourspel werd door mij veelvuldig vervloekt – en daarna eindeloos gespeeld! Het 10-jarig vakantiejubileum hebben we geloof ik al gehad – altijd leuk en gezellig om de gedachten in de zomer met jullie te verzetten: hersenloos een berg op fietsen, eten, slapen en de volgende dag weer. Ik mis de kaas van "In 't goede Uur" maar ik kom snel weer voor een rondje, en natuurlijk mag 't "verbrande paleis" dan niet ontbreken!

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FLOOR – we zien elkaar te weinig maar de klik is instant als we elkaar weer zien. Granada. Wat was het toch een mooie tijd – ook daarna hebben we nog mooie trips gemaakt naar Turijn en Piemonte. Het is toch altijd weer mooi om met jou op reis te gaan – zo relaxed, gezellig en we maken altijd wel weer wat geks mee. In 2018 reünie in Granada samen met Viv, Maartje en 20 andere toppertjes – ik kijk er naar uit!

BART Mooie herinneringen gaan terug naar de toetsen Duits op de middelbare school, bij meneer Wierda. Frans mondeling staat ook in mijn geheugen gegrift – wie had gedacht dat jij nog eens in Parijs zou belanden?! Ik en mevrouw van Straaten hadden het niet kunnen voorspellen. Ondanks dat we beiden telkens veranderen van stad en land, lukt het toch om elkaar geregeld te zien. Altijd heel gezellig om bij te kletsen, te poolen en keihard te verliezen. Revanche blijft gelukkig nooit lang uit.

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Curriculum Vitae

Marinus Winters was born on the 26th of April 1987 in Haarlem, The Netherlands. After high school graduation at the 'Eerste Christelijk Lyceum' in 2004, he studied Human Resources Management at the University of Applied Sciences in Haarlem. Soon Marinus found out that Physiotherapy was what he was actually passionate about, and, as of 2005, he continued his education at the University of Applied Sciences in Leiden. He spent 9 months in Granada, Spain, completing his Bachelor's thesis in collaboration with research physiotherapists at the University of Granada under supervision of dr. Manuel Arroyo-Morales. In 2010, he received his Bachelor of Science degree in Physiotherapy. Subsequently he studied Clinical Epidemiology at the Academic Medical Centre - University of Amsterdam where he obtained his MSc degree in 2012, under supervision of dr. Eric W.P. Bakker. While finishing his Clinical Epidemiology degree, Marinus initiated several research projects in the area of MTSS which led to a PhD position at the University Medical Centre in Utrecht, in the fall of 2012. Since then Marinus worked on his thesis under supervision of prof. dr. Frank J.G. Back, dr. Maarten H. Moen and dr. Eric W.P. Bakker. Concurrent to working on his PhD thesis, Marinus completed a MSc in Manual Therapy at the University of Applied Sciences in Rotterdam in 2016. Since obtaining his BSc in Physiotherapy, Marinus has been working in several physiotherapy practices, in Hillegom, Castricum and The Hague, The Netherlands, and in London, United Kingdom.

Marinus is a Senior Associate Editor to the ***British Journal of Sports Medicine*** and in May 2017 he accepted a position at the Research Unit for General Practice in Aalborg, Denmark, where he has started as a Research Assistant and hopes to soon be appointed as a Post-doctoral fellow. In his new position, Marinus will focus on optimising care for adolescents with knee pain.

PHD PORTFOLIO SUMMARY

Name PhD Student:	Marinus Winters
UMC Utrecht Department:	Rehabilitation, Physiotherapy Sciences and Sport
PhD period:	2012 - 2017
Promotor	Prof. dr. Frank J.G. Backx
Co-promotors:	Dr. Eric W.P. Bakker, dr. Maarten H. Moen

1. PHD TRAINING

	YEAR
Courses	
Good Clinical Practice (London, UK)	2016
Introduction to Network Meta-Analysis (Bristol, UK)	2017
Indirect and Mixed Treatment Comparisons (Leicester, UK)	2017
National conference (attendance)	
Dutch Sports Medicine Society Annual Conference, Ermelo, The Netherlands	2012
Dutch Sports Medicine Society Annual Conference, Ermelo, The Netherlands	2013
Dutch Sports Medicine Society Annual Conference, Eindhoven, The Netherlands	2015
Dutch Sports Medicine Society Annual Conference, Ermelo, The Netherlands	2016
(Inter-)national conferences - podium presentations	
Workshop lower leg injuries - invited lecture Dutch Sports Medicine Society Annual Conference, Ermelo, The Netherlands	2012
Medial tibial stress syndrome: an update of treatment options - invited lecture Dutch Sports Medicine Society Annual Conference, Ermelo, The Netherlands	2013
Medial tibial stress syndrome: Diagnosis, Pathogenesis and Treatment - invited lecture Dutch Sports Medicine Society Annual Conference, Eindhoven, The Netherlands	2015
Other podium presentations	
The pathology of MTSS; fascia, periosteum or bone? "Muscles and Movement" Symposium, London, United Kingdom	2016
Treatment of medial tibial stress syndrome - invited lecture "Komt een sporter bij de fysiotherapeut" Symposium, Ede, The Netherlands	2016 2017

Medial tibial stress syndrome; new insights and alternative facts- invited lecture	2017
Symposium "Lower leg pain", Aalborg, Denmark	

2. OTHER ACTIVITIES

	YEAR
Senior Associate Editorship:	
British Journal of Sports Medicine	2017-Present
Reviewer for (inter-)national journals:	
British Journal of Sports Medicine	2013-Present
Journal of Sports Sciences	2014-Present
Sports Medicine	2017-Present
Journal of Foot and Ankle Research	2014-2015
Sport & Geneeskunde	2016

LIST OF PUBLICATIONS

Peer-reviewed publications

1. Winters M, Bakker EWP, Moen MH, Barten CC, Teeuwen R, Weir A. Diagnosticeren van pijnsyndroom MTSS. Anamnese en lichamelijk onderzoek afdoende. Fysiopraxis September 2017;sep (8):40-41.

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11. Winters M, Moen MH, Zimmermann WO, Lindeboom R, Weir A, Backx FJ, Bakker EW. [De mediaal tibiaal stress syndroom score: een nieuwe patiënt gerapporteerde uitkomstmaat] Sport & Geneeskunde 2016;3:28-31.

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14. Winters M, Barten CC, Teeuwen R, Bakker EW, Moen MH, Backx FJ, Weir A. Medial tibial stress syndrome: reliably diagnosed using history and clinical examination?: 195 Board #32 June 1, 11: 00 AM - 12: 30 PM. Med Sci Sports Exerc. 2016 May;48(5 Suppl 1):39. doi: 10.1249/01.mss.0000485126.17827.3e.

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Books:

Contributor to:

- Chapter 42: Ankle Pain (p. 917 - 936) in Brukner P et al. (eds). 'Brukner & Khan's Clinical Sports Medicine', Volume 1 Injuries. 5th Ed. Australia: McGraw-Hill Education, 2017
- Chapter 43: Foot pain (p. 937 - 972) in Brukner P et al. (eds). 'Brukner & Khan's Clinical Sports Medicine', Volume 1 Injuries. 5th Ed. Australia: McGraw-Hill Education, 2017