"AETIOLOGY, IMAGING AND TREATMENT OF MEDIAL TIBIAL STRESS SYNDROME"

"Maarten Hendrik Moen"

AETIOLOGY, IMAGING AND TREATMENT OF MEDIAL TIBIAL STRESS SYNDROME

ETIOLOGIE, DIAGNOSTIEK EN BEHANDELING VAN MEDIAAL TIBIAAL STRESS SYNDROOM

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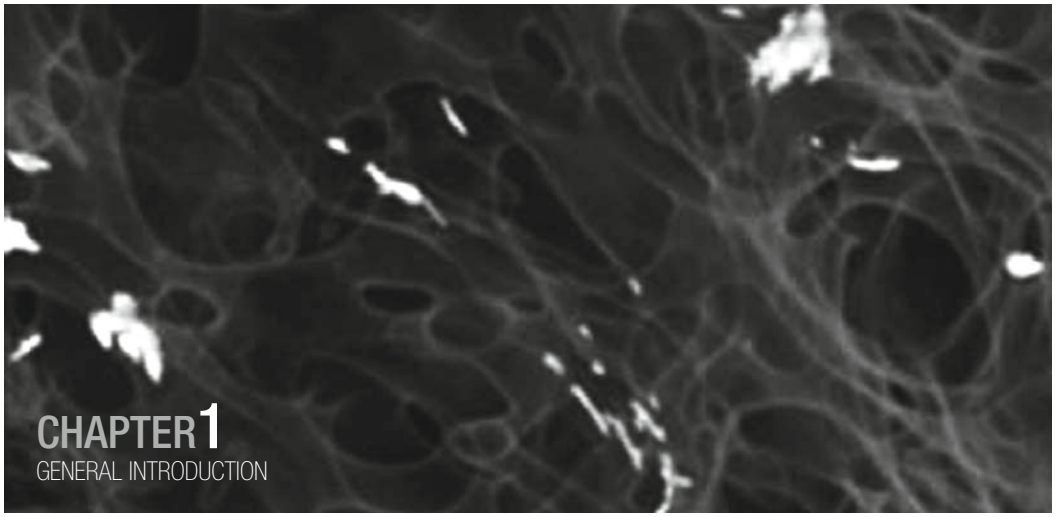

CHAPTER 1
GENERAL INTRODUCTION

Medial tibial stress syndrome (MTSS) is a not well understood entity in the lower leg. The work based in this thesis will advance the field of knowledge on the topic of MTSS further. For a common lower leg complaint as MTSS is, very few original research studies have been conducted. The exact aetiology is still unknown and the evidence for the optimal treatment and prevention is absent. Many studies show that MTSS is one of the most frequent causes of complaints of the lower leg in athletes and military populations (Brushoj et al., 2008; Clanton & Solcher, 1994; D'Souza, 1994; Hespanhol et al., 2011; Orava & Puranen, 1979; Taunton et al., 2003), with a percentage of 14,6-24,1% of all lower leg complaints (Brushoj et al., 2008; Taunton et al., 2003). Incidences of 4-35% were reported in athletic and military populations (Andrish et al., 1974; Bennett et al., 2001). Understanding the aetiology of this common injury would aid in designing adequate interventions for treatment and prevention in MTSS. Until now, only few treatment and prevention studies on MTSS have been conducted.

TERMINOLOGY AND AETIOLOGY

Over the past seventy years many terms for MTSS have come into existence. One of the most commonly used synonyms is shin splints. On the internet the hits for shin splints exceeds the number of hits for MTSS (Google; search term "shin splints" 548.000 hits versus 45.900 hits for "medial tibial stress syndrome" (searched in September 2011)).
The term shin splints was documented first in 1948, while the term MTSS was not coined until 1982 (Pearson et al., 1948; Mubarak et al., 1982). The section below gives a historical overview of the terminology that have been used in the literature and eventually lead to the term MTSS.

The term shin splints was first used in 1948 by Pearson et al. (Pearson et al., 1948). They stated that shin splints was located in the pretibial region and involved the muscles. In 1958, Devas described that shin splints was similar to shin soreness and Charlie horse (Devas, 1958). This shows that from the start, several terms were used to describe the same condition. But matters would be even more complicated in the following years. With shin soreness, Devas meant "… a particular form of a tibial stress fracture… involving only one cortex of the bone". Later Devas stated that the name shin splints had its origin in horses. He described that in horses there is occasionally a swelling over the shin, in which the rudimentary third and fourth metacarpal bone (or "splint bones") are situated. Leg complaints in horses were then called splint disease, or shin splints (Devas, 1967).
In the early sixties, another article also appeared, that stated that shin splints was located in the anterior leg region (Paul, 1963). At that point, and to this day, the medical world seems to be confused on the shin splints topic. That is possibly

why, at the Eighth National Congress on the Medical Aspects of Sports held in Las Vegas in 1966, several presentations were held on shin splints, of which one was titled "Shin splints confusion". In the same year a multidisciplinary subcommittee of the Committee on Medical Aspects of Sports presented the first definition of shin splints (Rachun et al., 1966). After interviewing hundreds of physicians, trainers and physical educators shin splints were defined as "pain and discomfort in the leg from repetitive running on hard surface or forcible, excessive use of foot flexors; diagnosis should be limited to musculotendinous inflammations, excluding fracture or ischemic disorder". This definition was backed up by Slocum, in the first review on shin splints (Slocum, 1967). Slocum presented a table (see table 1.1) to show the differential diagnosis of shin splints and define shin splints more precisely, although nowadays this table seems outdated.

Despite the Las Vegas 1966 definition, the confusion about this entity did not disappear and a new term was described in 1974: tibial stress syndrome (Clement, 1974). To prove that no patients with a stress fracture were included in the study, x-rays were performed and most of them were negative. Clement described that tibial stress syndrome was a prologue to the end state of a stress fracture. In the same year a report by Rasmussen stated that shin splints could be subdivided in 1) anterior tibial syndrome, 2) stress fractures, 3) interosseous membrane tearing, 4) anterior tibial tenosynovitis and 5) partial bony avulsions (Rasmussen, 1974).
In the late seventies Benas and Jokl divided shin splints in three categories: stress fractures of the tibia, ischemia of the deep posterior compartment and myositis / fasciitis / periostitis (Benas & Jokl, 1978).
In the early eighties Delacerda performed several etiological studies on shin splints (Delacerda, 1980; Delacerda, 1982) and postulated that shin splints was caused by small tears within the muscle and at the periosteal attachment. The theory that traction of the foot flexors and foot invertors caused periostitis was proposed in the eighties (Mubarak et al., 1982; Michael & Holder, 1985). After these studies, this etiological theory of shin splints became widely used. However, a new etiological theory was proposed as well.
Several studies suggested that increased pressure in the deep posterior compartment of the leg was the aetiological factor for shin splints (D'Ambrosia et al., 1977; Wallensten & Eklund, 1984). Finally, other studies suggested that shin splints was due to tendonitis of the flexor digitorum longus muscle, the flexor hallucis longus muscle or the tibialis posterior muscle (Mills et al., 1979; Saxena et al., 1990; Viitasaalo & Kvist 1983).
In 1986, a frequently referred paper was published, combining different etiological theories, written by Detmer in Sports Medicine. This paper stated that three subtypes of shin splints exist. Type I consists of bone stress reaction or cortical fracture, type II is periostalgia or avulsion of the periosteum and type III consists of chronic deep compartment syndrome, see figure 1.1 (Detmer, 1986). Even in 2009, this subdivision of shin splints / MTSS is still supported in the literature (Crabtree et al., 2009).

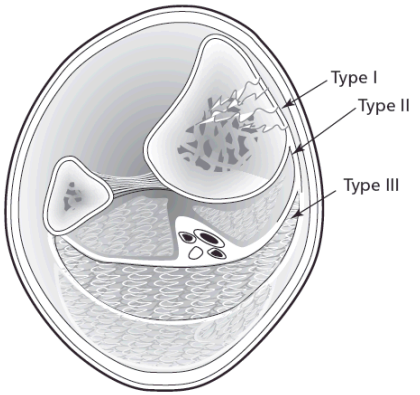

Figure 1.1: The three subtypes of MTSS and their location adapted from Detmer, 1986. Type I: stress fracture / microfracture of the tibia, type II: periostalgia due to chronic avulsion of the periosteum, type III: chronic deep deep compartment syndrome. (Reprint permission granted by Wolter Kluwers).

In conclusion the terminology and aetiology for MTSS has shown to be inconsistent and not clearly defined in the past decades. Only in 2004 Yates & White published a new definition of MTSS, in an attempt to clarify the ongoing confusion regarding MTSS (Yates & White, 2004). They defined MTSS as "pain along the posteromedial border of the tibia that occurs during exercise, excluding pain from ischemic origin or signs of stress fractures". In this thesis the term MTSS is used and this is defined according to Yates and White.

IMAGING AND MTSS DIAGNOSIS

With no consensus on the definition of MTSS various studies aimed at establishing the diagnosis MTSS by imaging (Anderson et al., 1997; Aoki et al., 2004; Batt et al., 1998; Gaeta et al., 2005). Different modalities, such as CT-scans, MRI scans and bone scintigraphy have been used for this purpose. CT-scans can depict stress reaction of the tibia, MRI scans may show oedema of the periosteum and bone marrow and changes of the soft tissues, while bone scans are frequently used when bone overload is suspected. However, as with the terminology, it is not

Table 1.1: The differential diagnosis of shin splints according to Slocum in 1967 (reprint permission granted by Elsevier and Am J Surg).

Data	Shin splints	Tenosynovitis	Stress fracture	Acute ATC(*)	Chronic ATC(*)	Postembolic / post-thrombotic ATC(*)	Muscle hernia
Lesion	Sterile inflammation due to strain or minimal tears of periosteum, interosseous membrane, muscle belly or muscle-tendon junction	Mechanical inflammation of the tendon sheath	Tibia or fibula	Muscle swelling, ischemia and necrosis	ATC (*) too small; swelling, ischemia and late necrosis	Femoral or popiliteal occlusion with ischaemia and necrosis	Anterior fascial defect near tibia
History							
Direct injury	0	0	0	0	0	+	±
Pain on repeated overexertion	+	+	+	+	+	+	+
Hard playing surface	+	+	+	±	±	±	0
Onset	Gradual	Gradual	Gradual	Acute to severe	Acute to mild prodrome	Acute to severe	With activity
Duration	10-24 days	10-21 days	To 3 months	No recovery unless operation performed	No recovery unless operation performed	No recovery unless operation performed	Chronic
Pain on use							
Walking			Late	Early	Early	Immediate	
Running	Late	Late	Early	Early	Early	Unable	+
Non-weight bearing	Early	Early	Late	Early	Early	Early	+
movement	Late	Late					0
Rest pain	Late and mild	Late and mild	Late and moderate	Early and severe	Late and severe	Early and severe	Not usual

Table 1.1: The differential diagnosis of shin splints according to Slocum in 1967 (reprint permission granted by Elsevier and Am J Surg) (continued).

Swelling	Periosteal or muscle	Extensor tendon sheath	Localized fracture site	ATC (*) marked if necrosis	ATC (*) marked if necrosis	ATC (*) marked if necrosis	Muscle bulge
Tenderness	Site of lesion	Lower one third of leg	Localized fracture site	ATC (*)	ATC(*)	ATC(*)	±
Inflammatory reaction	0	0	0	Early	Late	Early	0
Crepitation	0	±	0	0	0	0	0
Anterior tibial pulse	+	+	+	±	± (usually)	0	+
Anterior tibial group paralysis	0	0	0	Early and severe	Late	Early	0
Loss deep peroneal sensation	0	0	0	+	Late	+	0
Electromyogram denervation potential	0	0	0	+ 3 wk	±	+	0
Roentgen changed	Normal	Normal	+	Normal	Normal	Positive angiogram	Normal

Abbreviation: ATC (*) = anterior tibial syndrome

clear which modality to use best, if any, to establish the diagnosis. Furthermore, imaging could help in clarifying the aetiology of MTSS.

TREATMENT

Only a few treatment studies have been conducted on MTSS. Most of them are of low quality, with only a few prospective or randomised studies available (Andrish et al., 1974; Johnston et al., 2006; Nissen et al., 1994). The following interventions were investigated in these three trials: ice massage with ice massage and aspirin, ice massage and fenylbutazone, ice massage and heel-cord stretching and a walking cast (Andrish et al., 1974), active laser and placebo laser (Nissen et al., 1994) and a leg orthosis (Johnston et al., 2006). None of the randomised studies showed a treatment effect of the intervention group compared to a control group. This is why the need for more and high quality treatment studies is high.

THE AIMS AND OUTLINE OF THE THESIS

This thesis was conducted to study the aetiology of MTSS and to study whether treatment aimed at these etiological factors was more effective than currently used therapies. Based on the introduction above, it was concluded that a recent thorough summary of the literature on MTSS was lacking. Therefore, **Chapter 2** aimed to present a critical review on the aetiology, imaging, treatment and prevention of MTSS.
In **Chapter 3** a case-control study is presented. This study investigated whether aetiological risk factors could be identified that were more present in soldiers with MTSS compared to controls. In **Chapter 4** a rare case of MTSS is described, which was induced by methotrexate osteopathy, which is a very uncommon reason to develop MTSS. The patient described was not involved in strenuous sports and did not sustain much axial loading of the leg.
Diagnostic MRI findings in symptomatic athletes is presented in **Chapter 5**. This study also investigated the relationship between findings on MRI and several clinical parameters as well as time to recovery
To assess if MTSS, as a bone overload problem, could be probably be treated with medication that influences bone remodelling, two cases of MTSS were treated with biphosphonates. The findings are described in **Chapter 6.**
Chapter 7 is a prospective, controlled, non-randomized clinical study in which a group of athletes with MTSS was treated with a graded running program together with focused shockwave (known to stimulate osteoblasts). A group of athletes with MTSS treated with a graded running program alone comprised the control group. The hypothesis was that the group with the combined shockwave and graded running program recovered faster.
Pneumatic leg braces have been used previously in populations that sustained a tibial stress fracture. In **Chapter 8** the additional value of a pneumatic leg brace was investigated in a small randomized study in the military setting.
Chapter 9 is a randomized, controlled clinical study that investigated three commonly used treatment options for MTSS. One group performed a graded running program, the second group performed a graded running program and did stretching and strengthening exercises for the leg, while group three performed a graded running program, while wearing a compression sleeve.
In **Chapter 10** the main findings of this thesis are discussed and reflected on the literature. Also, future directions in imaging and treatment of MTSS are discussed. Surgical intervention and prevention strategies for MTSS are also discussed separately.

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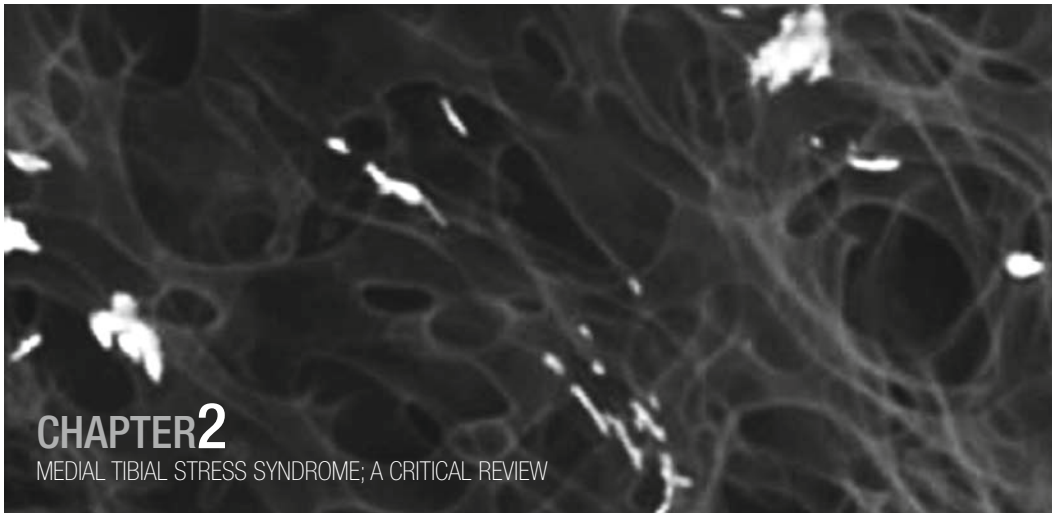

CHAPTER2
MEDIAL TIBIAL STRESS SYNDROME; A CRITICAL REVIEW

Moen MH, Tol JL, Weir A, Steunebrink M, de Winter ThC
Sports Med 2009; 39(7): 523-546

ABSTRACT

Using articles obtained after critical review of the literature this article discusses the aetiology, biomechanics, histology, patient evaluation, diagnostic imaging, risk factors, therapy and prevention of medial tibial stress syndrome (MTSS).
MTSS is the name given to the condition of pain on the posteromedial side of the tibia during exercise, with pain on palpation of the tibia for at least five centimeters.
The incidence of MTSS is reported as being between 4 and 35% in military personnel and athletes. Most probably it is caused by overloaded adaptation of the tibial cortex and not to periostitis as a result of traction, since histological studies fail to provide evidence. Evidence for overloaded adaptation of the cortex is found in studies describing MTSS findings on bone-scan, MRI, high resolution CT-scan and dual energy x-ray absorptiometry.
The diagnosis is made clinically, although only one study has been conducted about physical examination.
Additional imaging such as bone scan, CT-scan and MRI-scan is being of limited value. The prevalence of abnormal findings in asymptomatic subjects means that results should be interpreted with caution.
Excessive pronation of the foot while standing and female gender were found to be intrinsic risk factors in multiple prospective studies. Other prospectively found intrinsic risk factors such as body mass index, greater internal and external ranges of hip motion and calf girth were derived from solitary studies. No extrinsic risk factors were identified.
The treatment of MTSS has been studied poorly, since only two studies were conducted. In these studies rest is equal to any intervention.
The use of a neoprene or semi-rigid inlay may help prevent MTSS, since two large prospective studies provide evidence for this.

INTRODUCTION

Medial tibial stress syndrome (MTSS) is one of the most common causes of exercise induced leg pain. [23] Incidences varying from 4-35% are reported, with both extremes being derived from military studies.[4,13,95] This condition is most frequent among military personnel, runners and athletes involved in jumping, like basketball players and rhythmic gymnasts. [7,56]
A lot of controversy exists about the definition and terminology of this condition. Different authors have used different names such as: shin soreness [29], tibial stress syndrome [24], medial tibial syndrome [74], medial tibial stress syndrome [66] and shin splints syndrome [85]. In this review we chose to use medial tibial stress syndrome (MTSS) because, in our opinion, this best reflects the aetiology of the syndrome.

MTSS is characterized by exercise related pain on the posteromedial side of the distal tibia. In 1966 the American Medical Association defined the condition (then termed shin splints) as: “pain or discomfort in the leg from repetitive running on hard surfaces or forcible excessive use of the foot flexors; diagnosis should be limited to musculotendinous inflammations, excluding fracture or ischaemic disorder”.[2] This definition is the only available official definition given in literature. It does not describe signs on physical examination. More recently an updated definition was proposed by Yates et al.. [95] They described MTSS as “pain along the posteromedial border of the tibia that occurs during exercise, excluding pain from ischaemic origin or signs of stress fracture”. Additionally, on palpation with physical examination, a diffuse painful area of at least five centimetres should be present.
However, since no official definition exists, many authors use their own definition of MTSS. This makes comparison between studies difficult.
Before diagnosing MTSS the diagnosis tibial stress fracture and exertional compartment syndrome should be excluded.
Patients presenting with exertional compartment syndrome complain of cramping, burning, or aching pain and tightness in the leg with exercise. Palpation at rest is usually not painful. During exercise the leg is painful, but upon stopping the pain disappears quickly. The diagnosis can be confirmed by intra-compartmental pressure measurements.[31] In the nineteen seventies and eighties some thought that MTSS was caused by elevated leg compartment pressures. Puranen studied this in 1981 by measuring the pressure in 22 patients with pain on the medial side of the leg.[75] He found that on exertion patients had significantly higher increases in pressure than controls. On exertion the pressure ranges in patients and controls were 70-150 mmHg and 15-30 mmHg respectively. Other researchers failed to find elevated pressures. [26,66,91] In one study 14 track runners with MTSS showed no elevated pressures present in any compartment. [26] In a series of 12 patients with MTSS, compartment pressures were measured and compared to true chronic compartment syndromes. In the MTSS group, pressures were lower during exercise (respectively 84 mmHg (mean value) versus 112 mmHg). No confidence intervals were stated. [66] In 12 patients with MTSS the pressures during exercise were compared to pressures in compartment syndrome. Values in the compartment syndrome group were higher (respectively 28 ±12 mmHg and 70 ± 56 mmHg). [91] All four studies examining compartmental pressure in MTSS examined relatively few patients, and were of poor methodological quality.
The differentiation between stress fracture and MTSS can sometimes be challenging, especially since X-rays for stress fracture can be false negative. [56] In stress fractures, pain is usually more focal, while in MTSS the pain is more diffuse. Initially plain X-ray are normal and after a few weeks may show callus formation. Bone scintigraphy and magnetic resonance imaging (MRI) are widely used to confirm the diagnosis. [18]

Many sports medicine books refer to the classification system described by Detmer in 1986 to subdivide MTSS into three types. [28] Type I: tibial microfracture, bone stress reaction or cortical fracture, type II: periostalgia from chronic avulsion of the periosteum at the periosteal-fascial junction and type III: chronic compartment syndrome. In the literature of recent years stress fracture and compartment syndrome are qualified as separate entities.

The objective of this review is to provide a critical analysis of the existing literature on MTSS studying the articles published on this topic. Aetiology, biomechanics, histology, patient evaluation, diagnostic imaging, risk factors, therapy and prevention are discussed.

METHODS

Literature search
Electronical databases MEDLINE (1966-2007), EMBASE (1980-2007), CINAHL (1982-2007), SPORTDiscus (1975-2007) and Cochrane Library were searched for articles. The search terms ‘shin splints’, ‘medial tibial syndrome’, ‘medial tibial stress syndrome’ and ‘tibial stress syndrome’ were used with no restrictions for language. The references from obtained articles were screened for additional articles.
Using the search terms 382 possible titles were screened. Of these 334 were not relevant, discussing sports injuries in general, stress fractures, compartment syndromes or other topics. The 48 relevant titles were screened for related titles in the references. In total 96 references were found, of which 95 articles could be obtained.

Articles were judged using the Institute for Quality of Healthcare (CBO) classification system [48] (table 2.1) and methodological quality and level of evidence were assessed. A methodological quality status (A1, A2, B, C, D) and a level of evidence status (1, 2, 3, 4) was assessed (see table 2.2 and 2.3).
The assessment was done independently by two researchers (MM and MS). If methodological quality and level of evidence were scored differently, a third author (AW) made the final decision on two occasions.
Randomized controlled studies on the prevention and treatment of MTSS were also assessed using the Delphi scoring list [88] (table 2.4 and 2.5). This is a list of criteria for quality assessment of randomized clinical trials for conducting systematic reviews. This list contains nine points and each was scored as present or not. The maximal score for the Delphi list is nine points.

Table 2.1: Assessment of methodological quality and level of evidence[48].

Assessment of methodological quality of studies concerning intervention (treatment / prevention)
A1: Systematic review of at least two independently conducted studies of A2 level
A2: Randomized double blind clinical comparing study of good quality and size
B: Randomized clinical study, with moderate quality and size, or other comparing research (case-control study, cohort study)
C: Case series
D: Expert opinion

Assessment of methodological quality of studies concerning imaging and aetiology
A1: Systematic review of at least two independently conducted studies of A2 level
Imaging
A2: Research comparing to a gold standard / reference test, with an adequate amount of participants
B: Research comparing to a gold standard / reference test, with an inadequate amount of participants
Aetiology
A2: Prospective research with adequate and non-selective follow-up, with control for confounding
B: Prospective research with not all criteria mentioned under A2, or retrospective research
Imaging & aetiology
C: Case series
D: Expert opinion

Level of evidence
1: One systematic review (A1) or at least two independently conducted studies of A2 level (strong evidence)
2: One study of A2 level, or at least two independently conducted studies of B level (moderate evidence)
3: One study of B or C level (limited evidence)
4: Expert opinion (no evidence)

Table 2.2: Study characteristics and quality scores of studies concerning imaging.

Author, year of publication	Study design	Inclusion criteria	Imaging type	Number included	Description of population	Outcome	Methodological quality	Level of evidence
Holder and Michael, 1984 [46]	Prospective cohort	Pain on palpation of middle and distal posteromedial tibial border	Bone scan	10 subjects	Athletes, 50% M, 50% F. 6 runners, 2 hockey, 1 ballet, 1 basketball. 16-31 y.	9 scans abnormal uptake, 1 normal	B	2
Chisin et al., 1986 [22]	Prospective cohort	Not clearly stated	Bone scan	171 subjects were scanned with suspicion stress fracture	Male soldiers 18-21 y.	171 bone scans. 53% sharply defined abnormality: stress fracture. 35% irregular poorly defined uptake; compensatory remodeling. 12% normal	B	2
Batt et al., 1998 [10]	Prospective cohort	Exercise induced lower leg pain, pain on palpation > 5 cm on posteromedial tibial border	MRI / Bone scan / X-ray	23 subjects, 41 symptomatic tibias, 4 asymptomatic athletes	Athletes and students, 14 – 58 y, 48% F, 52% M.	X-ray: 9% periosteal elevation. Bonescan: 88% tibias abnormal MRI: 83% abnormal	B	2
Gaeta et al., 2005 [37]	Case-control	Lower leg pain < 1 month, X-ray normal, clinical exam not stated	MRI / Bone scan / CT-scan	42 subjects, 50 tibias. 10 asymptomatic	Recreational and competitive athletes. 16-37 y. 38% F, 62% M.	MRI: 88% abnormal CT: 42% abnormal Bone scan: 74% abnormal. MRI and CT normal in asymptomatic	B	2
Gaeta et al., 2006 [38]	Case-control	Exercise related pain at posteromedial tibial border	High resolution CT-scan	20 asymptomatic athletes, 10 asymptomatic non athletes, 11 symptomatic (14 tibias)	Distance runners, 18-26 y. 32% F, 68% M.	Asymptomatic non athletes: 95% tibias normal. Asymptomatic athletes: 45% abnormal. All 14 painful tibias; abnormal	B	2
Fredericson et al., 1995 [33]	Retrospective cohort	Runners with tibial pain with confirmation of MTSS, tibial stress reaction of tibial stress fracture on bone scan	MRI / bone scan	14 subjects, 18 tibias	Runners; track, hurdles, distance runners 18-21 y. 21% M, 79% F.	Grade I and II: periosteal edema and bone marrow edema on T2 weighted. Grade III and IV: periosteal edema on T2, marrow edema on T1 and T2. Correlation bone scan / MRI in 78%	B	3
Arendt et al., 2003 [8]	Retrospective cohort	Athletes that underwent MRI with suspicion of stress fracture	MRI	26 subjects	Athletes; basketball, runners, football, gymnastics, ice hockey, track, tennis, softball. 31% M, 69% F.	The more severe the lesion on MRI the longer the time to return to sport	B	3

Abbreviations: MTSS; medial tibial stress syndrome, M; male, F; female, T1; T1 weighted, T2, T2 weighted

Table 2.2: Study characteristics and quality scores of studies concerning imaging (continued).

Author, year of publication	Study design	Inclusion criteria	Imaging type	Number included	Description of population	Outcome	Methodological quality	Level of evidence
Rupani et al., 1985 [80]	Case series	Not clearly stated	Bone scan	44 subjects	Recreational and competitive athletes. Age 11-72 y. Female / male ratio not clearly stated.	Distinguishing tibial stress fractures and MTSS is possible with bone scan	C	3
Nielsen et al., 1991 [68]	Case series	Pain along the posteromedial border	Bone scan / X-ray	22 subjects, 29 tibias	Male soldiers (age unknown)	X-ray: 45% abnormal. Bone scan: 83% abnormal uptake. 17% normal	C	3
Anderson et al., 1997 [3]	Case series	Activity related lower leg pain and tenderness on palpation along the posteromedial tibia	MRI / X-ray	19 subjects	Competitive and recreational athletes 17- 54 y. 58% F, 42% M.	37% MRI normal, 26% MRI periosteal fluid. 26% MRI bone marrow edema, 11% stress fracture. X-ray: 5/5 normal	C	3
Matilla et al., 1999 [60]	Case series	Medial tibial pain within 500 meters of marching, X-ray normal, pain > 5cm along tibial shaft	MRI	12 subjects, 14 tibias	Male soldiers 17-25 y.	93% periosteal edema. 29% intraosseous bright signal and periosteal edema.	C	3
Aoki et al., 2004 [6]	Case series	Pain in the middle or distal portion of the medial side of the leg. Normal X-ray	MRI	14 subjects with MTSS, 8 subjects with stress tibial fracture	Athletes, 13-33 y. 59% M, 41% F. Runners, basketball, volleyball, kendo, soccer players.	14/14: linear abnormally high signal along posteromedial border. 50% abnormally high signal of bone marrow. 36% both abnormal signals seen. After 4 weeks, with continued exercise, MRI signals diminished in 5 patients	C	3

Abbreviations: MTSS; medial tibial stress syndrome, M; male, F; female

Table 2.3; Study characteristics and quality of studies concerning risk factors.

Author, year of publication	Study design	Inclusion criteria	Number included	Description of population	Specification of determinant	Outcome	Methodological quality	Level of evidence
Intrinsic risk factors								
DeLacerda, 1980 [27]	Prospective cohort	Pain along the posteromedial aspect of the tibia	81 subjects	Female body mechanics physical education students 18-21 y.	Risk factor: navicular displacement weight bearing / non-weight bearing	Incidence MTSS 37% . Navicular drop 8.90 ± 2.89 mm in MTSS group, control 5.56 ±2.32 mm	A2	2
Bennett et al., 2001 [13]	Prospective cohort	Pain with palpation over the distal 2/3 of the posterior medial tibia.	125 subjects	Cross-country 14–17 y. runners. 46% M, 54% F.	Risk factor: navicular drop test	Navicular drop test (p=0.01), female gender (p=0.003)	A2	2
Burne et al., 2004 [21]	Prospective cohort	At least one week medial tibial pain on exertion and >10 cm pain on palpation at distal 2/3 of posteromedial tibia	158 subjects	Military cadets, 17-21 y. 77% M, 23% F.	Risk factors (for men only): greater internal and external hip ROM, leaner calf girth	Incidence MTSS 15%. Incidence 15% F, 10% M. Greater internal and external ROM (p<0.05), leaner calf girth (p=0.04)	A2	2
Yates and White, 2004 [95]	Prospective cohort	Pain, due to exercise along the posteromedial tibial border, on palpation diffuse >5 cm	125 subjects	Naval recruits 17-35 y. 75% M, 25% F	Risk factor: female gender (RR 2.03), more pronated foot type (RR 1.70)	Incidence MTSS 36%. Incidence 53% F, 28% M	A2	2
Plisky et al., 2007 [72]	Prospective cohort	Pain along the distal 2/3 of the tibia exacerbated with repetitive weight bearing activity	105 subjects	Cross country runners 14-19 y. 56% M, 44% F	Risk factor: higher BMI (RR 5.0)	Incidence MTSS 15%. 4,3 / 1000 athletic exposures (F), 1,7 / 1000 AE (M) .	A2	2
Gehlsen and Seger, 1980 [40]	Case-control	Not clearly stated	20 subjects, 10 symptomatic, 10 control	Female athletes, age not stated. 10 symptomatic, 10 control	Risk factor: increased plantar flexor strength. Decreased inversion flexibility (right ankle), increased angular displacement (achilles tendon / calcaneus)	Increased plantar flexor strength (p<0.05). Decreased ankle inversion (p<0,05). Increased angular displacement (p<0.05)	B	3

Abbreviations: MTSS; medial tibial stress syndrome, M; male, F; female, RR; relative risk, ROM; range of motion, AE; athletic exposure

Table 2.3; Study characteristics and quality of studies concerning risk factors (continued).

Author, year of publication	Study design	Inclusion criteria	Number included	Description of population	Specification of determinant	Outcome	Methodological quality	Level of evidence
Viitasalo and Kvist, 1983 [89]	Case-control	Regular or long lasting pain on the medial border of the distal 2/3 of the tibia	48 subjects; 13 controls, 13 with frequent and long lasting MTSS, 22 slight MTSS	Male distance runners, judo, soccer, skiing, boxing, basketball. Age (control): 30.6 ±7 Age (frequent): 23.8 ± 7, age (slight): 19.8±5	Risk factor: increased mobility of inversion, eversion and sum. Achilles tendon angle displacement smaller during full support phase.	Passive mobility inversion (p<0.01), eversion (p<0.05), sum (p<0.001). Angular displacement during full support (p<0.01)	B	3
Sommer and Valentyne, 1994 [86]	Case-control	Regular or long lasting pain on the medial border of the distal 2/3 of the tibia	25 subjects, 10 controls, 10 cases of which 4 bilateral	Amateur folk dancers, 15-25 y. 80% F, 20% M. 10 previously diagnosed with MTSS, 15 controls.	Risk factor: combination of forefoot and hindfoot varus alignment. Standing foot angle < 140°	Forefoot and hindfoot varus (p= 0.047) Standing foot angle < 140° (p= 0.0001)	B	3
Taunton et al., 2002 [87]	Retrospective cohort	Not clearly stated	2002 subjects	Runners, mean age MTSS subgroup 30.7 y. 43% M, 57% F	Risk factor: below average activity history (OR 3.5 for males, OR 2,5 for females)	Incidence 5% MTSS	B	3
Madeley et al., 2007 [57]	Case-control	Exercise induced leg pain of the posteromedial border of the tibia. Pain on palpation greater than 40 mm on 100 mm Visual analogue pain scale.	60 subjects, 30 symptomatic with 59 painful tibias, 30 controls	Athletes, 17-47 y. MTSS group 53% M, 47% F, control group 53% M, 47% F	Risk factor: Standing heel-rise repetitions	Standing heel rise (p<0.001)	B	3

Abbreviations: MTSS; medial tibial stress syndrome, OR; odd's ratio, M; male, F; female,

Table 2.4: Methodological quality of randomized controlled trials according to the Delphi criteria (treatment) [88].

Authors, year of publication	Number included	Description of population	Intervention	Outcome	Delphi items [88]									Total score	Methodological quality	Level of evidence
Therapy					1a	1b	2	3	4	5	6	7	8			
Andrish et al. 1974 [4]	2777 subjects	First year male midshipmen. Age not stated.	Five groups. 1 ice application, 2 aspirin and ice, 3 phenylbutazone and ice, 4 heel-cord stretching and ice, 5 walking cast	Incidence MTSS 4%. No significant differences.	+	+	+	+	-	-	-	-	-	4/9	A2	2
Johnston et al., 2006 [51]	13 subjects, 7 experimental, 6 controls	Soldiers, 18-37 y. Sex not stated.	Two groups: 1 Leg orthosis and walk-to-run program, 2 walk-to-run program	No significant differences between groups in days to recovery (p=0.575)	+	+	+	-	-	-	-	+	+	5/9	A2	2

Explanation Delphi items
1a: Was a method of randomisation performed?
1b: Was the treatment allocation concealed?
2: Were the groups similar at baseline regarding the most important prognostic indicators?
3: Were the eligibility criteria specified?
4: Was the outcome assessor blinded?
5: Was the care provider blinded?
6: Was the patient blinded?
7: Were point estimates and measures of variability presented for the primary outcome measures?
8: Did the analysis include an intention-to-treat analysis?

Abbreviation: MTSS; medial tibial stress syndrome

Table 2.5: Methodological quality of randomized controlled trials according to the Delphi criteria (prevention) [88].

Author, year of publication	Description of population	Intervention	Outcome	Delphi items [88]									Total score	Methodological quality	Level of evidence
Prevention				1a	1b	2	3	4	5	6	7	8			
Andrish et al., 1974 [4]	2777 first year male midshipmen. Age not stated.	Five groups. 1 control, 2 heel pad of foam rubber, 3 heel cord stretches, 4 heel pad and stretches, 5 graduated running program prior to training	Incidence control group 3,0%, heel pad group 4.4%. No significance was found.	+	+	+	+	-	-	-	-	-	4/9	A2	2
Bensel and Kish, 1983 [14]	2841 army basic trainees, age 16-41 y. 73% M, 27% F.	Two groups. 1 hot weather boots, 2 black leather combat boots	Incidence: 1. M 0,27% 2. M 0.22% 1. F 1.18% 2. F 1.17% Not significant.	+	+	+	+	-	-	-	+	-	5/9	A2	2
Bensel and Kaplan, 1986 [15]	555 female soldiers. Age unknown.	Three groups. 1 urethane foam insole, 2 molded network of lever-like projections attached to material in grid form, 3 standard plastic mesh with nylon	Incidence MTSS with different insoles; varying from 5.9-7.4%. Not significant.	+	+	+	-	-	-	-	+	-	4/9	A2	2

Explanation Delphi items
1a: Was a method of randomisation performed?
1b: Was the treatment allocation concealed?
2: Were the groups similar at baseline regarding the most important prognostic indicators?
3: Were the eligibility criteria specified?
4: Was the outcome assessor blinded?
5: Was the care provider blinded?
6: Was the patient blinded?
7: Were point estimates and measures of variability presented for the primary outcome measures?
8: Did the analysis include an intention-to-treat analysis?

Abbreviation: MTSS; medial tibial stress syndrome, F; female, M; male

Table 2.5: Methodological quality of randomized controlled trials according to the Delphi criteria (prevention) (continued) [88].

Author, year of publication	Description of population	Intervention	Outcome	Delphi items [88]									Total score	Methodological quality	Level of evidence
Prevention				1a	1b	2	3	4	5	6	7	8			
Schwellnus et al., 1990 [83]	1388 military recruits, 17-25 y. Sex not stated.	Two groups: 1 neoprene impregnated with nitrogen bubbles covered with nylon. 2 no intervention	Incidence MTSS control: 6.8%, experimental 2,8% ($p<0.05$).	+	+	+	-	-	-	-	-	-	3/9	A2	2
Schwellnus and Jordaan, 1992 [84]	1398 male military recruits, age <25 y.	Two groups: 1 800 mg / day calcium supplementation, 2 no supplementation	Incidence MTSS control: 20.4%, calcium group 33,3%. Not significant.	+	+	+	-	-	-	-	-	-	3/9	A2	2
Pope et al., 2000 [73]	1538 male army recruits, age 17-35 y.	Two groups: 1 stretching gastrocnemius, soleus, hamstring, quadriceps, hip adductor and hip abductor muscle groups. 2 no stretching. Both groups same physical protocol.	Incidence MTSS 1,6%. No effect of stretching on injury risk. LR=1.24, HR 1.23.	+	+	-	+	-	-	-	+	+	5/9	A2	2
Larsen et al., 2002 [55]	146 military conscripts, men and one women. Age 18-24 y.	Two groups: 1 custom made biomechanic shoe orthose, 2 no intervention	Incidence MTSS control group 38%, intervention group 9% (p=0.005). RR 0,2, cost per prevented case $101 US.	+	+	+	-	+	+	-	+	+	7/9	A2	2

Explanation Delphi items
1a: Was a method of randomisation performed?
1b: Was the treatment allocation concealed?
2: Were the groups similar at baseline regarding the most important prognostic indicators?
3: Were the eligibility criteria specified?
4: Was the outcome assessor blinded?
5: Was the care provider blinded?
6: Was the patient blinded?
7: Were point estimates and measures of variability presented for the primary outcome measures?
8: Did the analysis include an intention-to-treat analysis?

Abbreviation: MTSS; medial tibial stress syndrome, F; female, M; male, RR; relative risk

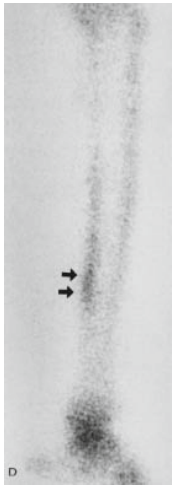

Figure 2.1: Bone scintigraphy showing abnormal longitudinal uptake in lateral view [5].

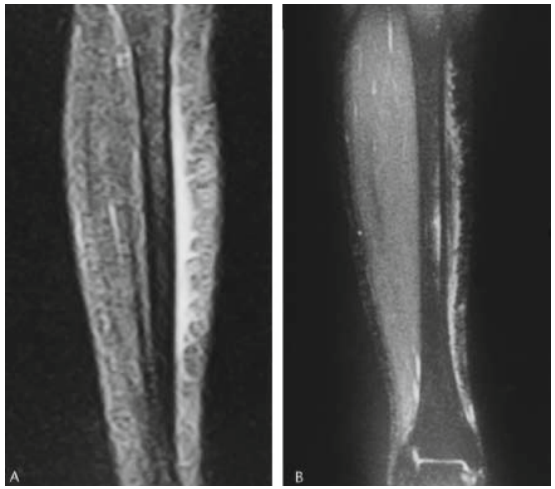

Figure 2.2a and 2.2b: Coronal MRI images showing abnormally high signal on the medial side of the tibia (fig 2.2a) and abnormally high signal along the medial border and the medial side of the bone marrow (fig 2.2b) [5].

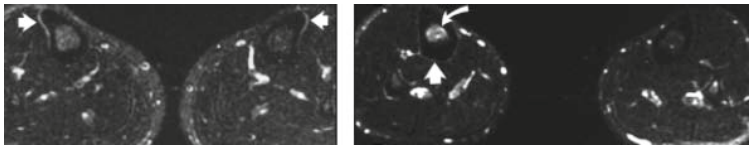

Figure 2.3a and 2.3b.: Axial T2 weighted images showing periosteal edema (straight arrows fig. 2.3a and 2.3b) and bone marrow edema in asymptomatic runners (curved arrow fig. 2.3b) [33].

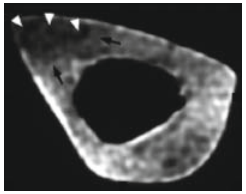

Figure 2.4: Axial CT-scan showing cortical osteopenia (black arrows) and small resorption cavities (white arrows) [35].

AETIOLOGY

Functional anatomy

A lot of controversy exists about the anatomical basis for MTSS. Post-mortem studies have been performed to examine the relationship between the location of the pain and the anatomical structures. The distal attachments of different leg muscles are compared to the site of symptoms in MTSS.

Michael [62] dissected 14 specimens and found fibres of the soleus muscle, but not the posterior tibial muscle on the posteromedial tibial border. Saxena [81] dissected 10 cadavera and found that the distal attachment of the posterior tibial muscle was 7.5 centimeters proximal to the medial malleolus and concluded from this that the posterior tibial muscle caused MTSS. Beck et al. [11] dissected 50 legs and concluded that if a traction was implicated in MTSS, the soleus muscle and the flexor digitorum longus muscle rather than the posterior tibial muscle could be involved. During dissection no fibres of the posterior tibial muscle were found on the distal half of the posteromedial border of the tibia. In the upper half of the distal tibia, fibres of the soleus muscle and flexor digitorum longus muscle were abundant. Although MTSS complaints are commonly felt in the distal one third of the tibia, few muscular fibres of the soleus muscle or flexor digitorum longus muscle were found at this location. [11]

Garth [39] concluded, after performing a case-control study in 17 athletes, that the flexor digitorum longus muscle caused the complaints. He found a decreased flexion range of motion of the second metatarsophalyngeal joint and weakness of the toe flexors in the symptomatic group. The hypothesis was that this was the result of permanent heightened activity of the flexor digitorum longus muscle, and this was the cause of MTSS.

BIOMECHANICS

In the literature two differing explanations for development of MTSS are found. The traction theory was first published in the nineteen fifties.[29] This states that complaints are due to repeated traction on the periosteum from the fibres of the tibialis posterior, soleus and flexor digitorum longus muscles. Symptoms, however, are not always felt at the site of distal attachment of the tibialis posterior, soleus and flexor hallucis longus muscles.[11] The traction theory has only recently been investigated for the first time using three cadaver specimens to measure traction on the periosteum during soleus, posterior tibial and flexor digitorum longus activity.[19] As tension on the tendons of the aforementioned muscles was increased, strain in the tibial fascia increased in a linear manner.

The second theory states that repeated tibial bending or bowing causes MTSS. [44] This mechanism has similarities to the aetiology of a tibial stress fracture. [12] Animal studies showed that repeated bending causes adaptation of the tibia,

predominantly at the site where bending forces are the greatest. [43,52] The site of most profound bending is where the tibial diaphysis is narrowest [63]; approximately at the junction of the middle and distal thirds. The goal of adaptation is to strengthen the bone to resist future loading. The adaptation is described in Wolff's law and the Utah paradigm.[25,32,34,35,36] Bone microdamage has an operational threshold strain range, that lies above the bone remodelling threshold range. Strains above the operational threshold can cause enough microdamage to escape repair and accumulate. [34]
Animal and human studies showed that diminished muscle forces negatively influences the bone adaptation process; when weaker muscles opposing tibial bending allow more bending to occur.[45,71,76,93] A recent study showed greater in vivo tibial strain, when muscles were fatigued.[64]
A combination of biomechanical theories is also a hypothesis. The adaptation to loading of the tibia is further challenged by the traction of the soleus and flexor hallucis longus muscles on the periosteum.[12]

HISTOLOGY

Histologic evidence for periostitis is sparse. Two studies from the nineteen eighties describe two patients with inflammation or vasculitis found in the fascia after biopsy.[62,66] In the study by Michael and Holder a thickened periosteum was seen and termed periostitis. [62] In larger studies inflammatory cells were not often found in the periosteum.[17,50] Inflammatory changes were found in the crural fascia in 13 of 33 athletes upon biopsy. [50] In the same specimens, one biopsy sample showed evidence of plasma cell infiltration surrounding wide lymphatics in the periosteum, along with a thickened periosteum and increased osteoblast activity which was also found by Bhatt et al. [17] Bhatt et al. also found fewer osteocytes compared to normal bone, although this finding just failed to achieve significance. [17] They did not describe the activities of their patient population.
In recent literature, evidence is gathering that osteocytes have a role in mechanotransduction; a mechanism whereby bone senses mechanical stimuli. Osteocytes probably promote bone remodelling in response to a direct mechanical stimulus or bone microdamage. [67] In bone remodelling apoptosis of osteocytes is seen and this apoptosis may influence osteoclast formation and / or function.[69]
Low regional tibial bone density in patients with MTSS has been found when compared to healthy athletes.[58] Bone density in the mid to distal tibia, measured by dual energy x-ray absorptiometry (DXA) was 23 ± 8 % less in patients with MTSS. The bone density regained normal values when the athletes had recovered after a mean of 5.7 years (4-8 year). [59]

PATIENT EVALUATION

History
Most patients with MTSS present with exercise induced leg pain. The pain is located along the posteromedial border of the tibia, usually in the middle or distal thirds. Initially symptoms are present on starting activity and subside with continued exercise, but later on pain continues to be present during activity. If symptoms worsen, then the pain can be felt even after the activity ceases. [5,54]
This has also been described in stress fractures, so the physician should be cautious with this symptom. In severe cases even performing activities of daily living will provoke symptoms.

Physical examination
No articles were found concerning physical examination and MTSS. Ugalde has performed non-published research (personal communication 2006). In this research an attempt was made to determine the sensitivity and specificity of physical examination tests. Symptomatic athletes and control athletes were included. The gold standard in this study was bone scintigraphy. Three tests were examined; diffuse posteromedial pain on palpation, pain on hopping and pain on percussion. Diffuse posteromedial pain on palpation was the most sensitive test.
During physical examination pain is present on palpation of the distal two-thirds of the posteromedial tibial border. Mild swelling of the tibia can sometimes be present. [5,31,54]
Differentiation between MTSS, tibial stress fracture and exertional compartment syndrome can usually be accomplished without additional imaging. In stress fractures, pain is more localized compared to MTSS. Also, night pain and pain on percussion are not usually present in MTSS. In compartment syndrome, a tight feeling in the muscles and sometimes neurological symptoms such as sensory abnormalities can exist.
Several intrinsic risk factors exist for MTSS (see below) and attention should be paid to these during physical examination.

IMAGING

There is a fair amount of literature on MTSS and imaging. Most of the studies looking at imaging findings in patients with and without MTSS use the clinical diagnosis as the gold standard when establishing sensitivity and specificity of imaging modalities. [10,37,38] The fact that history and physical examination is used as the gold standard confirms the fact that the diagnosis is made clinically and that the role of additional investigations is limited.
Table 2.2 describes the study characteristics, methodological quality and results of the imaging studies.

X-ray
Imaging MTSS with X-ray is not appropriate, with most authors reporting normal X-rays.[3,6,20,58] Callus formation is seldom seen on the medial side of the tibia. In one study 4 of 46 patients with pain on palpation for at least five centimetres along the posteromedial tibia, periosteal elevation was found to be present on X-ray.[10] In other research describing callus formation the inclusion criteria for the study were less clear.[62,66]

Bone scan
In 1984 Holder and Michael [46] were the first to examine MTSS with three-phase bone scan (angiograms, blood-pool images and delayed images) in a prospective study. On delayed images, longitudinal tibial lesions on the posterior cortex, involving one third of the length of the bone were seen (figure 2.1). They suggested that MTSS was a condition in which the periosteum is irritated and osteoblasts are activated. Some years later other researchers studying different athletic populations reached the same conclusions.[68,80] Prospective studies on bone scans by Batt and Ugalde [10], and Gaeta [37] showed a 74-84% sensitivity. Batt and Ugalde found a 33% specificity. The low specificity is explained by the high number of positive scans in asymptomatic athletes and controls.

In 1987 and 1988 Zwas et al. [96] and Matin [61] developed a grading scale for the severity of abnormalities found on bone scan for bone stress injuries. They divided scintigraphic findings into four or five grades. Although the study of Zwas et al. was aimed at stress fractures of the tibia, the results of his study were later used to distinguish between stress fracture and MTSS. Suggestions of a continuum between MTSS and stress fracture were already made in 1979.[79] Differentiating between these two entities has proved difficult with bone scan.[10,22]
Batt and Ugalde found in their prospective study, including mainly dancers and runners, that 4 out of 5 asymptomatic athletes had abnormalities on bone scan.[10] Other studies also showed false positive bone scans. [46,68] A study of 100 athletes presenting with back complaints, where bone scans were performed, examined the incidence of abnormalities in the lower leg.[30] 34 % of the athletes had abnormalities in the lower extremity. None of the regions of abnormal lower extremity uptake was symptomatic at the time of initial evaluation. They were referred to a sports medicine clinic and remained asymptomatic after 8-14 months of follow up.

MRI
In the last decade MRI has increasingly been used for studying MTSS. On MRI periosteal edema and bone marrow edema can be seen (figure 2.2a and 2.2b).[3,60] There are only two studies that prospectively examine the sensitivity and specificity of MRI in MTSS. Researchers found a 79-88% sensitivity and 35-100% specificity for MRI.[10,37] The 100% specificity Gaeta et al. [37] described is based on 10 asymptomatic athletes with no abnormalities on MRI.
Fredericson et al. [33] and Arendt et al. [7] both developed a grading system for MTSS on MRI, in which Arendt's system was modified from Fredericson's. In this grading system MTSS and stress fracture are separated and the severity was graded. In stress fractures more bone marrow edema and sometimes a fracture line is seen when compared to MTSS.
Arendt et al. [7] found in a retrospective study that MRI can estimate the time to return to sport. To estimate this, they used a MRI grading scale, previously developed by Fredericson.[33] Grade I (positive Short T1 Inversion Recovery (STIR) image) returned to sport in about 4 weeks. Grade II (positive STIR and positive T2-weighted) returned to sport in about 6 weeks.
It is not clear whether grading on bone scan and MRI can be compared. Batt et al. [10] found a positive correlation between the two imaging techniques in 23 athletes where both bone scan and MRI was performed. Fredericson found no correlation when the MRI and bone scan was compared in 14 athletes with MTSS.[33]
Research from Japan [6] points out that MRI can distinguish between stress fracture and MTSS soon after the beginning of tibial complaints. No MRI scans of patients with MTSS showed a signal extending throughout the whole bone marrow, which was present in stress fractures. In MTSS a linear abnormally high signal along the posteromedial border of the tibia and the bone marrow was seen. This study also showed that five athletes with MTSS, who were followed up by MRI four weeks after initial MRI, and who continued sports activity, did not develop a stress fracture.
In chronic cases (defined as complaints for more than 46 months in a study investigating athletes, mainly runners) MRI scans were normal in 7 patients.[3]

Despite abnormalities found on MRI in symptomatic patients, Bergman et al.[16], in a study with 21 distance runners, showed that 43% had a tibial stress reaction while asymptomatic (figure 2.3a and 2.3b). These runners ran 80-100 km a week for eight weeks and continued doing this. None of these runners developed complaints.

High resolution CT scan
With high resolution CT scan, Gaeta et al. [37,38] showed osteopenic changes in the tibial cortex. A few resorption cavitations could also be seen (figure2.4). A case-control study found a sensitivity and specificity of 42% and 100% respectively.[37] In 10 asymptomatic controls not involved in sport, one tibia showed mild abnormalities (slightly reduced cortical attenuation). In 20 asymptomatic runners 18 of the 40 tibias showed abnormalities (ranging from slightly reduced cortical attenuation to cortical osteopenia). All symptomatic tibias in patients with MTSS showed cortical osteopenia.[38]

Imaging summary
The diagnosis of MTSS should be made clinically. In cases where the diagnosis is unclear the physician may perform bone scan or MRI, which have approximately the same sensitivity and specificity. Compared to these values the sensitivity of CT-scanning is lower, with a higher specificity.

RISK FACTORS

A number of prospective, case-control and retrospective studies have examined intrinsic risk factors. The methodological quality and results of these studies are described in table 2.3.
One of these intrinsic risk factors is over-pronation. [40,89,95] A difficulty in describing pronation related articles is that the descriptions of pronation in different articles vary. Pronatory foot type has been shown a risk factor in a prospective military study by Yates and White (RR 1.70) [95], using the Foot Posture Index. [53,78] Gehlsen [40] and Viitasalo [89] found increased pronation upon heelstrike to be a risk factor in two case-control studies among athletes. In the study by Gehlsen and Seger [40], the angular displacement between the calcaneus and the midline of the leg while running was significantly greater ($p<0.01$) in the MTSS group compared to the non-MTSS group. Viitasalo and Kvist described the same finding as Gehlsen and Seger. [89] The angle between lower leg and calcaneus at heel strike was higher for the symptomatic group ($p<0.01$).
Equivalents of pronation, measured with the navicular drop test and the standing foot angle have also been studied. Three prospective studies were published examining the navicular drop test (the difference in distance between the lower border of the navicular and the ground, loaded and unloaded). [13,27,72] The navicular drop test is an indicator of midfoot pronation. Attention to the navicular prominence is also paid in the Foot Posture Index [53,78]. In the study by Bennett et al. among 125 runners the navicular drop test was measured.[13] The mean drop distance in runners with complaints was 6.8 mm (±3.7mm), compared to 3.7 mm (±3.3mm) in the asymptomatic group ($p=0.003$). In the second study, a significant correlation was found between navicular tuberosity displacement and the incidence of MTSS (8.9 ± 2.9 mm compared to 5.6 ± 2.3 mm) ($p<0.01$). [27]
A third study [72] failed to find a significant relationship between navicular drop and MTSS.
Another equivalent of pronation was studied in a case-control study among dancers by Sommer and Vallentyne. [86] They found that a standing foot angle (the angle between medial malleolus, navicular and head of first metatarsal) of less than 140° was predictive of MTSS ($p<0.0001$). The 140° cut off value was chosen because this led to the best sensitivity and specificity (respectively 71.3% and 69.5%).
Female gender is also an intrinsic risk factor. [13,21,95] In a prospective study among naval recruits in Australia a MTSS incidence of 52.9% was found in females, compared to 28.2% in males (Relative Risk (RR) 2.03). [95] The incidence of MTSS in a group of high school cross-country runners in an other prospective study was 19.1 % in females and 3.5 % in males ($p<0.003$).[13] A prospective study among the Australian Defence Force Academy also showed female gender to be a risk factor (MTSS incidence females 30.6%, males 9.8% (Odds Ratio (OR) 3.1).[21]
A higher Body Mass Index (BMI>20.2) was shown to be an intrinsic risk factor in the study by Plisky et al. (OR 5.3).[72] The study prospectively investigated risk factors in a group of cross-country runners.
In the Australian military prospective study by Burne et al. greater internal and external ranges of hip motion was a risk factor ($p=0.01$-0.04 for left and right hip).[21] This was measured with the hip and knee flexed to 90°, with the hip rotated until a firm end feel. The extra amount of internal and external hip ranges of motion was 8-12°.
In the same study [21] the lean calf girth, the maximal calf perimeter corrected for skin thickness, was 10-15mm less among symptomatic cadets compared to asymptomatic cadets. Again, this finding was only significant among males ($p<0.04$).
Leaner calf girth, may also be biomechanically (see biomechanics) associated with MTSS due to reduced shock absorbing capacity.[45,71,76,93] However, lean calf girth is not strictly correlated with calf muscle strength.[9]
Madeley et al. found a significant difference, in a case-control study, in the number of heel raises that could be performed by MTSS patients, respectively 23 and 33 per minute ($p<0.001$).[57] The study demonstrated muscular endurance deficits in athletes with MTSS.
Another case-control study, published in 1980, reported significantly increased plantar flexion strength values ($p<0.05$), using cable tension procedures, in 10 athletes with MTSS compared to 10 healthy athletes.[40]
A case-control study by Viitasaalo and Kvist among male athletes, showed increased passive inversion (19.5° ± 8.6°) and eversion (10.7° ± 4.4°) in the ankle to be an intrinsic risk factor ($p<0.05$).[89] The inversion and eversion were measured manually and repeatedly. The correlation coefficient for this measurement was 0.84.
A retrospective Canadian study found that a below average activity history (< 8.5 years) was a risk factor (OR 3.5 in males, 2.5 in females).[87] Prior to analysis of the data, the activity history was divided between more or less than 8.5 years. The study evaluated the medical records of 2002 running related injuries between 1998 and 2000.
Although suggested in literature, reduced ankle dorsiflexion has not been shown to be an intrinsic risk factor.[21] Ankle dorsiflexion was 32° and 29° in the case group (males and females) and 31° and 27° in the control group.
Risk factors such as increased running intensity, running distance, change of terrain, change of shoes and running with old shoes are often mentioned [54], but there are no scientific studies supporting these claims.

THERAPY

Conservative

Only two randomized controlled trials have been conducted on treatment of medial tibial stress syndrome (table 2.4). The first study was conducted by Andrish et al. [4] in 1974. 97 marine recruits who had developed MTSS, defined by the 1966 American Medical Association (AMA) criteria [2], were randomized into five groups. The range of the duration of pain prior to inclusion was 1 to 14 days. Marines in group one did not run until they were pain free, and applied ice over the painful area three times a day. Group two did the same as group one, but added aspirin (650 mg four times daily) for one week. Group three also did the same as group one, but phenylbutazone (100 mg four times daily) for one week was added. Group four did the same as group one with additional calf muscles stretching three times a day for three minutes. In group five a plaster walking cast was applied for one week.

The number of days that the marines were not capable to perform at full activity was recorded. The marines were considered recovered if no pain or tenderness remained or when five hundred meters running was completed comfortably. The time to recovery for the separate groups was: rest and ice; 6.4 days, rest, ice and aspirin; 9.4 days, rest, ice and phenylbutazone; 7.5 days, rest, ice and heel cord stretching exercises; 8.8 days and cast; 10.8 days. The mean time to recovery was 8.6 days. No significant difference was found between the intervention groups.

The second study was published in 2006.[51] In this study, using the 1966 AMA criteria [2] for inclusion, a leg orthosis was compared with relative rest. The orthosis was an elastic neoprene sleeve with a padded aluminium bar designed to be centered over the most symptomatic portion of the medial leg. Exclusion criterium was any sign of stress fracture on bone scan. 25 soldiers were included, but half of them did not complete the study. Most of them dropped out of the study because of failure to return for follow-up or because of change of permanent training station. Randomization divided the soldiers in two groups: with and without a leg orthosis. Both groups followed an identical rehabilitation program consisting of activity modification and ice massage. Seven days after enrollment in the study a gradual walk-to-run program was initiated. Visual analogue scale (VAS) scores were recorded before and after running. The endpoint was the time until the soldiers could complete running 800 meters without pain. Only 13 soldiers completed the rehabilitation program. Days to completion of the program was 13.4 ± 4.5 days in the orthosis group and 17.2 ± 16.5 days in the control group. These differences were not significant (p= 0.575). In the literature the following treatment regimens are sometimes recommended: calf muscle training, using anti-pronation insoles, massage, maintaining aerobic fitness, electrotherapy [65], and acupuncture [82]. Randomized controlled trials or case series studying these treatment options were not found.

Surgery

Although some studies on surgery for MTSS were found, none of them was controlled and all of them were of poor methodological quality. In all studies diagnosis was made clinically and patients with suspected compartment syndrome were excluded.

Surgery is sometimes performed when complaints persist after conservative treatment fails. Different surgical approaches have been described. Some authors [47,49] performed a fasciotomy along the posteromedial border of the tibia using only local anesthesia. Others [90] used the same technique, but under general anesthesia. Abramovitz et al. [1], Detmer [28] and Yates et al. [94] added removing a strip of the periosteum from along the inner border of the tibia. The effect of the operation is thought to be less traction on the periosteum.[1]

Regarding the pain good to excellent results were found in 69-92% of patients (Yates et al. 69% [94] and Detmer 92% [28]).

Some of the surgical articles report the rate of return to sport.[1,28,47,94] The results mentioned have a broad range; 29 - 93% return to preoperative sports level. The study by Abramovitz et al. [1] showed 29% return to preoperative sports activity, Holen et al. [47] reported 31%, Yates et al. [94] reported 41%, while Detmer [28] showed 93% return to preoperative sports level.

PREVENTION

Seven randomized controlled trials were found on the prevention of MTSS (table 2.5). The first study by Andrish et al. [4] was part of the study which also studied treatment of MTSS. They divided 2777 soldiers randomly into five groups. Group one served as a control group and performed the normal training regime. The other four subgroups conducted the same training regime, but to each a preventative intervention was added. The second group wore a heel- pad in their shoes. Group three performed heel-cord stretching exercises three times daily for three minutes. The fourth group performed the same stretches as group three and wore a heel pad. Group five entered a gradual running program two weeks before the start of the training schedule and equaled the rest of the groups after the third week of training. They also performed fitness exercises. No significant difference was found between the different groups in incidence of MTSS. In the control group the incidence was 3.0%, in the heel-pad group 4.4 %, in the heel cord stretching exercises group 4.0%, in the heel-pad plus heel cord stretching exercises group 3.0% and in the group with graduated running program 6.0%.

The second study [14] examined the effect of two kinds of boots in 2841 soldiers over an eight week period of time. Training consisted mostly of physical training, although this was not further specified. One boot was constructed of leather, while the other boot had a nose of cotton and nylon (boot used in tropical environments). The study was conducted to acquire data regarding the effect of the two types of boots on type and frequency of leg disorders among soldiers. The

incidence of MTSS, defined as pain and tenderness of the tibia due to overexertion, was the same in both groups.
In the next study [15] 555 female soldiers were randomized to wear one of three kinds of insoles. A urethane foam insole and a custom made insole were compared to a standard insole. During nine weeks all female soldiers followed the same training program. There were no significant differences between the groups. A definition of MTSS was not stated.
The fourth randomized controlled trial was published in 1990.[83] 1538 soldiers were included, of which 237 were randomized into an intervention group. They performed nine weeks of training. The control group wore standard insoles and the intervention group wore neoprene insoles. After nine weeks of training 20.4% of the control group had developed MTSS, although this was not defined, compared to 12.8% in the intervention group. This was a significant difference.
The fifth study was conducted in 2002.[55] 146 soldiers were randomized to receive standard insoles or a semi-rigid insole, which was handmade and was adjusted per foot. After three months of training a significant difference ($p<0.005$) was present. Twenty-four (38%) soldiers with the standard insole developed MTSS, compared to 4 (8%) in the intervention group. In this study MTSS was not defined.
Schwellnus and Jordaan [84] examined if calcium supplementation prevented MTSS for which no definition was given. Of 1398 soldiers, 247 were randomly selected as an experimental group. Before the study started, dietary assessment took place of a selected number of soldiers in the control and experimental groups, not yet taking the calcium. Food supplements and calcium intake were calculated. No dietary differences were found. An additional 500 mg calcium per day was provided to the experimental group. No significant differences were found in number of patients with MTSS between the experimental and control groups.
The seventh preventative study [73] examined pre-exercise stretching: 1388 army recruits were randomly allocated to stretch or control groups. The stretching protocol consisted of 20 seconds of static stretching for the different lower leg muscles. The study revealed no significant effect on the occurrence of MTSS, which was not further defined.

DISCUSSION

A general weakness when reviewing literature on MTSS is the confusing terminology and the lack of consensus surrounding the definition. This makes comparison of different studies difficult. No widely used definition of MTSS is available in the current literature. Based on the literature reviewed a definition of MTSS is suggested: pain felt along the posteromedial border of the tibia. The pain is aggravated by weight bearing activity and subsides gradually on stopping. On examination there is recognizable pain on palpation of the posteromedial border over a length of at least five centimeters. This definition distinguishes MTSS from stress fracture, in which the pain is more focal.

The diagnosis has always been made clinically and at present it is not necessary to alter this. The high prevalence of abnormal imaging studies in asymptomatic athletes means that these techniques should not be used routinely to establish the diagnosis.
In the nineteen seventies Roub et al. [79] were the first to suggest that increased levels of stress to the tibia could result in a spectrum of bony overload. In this spectrum the endstage was a cortical fracture. In the beginning of this spectrum, when bone resorption outpaces bone replacement, MTSS occurs.
Several studies show that normal bone remodeling involves resorption of bone before the rebuilding of new bone structures occurs. [25,32,34,35,36] Imaging of tibiae of asymptomatic runners shows abnormalities mimicking the abnormalities found in MTSS. [16] This is thought to represent normal remodeling.
From the literature, it is unclear as to whether tibial stress fracture is a continuum of MTSS. Although suggested since the seventies and plausible since MTSS seems to be a metabolic bony problem, no conclusions can be made. In one study [6] athletes with MTSS kept on running after being diagnosed with MTSS. On follow-up MRI scanning, there was no evidence of stress fracture. This could mean that MTSS does not develop into a stress fracture, but also that some symptomatic tibiae healed before fracturing.
Another theory could be: MTSS is not in continuum with tibial stress fracture. MTSS and tibial stress fracture could be two distinct entities. It has been shown that different ways of loading: tension, rotation or compression, produce different types of microfracture, in which compression leads to longitudinal abnormalities.[41] Possibly, bone variations between individuals determine if one person develops MTSS and the other tibial stress facture. Further research is needed to better understand the mechanism of development of MTSS and tibial stress fracture. For example, histological samples of MTSS could be studied for microcrack patterns and compared to stress fracture findings. Recently O'Brien et al. [70] and Raesi et al. [77] studied the behaviour of microcracks in loaded bones. This behaviour could be compared in MTSS and stress fractures. Also, more studies using high-resolution CT-scanning, comparing findings between MTSS and stress fractures could be conducted. Recently micro-CT images were obtained to assess bone microdamage. [92] Slices of 10 µm thickness could be made with this CT device. Highly detailed images of microdamage in MTSS and stress fractures could possibly be studied.

Many controversies surround MTSS. This syndrome has had at least five different names over the past fifty years. Debate still continues as to what the underlying cause of MTSS is. For decades periostitis caused by traction of the tibialis posterior, flexor digitorum longus or soleus muscles was commonly cited as the mechanism causing MTSS. However, anatomical studies showed that complaints are regularly felt more distal to the most distal attachment of the tibialis posterior, soleus and flexor digitorum longus muscles. Only one study has investigated the role of traction in MTSS. [19] This study supplied some scientific data on trac-

tion as a possible contributor in the development of MTSS.
Recently bony overload of the medial tibia has been shown to be important as the underlying problem. There are four important findings that support the theory that bony overload forms the primary patho-physiological basis for MTSS. First, on triple phase bone scans the last phase is abnormal, showing that the bone and periosteum are involved. [10,46] Secondly, on high resolution CT-scan the tibial cortex is found to be osteopenic. [38] On MRI images bone marrow edema as well as a signal along the periosteum can be seen. [6,37] Fourthly, in patients with MTSS bone mineral density is reduced when compared to controls. [58] When symptoms improve the bone density returns to normal values. [59]

Through prospective studies a number of intrinsic risk factors for MTSS have been established. A pronatory foot type with standing, is an intrinsic risk factor. [95] Also, an indicator of mid-foot pronation, a positive navicular drop test, is an intrinsic risk factor. [13,27,72] Female gender [13,21,95], a higher Body Mass Index [72], greater internal and external hip ranges of motion [21] and leaner calf girth [21] are also prospectively found intrinsic factors.

Little research has been conducted on the therapy of MTSS. Only two randomized controlled trials, published thirty years apart, were found. [4,51] The result of these studies is that no intervention proved more valuable than rest alone. The use of common therapies such as massage, strengthening exercises for the calves and anti-pronatory orthosis has never been investigated.
Sometimes surgery is performed if conservative treatment fails. The quality of studies studying surgery and MTSS is poor. These studies point out that surgery can be useful for pain reduction, but only few athletes will participate at their pre-injury sports level.
Seven preventative studies on MTSS have been published. Three studies investigated the use of different kinds of insoles. Two studies, using a semi-rigid orthosis and a neoprene insole found significantly lower incidence of MTSS after this intervention.

CONCLUSION

MTSS is a common overuse injury affecting many thousands of athletes and military recruits worldwide. It is most probably primarily due to bony overload of the posteromedial tibial border. There is little evidence to support the commonly cited periostitis as a result of traction as the primary underlying aetiological factor. Whether or not MTSS and tibial stress fractures are on a continuum is yet to be established and should be investigated further.
MTSS is a clinical diagnosis and the prevalence of abnormal findings in asymptomatic subjects means that results should be interpreted with caution.
There is level 1 evidence showing that pronatory foot type and female gender are intrinsic risk factors. There is level 2 evidence showing that BMI, greater internal and external ranges of hip motion and calf girth are intrinsic risk factors.
There have been only two studies that examined the conservative treatment of MTSS. At present there is no evidence that any treatment is superior to rest alone. There is level 2 evidence that inlays may help in the prevention of MTSS.
A definition of MTSS is proposed: pain felt along the middle or distal third of the posteromedial border of the tibia. The pain is aggravated by weight bearing activity and subsides gradually on stopping. On examination there is recognizable pain on the palpation of the posteromedial border over a length of at least five centimeters.

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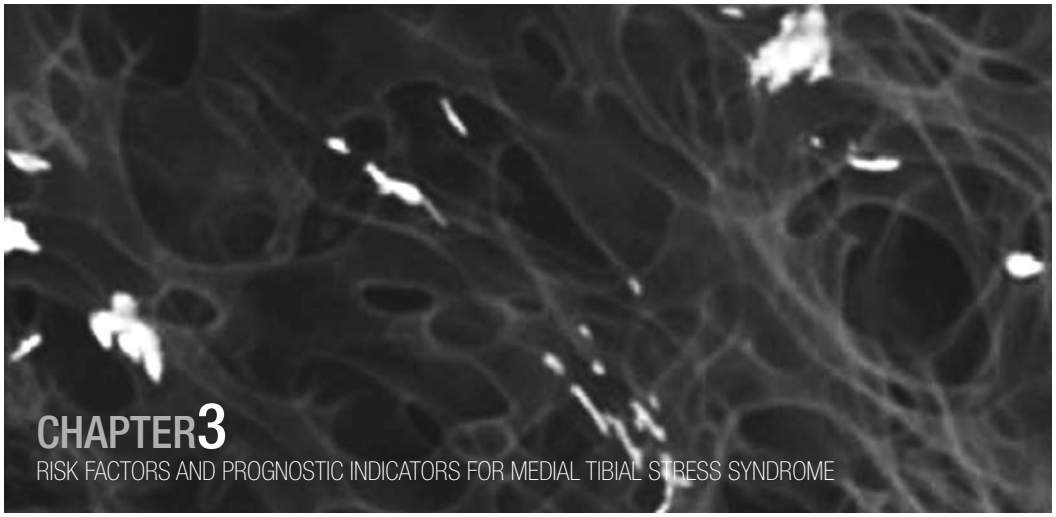

CHAPTER3
RISK FACTORS AND PROGNOSTIC INDICATORS FOR MEDIAL TIBIAL STRESS SYNDROME

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ABSTRACT

The objective of the study was to examine risk factors and prognostic indicators for medial tibial stress syndrome (MTSS). In total 35 subjects were included in the study. For the risk factor analysis the following parameters were investigated: hip internal and external ranges of motion, knee flexion and extension, dorsal and plantar ankle flexion, hallux flexion and extension, subtalar eversion and inversion, maximal calf girth, lean calf girth, standing foot angle and navicular drop test. After multivariate regression decreased hip internal range of motion, increased ankle plantar flexion and positive navicular drop were associated with MTSS. A higher BMI was associated with a longer duration to full recovery. For other prognostic indicators no relationship was found.

INTRODUCTION

Medial tibial stress syndrome (MTSS) is one of the most common exercise induced leg injuries (Clanton & Solcher, 1994). The highest incidences of MTSS were found in military studies (Yates & White, 2004). In the past MTSS was thought to be due to a traction induced periostitis. A recent systematic review concluded that MTSS is caused by bony overload, with several studies supporting this (Moen et al., 2009). Histological studies showed that no periostitis is present (Bhatt et al., 2000; Johnell et al., 1982). Imaging studies showed that the tibial cortex is osteopenic and that the bone marrow is involved (Aoki et al., 2004; Gaeta et al., 2006). Bone density studies showed that the tibial bone density in MTSS subjects is decreased and that bone density returns to normal values after recovery (Magnusson et al., 2001; Magnusson et al., 2003).
Several risk factors for MTSS have been identified from previous prospective and case control studies. Intrinsic risk factors that have been previously identified are increased pronation of the midfoot while standing (Yates & White, 2004; Bandholm et al., 2008; Raissi et al., 2009), higher body mass index (Plisky et al., 2007), female gender (Burne et al., 2004; Yates & White, 2004; Raissi et al., 2009), lean calf girth (Burne et al., 2004), increased hip internal and external rotation (Burne et al., 2004) and increased plantar flexion range of motion (Hubbard et al, 2009). Some of these risk factors, such as female gender, were found in multiple studies, but most risk factors were identified in single studies. A measure of pronation, the navicular drop test, was also examined in multiple studies.
The above mentioned risk factors could not be confirmed in all studies investigating risk factors and data are often conflicting (Hubbard et al., 2009; Plisky et al., 2007; Raissi et al., 2009). Several known risk factors are derived from just one single study (Burne et al., 2004). Identifying reliable risk factors for MTSS is necessary to specifically apply methods aimed at treating them. In order to prevent MTSS, identifying risk factors is necessary to target interventions.

Although several studies investigated risk factors for MTSS, no study aimed at describing prognostic clinical indicators for the recovery of MTSS. One retrospective study found that the degree of abnormalities on MRI could predict time to recovery (Arendt et al., 2003). This study was mainly aimed at early stress reactions of the tibia and stress fractures. No study is available to predict the time to recovery for MTSS specifically.
The first aim of this study therefore was to assess risk factors for MTSS to increase their reliability. The second aim of this study was to identify prognostic indicators to predict the duration of recovery.

MATERIAL AND METHODS

Subjects
Male subjects were recruited from two Royal Dutch Army bases. Subjects who were injured had to stop basic army training and were placed into a remedial platoon. When subjects reported leg symptoms, they were referred to the trained investigator. Subjects were included in the study if they fulfilled the inclusion criteria. The inclusion criteria were (Yates & White, 2004):
- exercise induced pain in the leg on the posteromedial tibial border
- pain on palpation of the posteromedial tibia for at least five centimeters
- symptoms present for at least two weeks

Subjects and controls were excluded if they had a history of a tibial fracture on either side. The control group was randomly selected from active platoons training at one of the two army bases. Recruits in the control group were included if they gave informed consent. Subjects were excluded if a clinical suspicion of compartment syndrome or tibial stress fracture was present. Subjects with compartment syndrome usually complain of burning and cramping over the involved compartment with exercise. Pain will often decrease with rest (Edwards et al., 2005). A stress fracture was suspected if pain was localized to the fracture site and on examination, palpation of the tibia was only focal (Edwards et al., 2005). The local medical ethical committee agreed with the study. All subjects gave their informed consent.

Demographic information and physical examination
One investigator obtained baseline demographic values with a standardized questionnaire and performed a standardized physical examination in the study and control group. The questionnaire recorded age, physical activity over the last 6 weeks, kind of sport prior to commencing training and past medical history. Subjects also completed a Sports Rated Activity Scale (SARS) (Borsa et al., 1998) form. The SARS score assesses functional activity which is expressed on a 0-100 scale (0= severe symptoms in daily activities, 100= no symptoms during heavy sport activity). Weight and height were measured (electronic scale to 0.1 kg and stadiometer 0.5 centimeter) and the body mass index (BMI) was calculated. With the physical examination the following parameters were measured: hip external and internal ranges of motion, knee flexion and extension, dorsal and plantar ankle flexion, subtalar eversion and inversion, hallux extension and flexion, maximal calf perimeter, lean calf girth, standing foot angle and navicular drop test. Ranges of motion were measured using a goniometer (Zimmer Ltd., United Kingdom), which has good intra- and inter observer reliability (Ekstrand et al., 1982).

Hip internal and external ranges of motion were measured with the patient supine and with the knee and hip 90° flexed. The hip was internally and externally rotated to a firm end feel (Burne et al., 2004).

Knee flexion and extension were both measured after reaching a firm end feel with the patient in supine position (Gogia et al., 1987).

Ankle dorsal and plantar flexion ranges of motion were obtained with the subject in prone position with the knees extended and the ankles hanging over the edge of the table. The measurement was obtained with the axis of the goniometer on the lateral malleolus; the stationary arm aligned with the head of the fibula and the movable arm was aligned with the fifth metatarsal. The investigator passively dorsiflexed and plantar flexed the foot until tension was noticed (Jonson & Gross, 1997).

Subtalar eversion and inversion of the ankle were assessed with the subject supine with the knees extended (Gheluwe et al., 2002).

Hallux extension and flexion were measured with the goniometer until tension was noticed, with the subject in supine position and the knees extended (Gheluwe et al., 2002).

Maximal calf girth was measured in centimeters with the subject standing relaxed and upright. A measuring tape was used to obtain the maximum girth of the relaxed calf (Zatsiorsky et al., 1990).

Lean calf girth was measured in centimeters after the maximal calf girth. A skin calliper was applied 10 mm distally to the left thumb and index finger used to raise a vertical fold on the relaxed calf. A corrected calf girth was calculated by subtracting the appropriate skin fold thickness from the maximal girth measurement (Burne et al., 2004).

The standing foot angle was measured according to Sommer and Valentyne (Sommer & Vallentyne, 1995). With the subject standing, the angle between the first metatarsal, medial malleolus and the navicular bone was measured.

Results were dichotomized to 140° or more and less than 140°. This cutoff was used since it had the best sensitivity and specificity (71% and 70% respectively (Sommer & Valentyne, 1995)).

The navicular drop test was performed after marking the navicular prominence with the subject sitting in a chair and the feet on the ground (non-weight bearing) in neutral subtalar position. The distance from the prominence to the floor was then measured. This test was repeated with the subject standing on both feet, shoulder width apart (weight bearing). The two measurements were subtracted and this resulted in a difference score in centimeters (Blackburn, 2002). The results were dichotomized to < 0.5 centimeter and ≥ 0.5 centimeter based on the study by Bennett et al. (Bennett et al., 2001).

Prognostic indicators
The subjects with MTSS (cases) were prospectively evaluated to study prognostic indicators. During follow-up independent variables were studied as possible prognostic factors. Days to recovery was the dependent variable. First, it was assumed that the longer the duration of symptoms, the longer recovery would take. Secondly, it was assumed that the lower Sports Rated Activity Scale (SARS) score (Borsa et al., 1998) at baseline the longer it would take to recovery. Thirdly, it was assumed that being able to run a longer distance without pain before the start of the treatment was a good prognostic sign. Finally, it was assumed that the presence of single risk factors found in this study after univariate regression, would lead to longer recovery.
Subjects were considered recovered when they were able to finish a rehabilitation protocol that included graded running three times weekly and physical therapy. The physical therapy consisted of strengthening exercises of the calves and stability exercise for the ankle, which were performed five times a week.
The graded running started with interval running and later continuous running according to a standardized schedule until 18 minutes could be run continuously without symptoms. This treatment was considered as standard care.
Before starting the rehabilitation protocol a running test was performed by the subject. The running test consisted of 1 minute of walking on a treadmill at 6 km / hour. The speed was then set at 10 km / hour and running started. The subject stopped running when pain was felt in the leg on the posteromedial border. The distance run without pain during the 10 km / hour running was recorded in meters. Before the test the researcher explained that the definition of pain was: more than ten consecutive strides with a pain score of four or higher (0-10).

Data analysis
After blinded, double data entry, all analyses were carried out using SPSS version 16.0. The odds ratio (OR) was used to express the association between the dependent and the independent variables. The frequencies of risk factors are presented with their mean and standard deviation (SD). In case of skewed distributions, median and interquartile ranges (IQR) were used. Groups were compared using the Independent Samples T Test or, in case of skewed distributions, the non-parametric Mann–Whitney U Test. A logistic regression analysis was used for calculating the associations between the dependent variable (MTSS or not) and the independent variables. After a univariate regression analysis, a multivariate logistic regression model (backward Wald) was run on the independent variables that showed a relationship to the presence of MTSS. Threshold for entry of independent variables in the multivariate model was $p < 0.05$ and for removal $p > 0.1$. The Nagelkerke R^2 was used to assess the explained variance of the model.

A linear regression analysis was used for calculating the associations between the dependent variable (time to recovery) and the independent prognostic variables. After a univariate regression analysis, a multivariate linear regression model was run on the independent variables that showed a relation to time to recovery. Threshold for entry of independent variables in the multivariate model was $p < 0.05$ and for removal $p > 0.1$.
The Nagelkerke R^2 was used to assess the explained variance of the model.

RESULTS

In total 35 male recruits participated in this study, 15 subjects and 20 control subjects. The demographic parameters and baseline values are presented in table 3.1. At baseline no significant differences were found between the groups, besides the BMI ($p = 0.04$). The comparison of the physical examination parameters between subjects and the control group is presented in table 3.2.
Univariate regression showed that BMI, decreased internal hip range of motion, positive navicular drop test and increased ankle plantar flexion were significantly associated with MTSS (table 3.3). After multivariate regression analysis increased ankle plantar flexion, decreased internal hip range of motion and a positive navicular drop test were significantly associated with MTSS.

Clinical prognostic factors
The mean time to recovery for the subjects was 58,1 days (SD 27.1). After univariate regression higher BMI was significantly associated with time to full recovery ($p = 0.005$; Nagelkerke R^2 value 0.497). The duration of symptoms ($p = 0.218$), the baseline SARS score ($p = 0.789$) and the distance run without pain ($p = 0.270$), decreased internal range of hip motion ($p = 0,375$), positive navicular drop test ($p = 0.292$) and increased ankle plantar flexion ($p = 0.750$) were not found to be significantly related to time to full recovery. The Nagelkerke R^2 values for these prognostic parameters were also low, respectively 0.124 / 0.006 / 0.100 / 0.066 / 0.092 and 0.009.

Table 3.1: Demographic parameters and baseline values.

	Subjects: mean (SD)	Controls: mean (SD)	p-value
Age (years)	19 (1.5)	19 (1.5)	0.60
Height (centimetres)	183 (6.5)	183 (6.3)	0.96
BMI (kg / (height)2)	23.8 (2.0)	22.5 (1.6)	0.04
Duration of complaints (days)	34.1 (17.9)	x	x
SARS score at baseline	71.3 (21.0)	x	x
Symptom free running distance (meters)	790.0 (550.0)	x	x

SARS: Sports Activity Rated Scale score

Table 3.2: Physical examination parameters.

	Subjects: mean (SD)	Controls: mean (SD)	*p*-value
Hip internal range of motion (degrees)	40 (9.3)	47 (8.7)	0.087
Hip external range of motion (degrees)	60 (13.7)	53 (12.5)	0.082
Knee flexion (degrees)	140 (6.3)	135 (9.6)	0.14
Knee extension (degrees)	5 (3.7)	5 (2.9)	0.13
Ankle dorsal flexion (degrees)	15 (5.5)	15 (6.2)	0.93
Ankle plantar flexion (degrees)	52 (8.6)	43 (5.6)	0.001
Hallux flexion (degrees)	35 (8.4)	30 (6.1)	0.55
Hallux extension (degrees)	50 (17.2)	50 (9.5)	0.89
Subtalar inversion (degrees)	30 (5.4)	30 (5.0)	0.17
Subtalar eversion (degrees)	20 (5.9)	20 (3.1)	0.95
Maximal calf girth (centimetres)	38.2 (2.0)	37.2 (2.1)	0.16
Lean calf girth (centimetres)	37 (2.1)	36 (2.1)	0.20
Dichotomised values			
Standing foot angle < 140 degrees (yes / no)	9/15	9/20	0.38
Navicular drop > 0,5 centimetres (yes / no)	6/15	1/20	0.027

Table 3.3: Univariate and multivariate regression analysis for MTSS risk factors.

Parameters	Univariate regression (95% CI)	Multivariate regression (95% CI)
Height	1.0 (0.9-1.1)	-
Weight	0.9 (0.8-1.0)	1.1 (0.8-1.4)
BMI	0.7 (0.4-1.0)	0.3 (0.1-1.5)
Internal hip range of motion	1.1 (1.0-1.2)	1.2 (1.0-1.4)*
External hip range of motion	1.0 (0.9-1.0)	-
Ankle dorsal flexion	1.0 (0.9-1.2)	-
Ankle plantar flexion	0.8 (0.7-1.0)	0.7 (0.5-0.9)*
Hallux flexion	1.0 (0.9-1.1)	-
Hallux extension	1.0 (1.0-1.1)	-
Subtalar inversion	1.1 (0.9-1.3)	-
Subtalar eversion	1.0 (0.8-1.1)	-
Standing foot angle	0.6 (0.1-2.1)	-
Navicular drop test	12.7 (1.3-121.5)	28 (1-691)*
Calf girth	0.8 (0.5-1.1)	-
Lean calf girth	0.8 (0.6-1.1)	-

- = not assessed with multivariate regression analysis since $p > 0.1$
* = significantly associated with MTSS after multivariate regression analysis

DISCUSSION

This case control study examined possible risk factors as well as prognostic indicators for MTSS. After multivariate regression analysis increased ankle plantar flexion, decreased internal hip range of motion and a positive navicular drop test were significantly associated with MTSS and defined as risk factors. A higher BMI was shown a prognostic indicator for a longer time to full recovery. All other prognostic indicators such as previous duration of symptoms, functional activity score, the symptom free running distance at baseline, increased ankle plantar flexion, decreased internal range of hip motion and positive navicular drop test were not associated with time to recovery.
A decreased range of hip internal rotation was found to be associated with MTSS in this study. This is in contrary to the findings of Burne et al. who found an increased hip internal range of motion (Burne et al., 2004). The mechanism

through which hip ranges of motion affects loading of the tibia is unclear. Burne et al. speculated that increased internal hip range of motion caused a specific pattern of running, which could lead to increased loading of the posteromedial tibia. Possibly, increased and decreased internal hip range of motion both influence running in a way that the posteromedial tibia is excessively loaded.
Our study found an increased ankle plantar flexion range of motion in subjects compared to controls. The plantar flexion range of motion was 52 degrees in subjects and 43 degrees in controls ($p = 0.001$). This was also found in a study among collegiate athletes (Hubbard et al., 2009). The plantar flexion in athletes with MTSS was 46° and 40° in athletes without MTSS ($p = 0.004$). Possibly, the increased plantar flexion in the MTSS subjects would lead to more forefoot landing. Previous in vivo work showed that forefoot landing resulted in increased strain on the posteromedial tibia compared to heel landing (Ekenman et al., 1998).
One of the most consistently found risk factors for MTSS is increased pronation of the foot. In this study a positive navicular drop test (> 0.5 centimeters) was associated with MTSS. In the literature equivalents of pronation have been investigated in many ways. To study pronation, standing foot angle and navicular drop test were used. We chose to dichotomize the test result in <0.5 cm and ≥0.5 cm based on the results in the study by Bennett et al. (Bennett et al, 2001). In our study, the navicular drop test was associated with MTSS, but not the standing foot angle test. The standing foot angle test was investigated by Sommer and Valentyne (Sommer & Valentyne, 1994). In their case control study with folk dancers a standing foot angle < 140° was significantly associated with MTSS ($p < 0.001$). Six studies examined the relationship between navicular drop and MTSS, of which five were prospective studies and one had a case control design. In four studies a positive association between a positive navicular drop test was found (Bandholm et al., 2008; Bennett et al., 2001; Raissi et al., 2009; Yates & White, 2004), while in two studies no association was present (Hubbard et al., 2009; Plisky et al., 2007).
This study could not find an association between increased BMI and leaner calf girth after multivariate regression. Plisky et al. found that a BMI > 20.2 was significantly associated with MTSS (Plisky et al., 2006). Another study found that lean calf girth was just lower than in symptomatic men compared to the controls. They found that the lean calf girth in the right leg was significantly lower compared to the controls ($p = 0.044$), this was not found in the left leg. In this study no significant difference in lean calf girth in subjects versus controls was found ($p = 0.20$).
Of the prognostic indicators, our study found a significant association between a higher BMI and time to full recovery ($p = 0.005$). The equation [(15xBMI) -280)] can be used to estimate time to recovery in days. This equation has to be evaluated in future studies to become practically relevant. Possibly, the association between BMI and time to full recovery is caused by increased bending of the tibia when more load (weight) is applied to the tibia. Increased bending has shown to lead to pronounced microdamage of the cortex (Judex et al., 1997). In this way, it is possible that more loading through a higher BMI would lead to postponed recovery. Our study did not show a significant relationship between either the duration of symptoms before treatment, SARS score at baseline, the distance run without pain, increased ankle plantar flexion, decreased internal hip range of motion, positive navicular drop test and time to recovery. In the literature no previous study was found which examined the relationship between prognostic indicators and time to recovery. It remains difficult to estimate the number of days until recovery for MTSS. One study investigated the relationship between the degree of abnormalities on MRI scan and time to recovery (Arendt et al., 2003). However, the study population consisted of subjects with early stress reactions and stress fractures and not specifically with MTSS. In the future more larger prospective studies on prognostic indicators for the recovery from MTSS are needed to predict the speed of recovery more accurately.

Although various significant differences in physical parameters were found in this study it has to be considered that the differences between subjects and controls were small. Also, it cannot be excluded that inter-individual measurements with a goniometer could have effected these differences (Gheluwe et al., 2002).
Our study has several limitations. First, the study was conducted in an army population. One can argue whether results of this study can be applied to the athletic population. We think that soldiers can be considered as highly athletic due to their extensive training and that results from military populations can be applied to athletes and visa versa. Secondly, in our study only 35 subjects were included. Despite this, we were able to show that several parameters were significantly associated with MTSS. We suspect that this relationship would become more evident in larger populations. The third limitation was the case control study design. With a retrospective design the studied physical parameters may have changed after the MTSS symptoms started. Furthermore, case control studies are to some extent open to information and selection bias and uncontrolled confounding (Kelsey et al., 1986). To control for information bias we tried to obtain information from subjects and controls in a similar way by using one investigator. To control for selection bias the control subjects were randomly selected.

PERSPECTIVES

In order to prevent MTSS, identifying risk factors is necessary to target interventions to alter them. This study provides more evidence for two existing risk factors (increased plantar flexion in the ankle and increased navicular drop) and found one previously unknown risk factor; decreased hip internal range of motion. The possible preventative effect of targeted interventions, such as an anti-pronatory orthosis should be studied in future randomized controlled trials.
This is the first study to have examined whether or not clinical baseline charac-

teristics are related to the time to recovery. The average time to recovery was 58.1 days (SD 27.1). A higher BMI was associated with a longer duration to full recovery. For other prognostic indicators and risk factors, no relationship was found.

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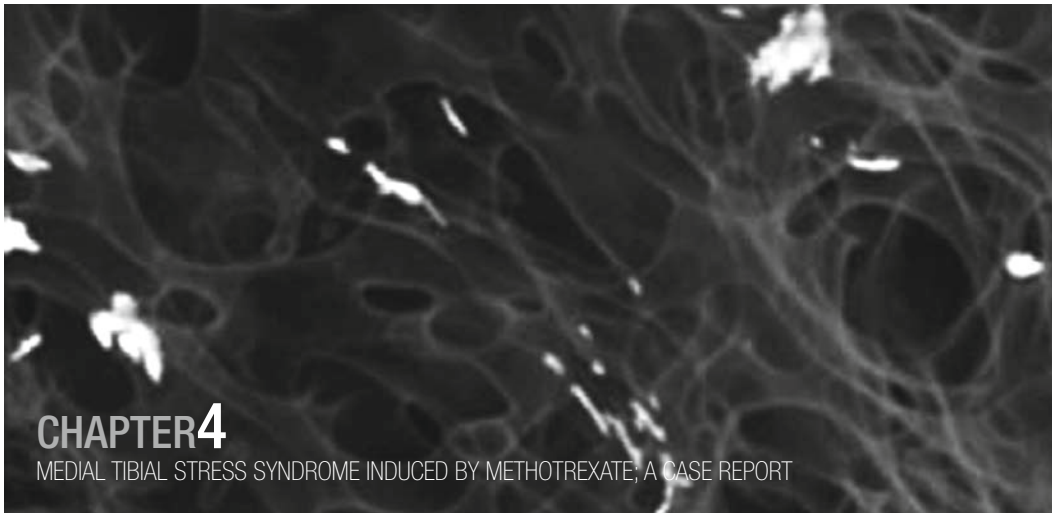

CHAPTER4
MEDIAL TIBIAL STRESS SYNDROME INDUCED BY METHOTREXATE; A CASE REPORT

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Turk J Rheumatol 2011; 26(3): 1-4

ABSTRACT

Normally, the cause of medial tibial stress syndrome (MTSS) is overload of the tibia, frequently seen in athletes and military recruits. This case report describes a physically inactive patient with psoriatic arthritis with the classical symptoms of MTSS. The symptoms were due to the use of methotrexate and ceased with lowering the methotrexate dosage.

INTRODUCTION

Medial tibial stress syndrome (MTSS) is a common overuse injury of the lower leg. For years it was thought to be due to periostitis [1,2]. A recent review showed that it is more likely that MTSS is caused by bony overload [3]. There are four important findings that support the theory that bony overload forms the primary pathophysiological basis for MTSS. First, on triple phase bone scans the last phase is abnormal, showing that the bone and periosteum are involved [4,5]. Secondly, on high resolution CT-scans the tibial cortex is found to be osteopenic, as can be seen in patients as well as in asymptomatic athletes as a sign of bone remodeling [6]. On MRI images bone marrow edema as well as a signal along the periosteum can be seen [7,8]. Fourthly, in patients with MTSS the bone mineral density is reduced when compared to controls [9]. When symptoms improve the bone density returns to normal values [10]. Normally, the bony overload is caused by the repetitive loading of the tibia in athletes and recruits.
This case report describes a patient with psoriatic arthritis, who had not repetitively loaded the tibiae, but still had the classical symptoms and signs of MTSS. The possibility that the use of methotrexate could lead to methotrexate osteopathy and therefore insufficiency fractures, was presented in a previous case series [11]. That is why for this case report, it was proposed that the patients MTSS was due to the methotrexate, used in the treatment of the psoriatic arthritis.

CASE HISTORY

A 49 year old male presented at the out patients department of a sports medical center in the Netherlands. He complained of a two year history of pain in the right shin while walking, but also on resting. The pain was felt on the medial and sometimes lateral side of the leg and could be present at night. As a prior treatment he had rested his shin, but this did not relieve his pain symptoms.
He was diagnosed with psoriatic arthritis in 2006, for which he had used methotrexate 10 mg per week for the past three years . This had had a good effect on his arthritic complaints and he was without complaints of his psoriatic arthritis at the time of presentation. Apart from hypertension, he had no other past medical history. He swam twice a week, but did not perform any other excessive

physical exercise and had a sedentary profession.
On physical examination inspection revealed no abnormalities locally and a normal alignment of the legs and feet. On palpation the posteromedial border of the tibia was tender over a length of ten centimeters. The pain was recognized by the patient as the pain he usually suffered. Resistance testing of the posterior tibial muscle and the plantar flexors of the foot was not painful. Some pain was felt on performing the resistance test of the peroneal muscles. The ankle and knee had a normal range of motion and were stable on assessing the ligaments. To differentiate from hypertrophic osteoarthropathy and primary hyperparathyroidism, no clubbing of the fingers, hypertrophic skin changes or palpable masses in the neck were observed. Laboratory analysis revealed; calcium 2.13 mmol/l, phosphate 1.24 mmol/l, albumin 44 g/l, ASAT 37 U/l, ALAT 34 U/l, CRP <3 mg/l.
A magnetic resonance imaging (MRI) scan of the right lower leg was performed. The T2 weighted, fat suppressed images revealed bone marrow oedema of the right tibia (figure 4.1). No periosteal edema was present and no fracture line was visible. No hyperintense signal or other abnormalities were found in or surrounding the peroneal tendons.
The diagnosis of MTSS was made by the sports medicine physician who referred the patient back to the rheumatologist, who was specialised in psoriatic arthritis. The dose of the methotrexate was lowered from 10 mg per week to 7.5 mg per week. Within two weeks after altering the methotrexate dose the complaints disappeared. After three months he developed symptoms of psoriatic arthritis of the right proximal-inter-phalangeal (PIP) joints. After 6 months the methotrexate dose was increased to 10 mg / week again after which the PIP joint complaints disappeared. There was no recurrence of his shin pain.

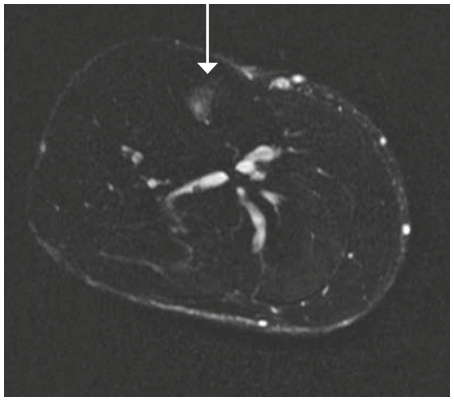

Figure 4.1: MRI of a 49 year old male with psoriatic arthritis. On the MRI the T2 weighted, fat suppressed axial image of the right leg shows bone marrow oedema in the tibia (arrow).

DISCUSSION

This case report presents a patient with MTSS, not caused by excessive axial loading of the tibia, but likely due to methotrexate osteopathy. The diagnosis of MTSS in this patient was made clinically according to the criteria by Yates *et al.* (2004) and also confirmed using MRI [12]. The abnormalities on MRI in MTSS patients have been previously described by different authors [4,7,13]. On T2 weighted images periosteal oedema and / or bone marrow oedema can be seen.
Methotrexate osteopathy is an uncommon side effect of methotrexate use [11,14,15,16]. In 2006 Alonso *et al.* described two cases in which MTSS was caused by methotrexate use [17]. In their report the methotrexate was ceased after the side effect was recognized. In addition to this bisphosphonates were started. With this treatment regimen one patient with MTSS was asymptomatic within one week and the other patient was without symptoms in four weeks. This is in keeping with the findings in this case report, in which symptoms disappeared after lowering the methotrexate doses in two weeks. Due to these findings, Alonso *et al.* suggested that there may be a relationship between methotrexate and MTSS [17].
Several reports described the influence of methotrexate on bone tissue. Back in 1965 Nevinny *et al.* described the effects on the short term use of methotrexate in humans. They found increased calcium and phosphate levels in the urine and faeces suggesting increased bone turnover / osteoclast activity [18]. An animal study from the eighties showed that bone turnover rates were about 60% lower due to methotrexate use. In this study, also reduced volume and thickness of the osteoid was found [19]. These findings were confirmed in humans in the study by Preston et al. in which the osteoid thickness and bone formation rate were also decreased by the use of methotrexate [20]. A recent in vitro study found that osteoblast proliferation was not impaired by methotrexate, but that osteoblast cellular activity and mineralization capacity were suppressed (21). In MTSS, bone turnover processes are also altered [22,23], so that the local bone density is decreased [9].
Although MTSS is normally caused by extensive axial leg loading, this case reports shows that methotrexate can induce the same clinical entity. Rheumatologists should also be aware that primary hypertrophic osteoarthropathy and primary hyperparathyroidism can cause leg complaints too [24,25]. Clinicians like oncologists and rheumatologists should be alert that in patients treated with methotrexate the cause of lower leg complaints can be MTSS. This overuse syndrome is commonly seen by sports physicians and orthopaedic surgeons, but less frequently by other specialists. The diagnosis can be made using simple clinical examination with recognisable tenderness along the posteromedial tibial border and with MRI. A lower dosage or the cessation of methotrexate alleviates the symptoms of MTSS.

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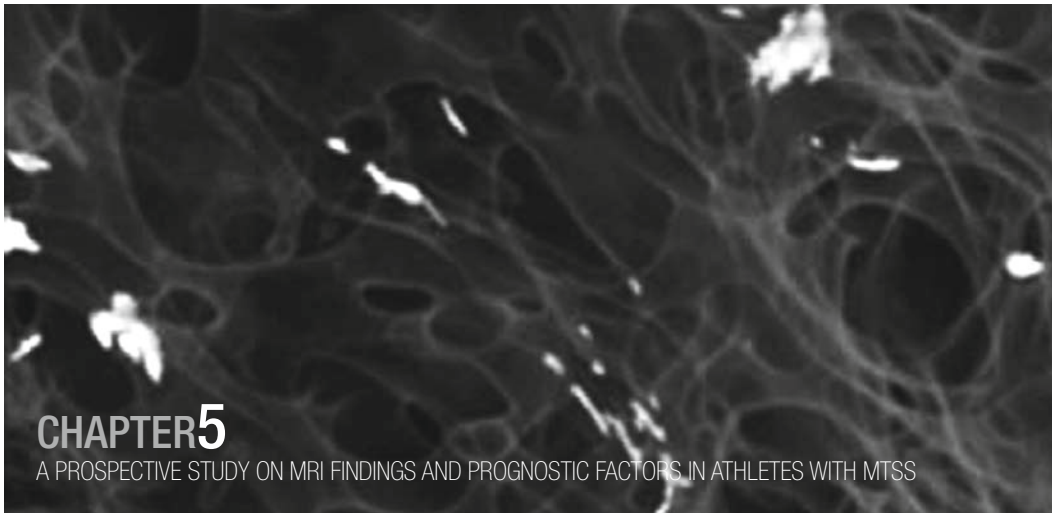

CHAPTER5
A PROSPECTIVE STUDY ON MRI FINDINGS AND PROGNOSTIC FACTORS IN ATHLETES WITH MTSS

Moen MH, Schmikli SL, Weir A, Steeneken V, Stapper G, de Slegte R, Tol JL, Backx FJG, Scand J Med Sci Sport 2012 (accepted)

ABSTRACT

In medial tibial stress syndrome (MTSS) bone marrow and periosteal oedema of the tibia on MRI is frequently reported. The relationship between these MRI findings and recovery has not been studied previously. This prospective study described MRI findings of fifty-two athletes with MTSS. Baseline characteristics were recorded and recovery was related to these parameters and MRI findings to examine for prognostic factors. Results showed that 43.5% of the symptomatic legs showed bone marrow or periosteal oedema. Absence of periosteal and bone marrow oedema on MRI was associated with longer recovery (p=0.033 and p=0.013). A clinical scoring system for sports activity (SARS score) was significantly higher in the presence of bone marrow oedema (p=0.027). When clinical scoring systems (SARS score and the Lower Extremity Functional Scale) were combined in a model, time to recovery could be predicted substantially (explaining 54% of variance, p=0.006). In conclusion, in athletes with MTSS, on MRI, bone marrow or periosteal oedema is seen in 43,5% of the symptomatic legs. Furthermore, periosteal and bone marrow oedema on MRI and clinical scoring systems can be regarded as prognostic factors. Future studies should focus on MRI findings in symptomatic MTSS and compare it to a matched control group.

INTRODUCTION

Medial tibial stress syndrome (MTSS) is one of the most common causes of leg pain in athletes (Clanton and Solcher, 1994). Until recently the aetiology of MTSS was thought to be a traction induced periostitis (Saxena et al., 1990; Detmer, 1986), but histological studies failed to show evidence for this theory (Johnell et al., 1982; Bhatt et al., 2000). Two reviews have highlighted that the cause of MTSS is likely to be bone overload (Beck, 1998; Moen et al., 2009). Imaging studies supported the theory of bone overload causing MTSS. Recent studies showed that with overloaded remodelling the cortex appears osteopaenic on computer tomography (CT) scans and that dual energy x-ray absorptiometry (DEXA) scans reveal decreased bone density (Gaeta et al., 2006; Magnusson et al., 2001). When MTSS symptoms subside the bone density returns to normal values, (Magnusson et al., 2003) suggesting that MTSS is related to mechanical overloading of the bone. Magnetic resonance imaging (MRI) also showed signs for bone overload. In several MRI studies periosteal and bone marrow oedema, reflecting bony overload, are frequently reported (Anderson et al., 1997; Aoki et al., 2004; Batt et al., 1998; Gaeta et al., 2005; Fredericson et al., 1995; Matilla et al., 1999). In some of these studies, bone marrow or periosteal oedema was reported in 83-89% of symptomatic tibiae (Batt et al., 1998; Fredericson et al., 1995; Gaeta et al., 2005).

In the field of MTSS, so far very few studies aimed at predicting the duration of recovery. One previous study showed a relationship between a higher BMI and longer recovery (Moen et al. 2010b). It may be that findings on MRI can be used to predict the duration of recovery. Arendt et al. found that MRI findings in bone stress reactions in general were correlated to the duration of recovery (Arendt et al. 2003). Until now, this relationship between MRI findings and recovery has not been investigated in athletes with MTSS.
The aim of this study was to describe the findings on MRI in MTSS athletes and relate them to the previous findings in the literature. The second aim was to investigate if clinical parameters and recovery were related to findings on MRI.

MATERIAL AND METHODS

Subjects
Fifty-five athletes were screened for eligibility and fifty-two athletes with the clinical diagnosis of MTSS were included in the study after signing informed consent. The local ethical committee agreed with the study beforehand (reference number for the study; NL 33896.041.10). The clinical diagnosis of MTSS was defined according to Yates et al. as: exercise induced pain on the posteromedial side of the tibia (Yates et al., 2004). Palpation pain with a minimum length of five centimetres over the posteromedial tibial border had to be present. Athletes were excluded if there was; clinical suspicion of compartment syndrome, clinical suspicion of tibial stress fracture or a history of tibial fracture in the past (Edwards et al., 2005; Yates et al., 2004). A subject was considered an athlete if he / she trained to compete in sports or exercises involving physical strength, speed or endurance (Collins, 2010).

Procedure
The athletes were recruited by informing sports physicians, orthopaedic surgeons and physical therapists about the study using internet and telephone. When an athlete was eligible for the study the athlete was referred to a sports physician (MHM). The sports physician included all athletes and performed the intake in a university hospital. At intake, several baseline characteristics; age, gender, length, weight, Body Mass Index (BMI), side of complaints, kind of sport, days with complaints, length of palpation pain, resistance tests of the tibial posterior and soleus muscles, pain on palpation of the muscles medial to the tibial border (yes / no), meters run on a treadmill without pain, the Sports Activity Rating Scale (SARS) and Lower Extremity Functional Scale (LEFS) were noted. (Binkley et al., 1999; Borsa et al., 1998). Length of palpation pain was scored by pressing the medial tibial border manually. The area over which any pain was present as indicated by the athlete, was noted. The resistance tests for the tibial posterior and soleus muscles were scored as painful yes or no by applying resistance to inversion / plantar flexion (Oberg et al., 1987; Karnofel et al., 1989).

Running test
A running test was performed prior to the MRI to measure the number of meters run on a treadmill without pain. The running test consisted of running on a treadmill at a fixed speed, while wearing the athlete's own running shoes. Although the running test is not validated for the use in MTSS athletes it has been used previously in treatment studies on MTSS (Moen et al., 2010a; Moen et al., 2011). First, the athlete was shown a visual analogue scale (VAS) for pain by the investigators. Then, it was explained to the athlete that when a four (on a 1-10 VAS scale) for MTSS was reached, defined as when the pain was starting to become annoying, the running test had to be terminated. The running test started at 7,5 km/hour for two minutes. After this initial warming-up phase the running speed was increased to 10km/h. The distance ran at 10 km/hour until a four on the VAS scale was noted and was called "meters run at 10km/h".

Imaging
An MRI scan was performed within 10 days of the intake. MRI imaging was done with a 1.5 Tesla system (Philips; Best, The Netherlands). With the use of the body coil, images of both legs were performed in coronal and transversal planes. T1 spin-echo (SE) images in coronal and transversal planes were acquired with a echo time (TE) of 10 ms and a repetition time (TR) of 500 ms. The slice thickness was 4 mm and the gap 4 mm. Field of view (FOV) was 350 x 200 mm and the used matrix 480. The T2 spin-echo short inversion recovery (STIR) images were also performed in a coronal and transversal plane with the following parameters; TE was 60 ms, TR was 2000 ms for the coronal plane and TE was 70 ms and the TR was 5745 ms for the transversal plane. The slice thickness, gap, FOV and the matrix were the same compared to the T1-images.
The MRI images of both legs were examined and judged by two experienced musculoskeletal radiologists (GS and RdS), each with more than 20 years experience. The radiologists were blinded to the clinical status of the athlete. When the radiologists did not agree on describing the findings on the MRI scan, consensus was reached in a separate meeting.

On MRI, oedema of the bone marrow and periosteum was scored in three categories (Batt et al., 1998; Fredericson et al., 1995). Bone marrow was subdivided in: a) no oedema, b) oedema visible on T2 images and c) oedema visible on T1 and T2 images. Periosteal oedema was divided in: a) no oedema, 2) mild to moderate oedema and c) moderate to severe oedema. The subdivision of findings by Batt et al. and Fredericson et al. was used as well in the current study describing the MRI scans (Batt et al., 1998; Fredericson et al., 1995). When bone marrow and periosteal oedema were scored; c) is more severe than b) which is more severe than a). In addition, bone marrow and periosteal oedema present yes or no was scored. If either periosteal or bone marrow oedema was present, this was also described dichotomously as "any abnormality" present or absent for each leg separately. Only if analysed at the level of athletes, "any abnormality" in athletes with bi-

lateral complaints MRI findings were across both legs. The location of periosteal oedema, if present, was also noted.

Clinical parameters
The relationship between five baseline characters, days with complaints, length of palpation pain along the medial tibial border, meters run on a treadmill without pain, the Sports Activity Rating Scale (SARS) (Borsa et al., 1998) and Lower Extremity Functional Scale (LEFS) (Binkley et al., 1999) with MRI findings was examined.

Treatment protocol and follow-up
Athletes were treated and followed-up according to the protocol described in the study by Moen et al. (Moen et al., 2011). Briefly, treatment consisted of a combination of a graded running program, which was performed three times per week (see table 5.1) and focused shockwave therapy. Five treatment sessions of focused shockwave were provided in a nine week course (week 1, 2, 3, 5, 9). The energy flux varied between 0,15 mJ/mm^2 and 0,25 mJ/mm^2, while the number of shocks per session was either 1000 or 1500. The treatment frequency was 2.5 shocks per second. For a detailed treatment protocol see Moen et al. (Moen et al., 2011).
For follow-up, athletes were provided feedback on progression every two weeks until full recovery. If an athlete had unilateral complaints, half a year after inclusion a telephone call was made to see if complaints in the asymptomatic leg had developed.

Table 5.1: Running program.

Running phase	Surface	Minutes	Total	Speed / intensity
1	Treadmill	2 2 2 2 2 2 2 2	16 minutes	2 = running at 10km/hour, 2 = walking at 6km/hour
2	Treadmill	2 2 2 2 2 2 2 2	16 minutes	2 = running at 12km/hour, 2 = walking at 6km/hour
3	Concrete	3 2 3 2 3 2 3 2	20 minutes	Intensity 1-2 (*) 3 = running, 2 = walking
4	Concrete	3 2 3 2 3 2 3 2	20 minutes	Intensity 2-3 (*) 3 = running, 2 = walking
5	Concrete	Continuous running	16 minutes	Intensity 1-2 (*)
6	Concrete	Continuous running	18 minutes	Intensity 2-3 (*)

(*): Intensity 1; running speed: light jogging. Intensity 2; running speed; jogging while able to speak. Intensity 3; running speed: jogging while speaking becomes difficult

Definition of recovery
An athlete was considered recovered if the running program could be finished with a pain score of four or less on a 1-10 pain scale. When the running program was finished the athlete was able to run 18 consecutive minutes at a pace when speech was becoming difficult (Moen et al., 2010a; Moen et al., 2011). The time between starting the intervention program and completing the running program was called "days to full recovery". Days to full recovery were compared with the MRI findings.

Data analysis
MRI results were described by means of the frequency of abnormalities. Outcome parameters (meters run, days of complaints, days to full recovery, SARS and LEFS, length of palpation pain) were described using the mean and standard error of the mean.
Differences in MRI results between asymptomatic and symptomatic legs were primarily tested using the Wilcoxon signed-rank test for two related samples in athletes with unilateral complaints only.
As an addition, to test for differences in MRI results between asymptomatic and symptomatic legs in all athletes – hence, with either unilateral or bilateral complaints - Pearson Chi square tests were applied. This test assumes that data from asymptomatic and symptomatic legs are independent. With bilateral cases included twice in the data - one leg in each of the two independent groups – variability will be reduced artificially and the estimated significance of differences may be false. To correct for this undesirable effect, data were weighted, by reducing the contribution to the test statistic of each leg by a half for athletes with bilateral complaints only.

To test if MRI observations of symptomatic legs caused differences in the outcome parameters at athlete level (maximum N=52), univariate non-parametric tests were used (Mann-Whitney U with two distinguished categories of MRI findings and Kruskal-Wallis one-way analysis of variance with three groups categories of MRI findings). Because the outcome parameter length of palpation pain was leg specific, these tests analysed legs with complaints (maximum N=92). If cell count was less or equal to five, *p*-values were based on Exact significance calculations.
The relationship between days to full recovery and baseline characteristics was analysed using a using a stepwise linear regression method. Due to the small number of cases with information about time to recovery, (max N=24) and the rule of thumb that at least 10 degrees of freedom are necessary to include one predictor in a regression model, only the two strongest predictors were allowed in the equation. Time to recovery was log transformed to handle deviation from normality of the residuals. Significance was set at 5% to test for significance of the total model with two predictors.

RESULTS

Subjects

Three out of fifty-five consecutive athletes were excluded, because their complaints did not match the inclusion criteria. In all three athletes the complaints were located in the calf muscle and not along the medial tibial border. A total of 52 athletes were used for further analysis. The radiologists did not agree on describing their MRI's in two cases (3.8%) after which consensus was reached in a separate meeting. The athletes were involved in different sports, with running, soccer and fitness being the most prevalent (respectively 40.5%, 13.5% and 9.6%). For the other baseline characteristics see table 5.2.

MRI findings in general

MRI data from 52 athletes could be used for final analysis. Periosteal or bone marrow oedema was detected in 43.5% of the symptomatic legs. Of the 52 athletes 12 (23,1%) had unilateral and 40 (76,9%) had bilateral complaints. In 35.0% of the athletes with bilateral complaints (n=14), no periosteal or bone marrow oedema was scored. Bone marrow oedema (see figure 5.1) in one of the legs was seen in 63.5% of the athletes, while periosteal oedema (see figure 5.2) in one of the legs was seen in 34.6%. If periosteal oedema was visible, mostly is was found on the anteromedial border of the tibia (70.0%). For a detailed overview of the MRI findings see table 5.3.

Table 5.2: Baseline characteristics.

	Mean	Standard error of the mean
Age (years)	26.8	1.6
Length (cm)	172.9	1.3
Weight (kg)	70.1	1.6
BMI	23.3	0.4
Days with complaints	449.2	62.2
Length of palpation pain medial tibial border right (cm)	13.7	1.4
Length of palpation pain medial tibial border left (cm)	15.6	1.4
Meters run on treadmill without pain	984.8	148.6
SARS score (0-100)	72.9	3.5
LEFS score (0-80)	55.2	2.1
Days to full recovery	68.9	9.6

Gender (% female)		63.5
Side of complaints (%)	Left: Right: Both:	13.5 9.6 76.9
Pain on palpation muscles medial (% yes)		31.5
Pain on resistance TP (% yes)		5.8
Pain on resistance soleus (% yes)		3.8

Abbreviations: cm: centimetres, kg: kilograms, TP: tibial posterior muscle, SARS: Sports Activity Rating Scale, LEFS: Lower Extremity Functional Scale

Table 5.3: MRI findings in the athletes.

Symptomatic athletes		%
Bone marrow edema (most severe of two legs combined)	None Visible on T2 images Visible on T1 and T2 images	36.5 42.3 21.2
Periosteal edema (most severe of two legs combined)	None Mild to moderate Moderate to severe	65.4 25.0 9.6
Any abnormality in one of the legs	Yes No	71.2 28.8

Symptomatic legs		
Periosteal edema right	None Mild to moderate Moderate to severe	84.6 13.5 1.9
Periosteal edema left	None Mild to moderate Moderate to severe	74.5 15.7 9.8
Bone marrow edema right	None Visible on T2 images Visible on T1 and T2 images	65.4 21.2 13.5
Bone marrow edema left	None Visible on T2 images Visible on T1 and T2 images	53.8 32.7 13.5

Twelve of the 104 athlete legs (11.5%) were asymptomatic. In 58.3% (N=7) of these legs, abnormalities could be detected. These consisted of periosteal oedema (N=2), bone marrow oedema (N=3), while two legs demonstrated bone marrow and periosteal oedema.

In athletes with unilateral complaints (N=12), MRI findings in symptomatic legs and their asymptomatic legs showed no significant difference in the pattern of periosteal oedema (none, mild to moderate, moderate to severe) or bone marrow oedema (none, seen on T2 images, seen on T1 and T2 images). Similarly, no differences were found for periosteal oedema (yes or no) and bone marrow (yes or no) or any MRI abnormality visible (yes or no) between the symptomatic and asymptomatic legs. In athletes with unilateral and bilateral complaints, also no indication was found that symptomatic legs were different from asymptomatic legs on any of the MRI parameters.

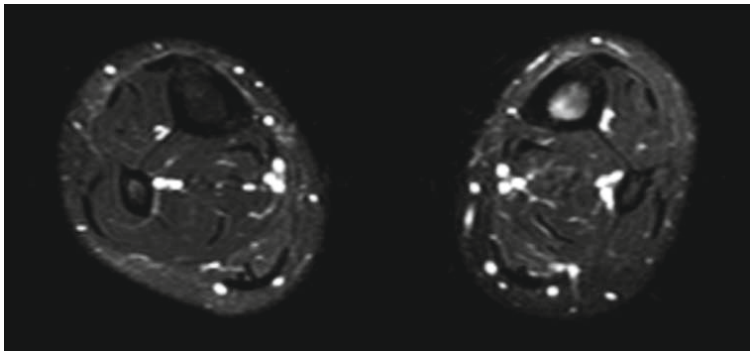

Figure 5.1: Axial T2-weighted image of the legs, showing bone marrow edema in the left leg of an athlete with MTSS.

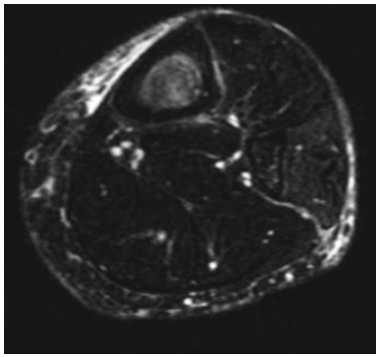

Figure 5.2: Axial T2-weighted image of an athlete with MTSS showing periosteal edema on the anteromedial side of the tibia.

Association between MRI findings and clinical parameters at baseline
The SARS score was significantly higher in the presence of bone marrow oedema (mean 80 ±19 vs 67 ± 27 when bone marrow was absent, *p*=0.008) or any abnormality in the symptomatic legs (mean 80 ± 18 vs 67 ± 27 when no abnormality was seen, *p*=0.008). No significant association was found between any other MRI finding and the clinical parameters days with complaints, length of palpation pain along the medial tibial border, meters run on a treadmill without pain and LEFS score.

Association between MRI findings and recovery
A significant relationship was present for any bone marrow finding (yes or no) and days to full recovery (*p*=0.013). The absence of bone marrow oedema indicated a longer recovery. If no bone marrow oedema was present the mean duration of recovery was 78.7 ± 47.3 days. If bone marrow was present on MRI, the mean duration was 51.8 ± 44.3 days. In a similar manner to bone marrow oedema, periosteal oedema showed a significant relationship with time to recovery (p=0.033) (duration of recovery with oedema: 43.6 ± 17.1 days; without oedema 77.9 ±51.6 days). Also, any MRI abnormality present in the symptomatic legs was also significantly associated with recovery (p=0.02), in which no MRI-abnormalities indicated longer recovery times.

Association clinical parameters and recovery
Two of the five parameters (SARS score and LEFS score) were significantly associated with recovery. The SARS and the LEFS score explained 54% of the variance (F 8.8, *p*=0.006). The formula for calculating days to full recovery was as follows: 10log of duration of recovery = 3.4 -.018*LEFS-.007*SARS. As an example the average athletes with a SARS-score of 72 and a LEFS-score of 56 would have an estimated recovery time of 77 days. If SARS would however be 10 points lower with LEFS unchanged, the recovery time would increase to 91 days.

DISCUSSION

This is the first study that examined MRI findings in athletes with MTSS and compared them with recovery. This study showed that on MRI bone marrow and periosteal oedema is present in 43.5% of the symptomatic legs of athletes with MTSS. In these symptomatic legs, the absence of bone marrow and periosteal oedema was related to a higher number of days to full recovery. Finally, this study showed that clinical scoring systems for sports activity (SARS score) and functional activity level (LEFS score) could predict days to full recovery substantially. Although MRI findings in symptomatic legs were seen frequently, the prevalence of findings was lower than previously described in the literature (83-89%) (Batt et al., 1998; Fredericson et al., 1995; Gaeta et al., 2005). An explanation for the differences in findings could be the difference in duration of symptoms in the present and previous studies. The duration of complaints in most of the studies investigating MRI findings in MTSS athletes and describing days with complaints, was relatively short (mean 30-84 days) (Aoki et al., 2004; Batt et al., 1998; Matilla et al., 1999) compared to the current study (mean 449 days). Anderson et al. showed that more normal MRI scans were seen in athletes with a longer duration of MTSS complaints compared to a group of athletes that had had symptoms for a shorter period (Anderson et al., 1997). A relationship between symptom duration and findings on MRI scan could not be found in this study.

No differences in the appearance and severity of bone marrow and periosteal oedema was found between symptomatic and asymptomatic legs. One other study also evaluated findings in asymptomatic and symptomatic legs in patients with MTSS. Batt et al. showed that four out of five asymptomatic legs showed moderate to severe periosteal and bone marrow oedema on T2 images (Batt et al., 1998). Bergman et al. performed a study in which an MRI scan was performed in 21 asymptomatic runners who ran 50-70 miles each week (Bergman et al., 2004). 43% of them showed findings on MRI scans (five unilateral findings and four bilateral findings). The findings varied from mild to moderate periosteal oedema to periosteal oedema and bone marrow oedema on T1 and T2 images. None of the runners developed complaints in the 48 months follow-up period. This suggests that the use of MRI in the evaluation of MTSS is limited.

The high prevalence of MRI findings in asymptomatic legs in this study and in the study by Batt et al. cannot be easily compared with the Bergman et al. study. In the present study and in the Batt et al. study the asymptomatic legs could have subclinical complaints of MTSS. This could be present although the athletes with unilateral complaints were follow-up for 6 months and no complaints developed. In the future an MRI study should be undertaken in which a true matched control group of athletes is compared to a group of athletes with MTSS. The findings in the present study and previous studies indicate that periosteal oedema and bone marrow oedema in the tibia are not exclusively found in MTSS (Batt et al., 1998; Bergman et al., 2004). Previous human studies also showed findings in the periosteum and bone marrow in asymptomatic athletes (Brunner et al., 1989; Lazzarini et al., 1997; Lovell et al., 2006; Major and Helms, 2002; Schweitzer and White, 1996). Schweitzer and White performed a study in which the loading pattern of the foot and leg was altered (Schweitzer and White, 1996). This resulted in a diffuse increase of bone marrow in the foot, tibia and femur. In a mouse study by Papuga et al. increased loading of the bone lead to increased bone marrow oedema on MRI and increased osteoclast levels suggestive of increased remodelling (Papuga et al., 2011). It is likely that periosteal and bone marrow oedema in the tibia depict bone remodelling (Papuga et al., 2011; Schweitzer and White, 1996). This bone remodelling process is necessary to make load-bearing bones stronger (Frost, 2004).

The SARS score was significantly related to the presence of bone marrow oedema and the presence of any abnormality in one of the legs, while other clinical parameters were not. Previous studies did not investigate the relationship between MRI findings and the SARS score. Only one other study, in 19 athletes, has examined the relationship between clinical parameters and MRI findings in MTSS. Contrary to the present study a significant relationship between MRI findings and duration of symptoms was found (Anderson et al., 1997).

In the present study, the presence of bone marrow oedema indicated a shorter recovery period (mean 51.8 ± 44.3 v 78.7 ± 47.3 days when bone marrow oedema was absent). No previous studies investigated the relationship between MRI findings in MTSS athletes and recovery, which makes comparison impossible. One retrospective study on bone stress injuries in general used a grading system of bone stress injuries on MRI, which was compared with time to recovery (Arendt et al., 2003). The more MRI findings (periosteal or bone marrow) were present, the longer the time to recovery.
The grading system used by Arendt et al. consisted of four grades in which the different findings were described (Arendt et al., 2003). In total 26 of the stress injuries were located in the tibia, but grading for the tibial stress injuries specifically was not mentioned. In their study the grade of injury was significantly correlated with the time to return to sport. Prior to starting this study attempts were made to use the Arendt et al. grading system as well, but a lot of MRI findings did not fit into their subdivision of findings. For example, some athletes in the present study were found to have bone marrow oedema on T1 and T2 images without the presence of periosteal oedema. This combination of findings did not fit into the Arendt et al. grading system. Therefore, it was decided to score for periosteal and bone marrow oedema separately. No explanation for the contrast in findings of the relationship between MRI findings and recovery of this study and the study by Arendt et al. can be provided, apart from the fact that the Arendt et al. study had a retrospective design. This might introduce information bias.
Because a higher SARS score is associated with the presence of bone marrow oedema and the presence of bone marrow oedema is associated with a shorter recovery period this supports previous findings in the literature that bone marrow oedema indicates active remodelling (Papuga et al., 2011; Schweitzer and White, 1996). Perhaps, a lower SARS score and the absence of bone marrow oedema indicates decreased remodelling. Since remodelling is needed for increasing strength of bones, this could explain why a lower SARS score and the absence of bone marrow oedema are associated with a longer recovery.

A previous clinical study examined the relationship between several clinical parameters and recovery in MTSS patients (Moen et al., 2010b). The duration of symptoms, distance run on a treadmill without pain, and some intrinsic risk factors (BMI, increased hip internal range of motion, positive navicular drop test and increased ankle plantar flexion) that were associated with MTSS were investigated for a relationship with recovery. Only BMI showed a significant relationship with recovery (p=0.005). The present study did not show a relationship between BMI and recovery. A significant relationship was found between the SARS and LEFS score and recovery (p=0.006). This was shown a strong relationship, as 54% of the variance of duration to full recovery could be explained by these two factors. This could be a useful finding for clinicians.

The MRI findings of bone marrow oedema could not be taken into account in the formula calculating the days to full recovery, because only two parameters could be reliably taken into account due to the number of athletes that followed the advised recovery protocol. Only the two strongest predictors of days to full recovery were taken into account.

Although a relative high number of athletes could be evaluated in this study, there are some limitations. One of them was that despite that 52 athletes were included, only 24 athletes rehabilitated as advised. For most athletes, focused shockwave could not be found close to their homes, so that another rehabilitation program was performed. As we wanted to include athletes only that performed the exact same rehabilitation program for the recovery relationship analysis, the other athletes were excluded from this analysis. Furthermore, the grading system used to classify the severity of findings on the MRI scans has not been tested for reliability, but was frequently used in previous studies (Batt et al., 1998; Fredericson et al., 1995). In this study no asymptomatic and matched controls were included. With the high percentage of bilateral complaints we cannot exclude that the asymptomatic control legs represent a subclinical manifestation of MTSS, which could have influenced the parameters.

CONCLUSION

This is the first study that prospectively examined MRI findings in MTSS and compared them with recovery. The absence of abnormalities on MRI was associated with a longer time to recovery. A relationship between a worse SARS and LEFS score and longer recovery was also found. MRI findings in both symptomatic and asymptomatic legs were seen frequently, but no significant differences in the pattern of MRI findings was found making the use of MRI in the evaluation of MTSS limited. In the future, MRI findings in symptomatic legs should be compared not only to asymptomatic legs in athletes with MTSS, but also to a group of matched control athletes.

PERSPECTIVES

An MRI scan of the symptomatic leg(s) can be of prognostic value in athletes with a clinical diagnosis of MTSS. The presence of periosteal or bone marrow oedema is associated with a quicker recovery. The Sports Activity Rating Scale and Lower Extremity Functional Scale score at baseline may help distinguish between athletes with a faster and slower recovery.

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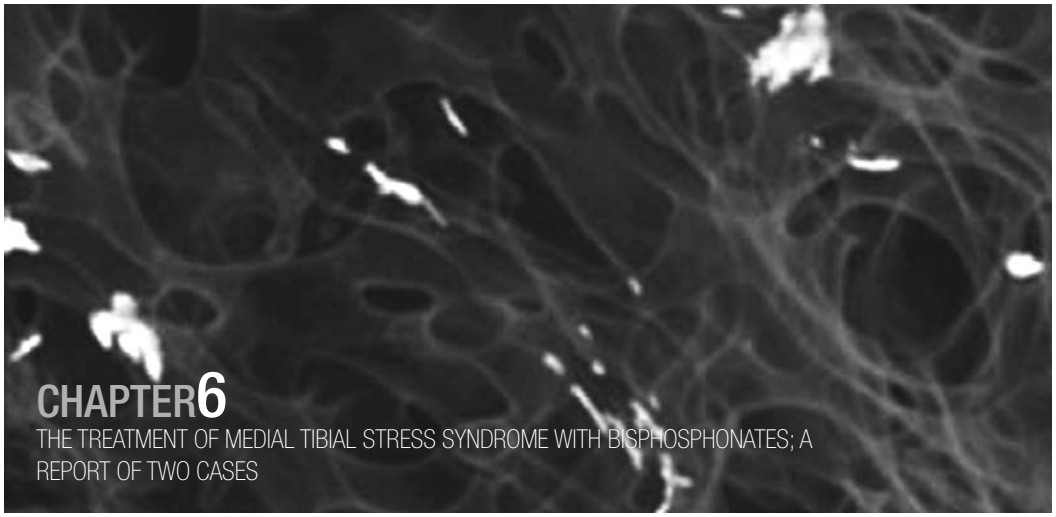

CHAPTER6

THE TREATMENT OF MEDIAL TIBIAL STRESS SYNDROME WITH BISPHOSPHONATES; A REPORT OF TWO CASES

Moen MH, Ratnayake A, Weir A, Suraweera HJ, Backx FJG
Dutch J Sports Med Sports Sci 2011; 1: 1-4

ABSTRACT

This case report describes two athletes in which bisphosphonates were started for medial tibial stress syndrome (MTSS). The treatment with bisphosphonates has never been described for MTSS before. 70 and 77 days after initiation of the bisphosphonates the athletes trained again at their preinjury level. Compared to the rehabilitation of MTSS described in the literature, this new treatment for MTSS seems promising. A larger prospective case series is needed.

INTRODUCTION

Medial tibial stress syndrome (MTSS) is one of the most common causes of exercise induced leg pain [1]. Incidences in training programs varying from 4-35% are reported, with both extremes being derived from military studies [2,3]. A recent systematic review reported a lack of good quality studies on the treatment of MTSS despite these high incidences [4]. Only three randomized studies were found and they were all of poor quality [2,5,6]. The review reported that no treatment has been shown superior to rest alone. It was suggested that clinical trials should be performed on the treatment of MTSS. The same review proposed that MTSS is a problem of bony overload [4]. Different imaging studies provided evidence for the bone overload theory [7,8,9,10,11,12]. These findings suggest that the pathology of MTSS has similarities with tibial stress fractures. In the seventies Roub et al. already suggested a continuum between stress reaction of bone and stress fractures [24].
Since bony overload has been shown the underlying problem in MTSS, possibly treatment options for bone overload / resorption of the bony cortex could apply to MTSS. In the last decade few studies have been conducted, which examined the role of bisphosphonates in bone overload. These studies, in humans, consisted of some case series about treatment of stress fractures and localized transient osteoporosis [13,14]. More commonly it has been used in the treatment of osteoporosis [15,16]. Bisphosphanates inhibit bone resorption by being selectively taken up and adsorbed to mineral surfaces in bone, where they interfere with the action of osteoclasts. In this way osteoclast activity is reduced and apoptosis of the osteoclast may occur [17].
So far, no publications were found that treated MTSS with bisphosphonates. This case report describes two cases in which bisphosphonates were started in MTSS patients.

Case 1 :
A 27 year old male rugby player from Sri Lanka presented with bilateral shin pain for more than 2 years. The pain was present on the posteromedial side of the tibia. The complaints worsened during training and matches and persisted

for several days after severe exercise. He insisted on playing the key matches of the season and did not take adequate rest. On examination he walked with an antalgic gait. On inspection he was found to have pronated feet with lowering of the medial arch. Inspection of his shins revealed no swelling or erythema. The medial borders of the middle third of the tibiae were painful on palpation. Resistance testing for the muscles of the lower leg was not painful. Examination of the ankles and knee joints was normal and also the neurovascular examination of the lower leg. X-rays of the tibiae showed periosteal reaction on both sides. MRI revealed bone marrow oedema and periosteal reaction of the tibia. Based on his history, findings on examination and imaging the diagnosis of MTSS was made. As first phase of conservative treatment, taping of the shins was performed and the athlete was prescribed a shin support (sleeve). He did not train for four weeks, apart from light jogging and crosstraining. Also orthoses were prescribed. After four weeks he was re-evaluated and the pain was reduced, but still he experienced pain on the posteromedial border of the tibia after 700 meters jogging. Then, Sodium Alendronate 10mg with Calcium lactate 500mg daily was started for three months. The athlete was advised to start cross training, running in a pool, swimming and cycling. After three weeks, the shin pain decreased gradually so that he could start his normal training program after eight weeks. 11 weeks after the Sodium Alendronate was started he was able to compete at his pre-injury level. There were no side effects reported from the medication.

Case 2:
An 18 year old female high-level athlete from Sri Lanka who ran 800, 1500 and 400 meters relay, presented to a sports medicine clinic with bilateral shin pain for more than 18 months. The pain was located along the posteromedial border of the tibia and started after 300-400 meters of running. On stopping, the pain gradually decreased over the course of the next few hours. She trained 5 times per week for two hours. She did not report menstrual disorders or a changed pattern of the menstrual cycle. No treatment was performed before the consultation. Inspection of the legs was normal with a neutral alignment and feet. Tenderness of both tibiae along the posteromedial border over the middle one third was present on palpation. X-rays of both tibiae showed evidence of periosteal reaction on the middle third. An isotope bone scan revealed a longitudinal uptake pattern on both tibiae, the right more marked than the left, which excluded a stress fracture.
The athlete was advised to refrain from weight bearing sporting activity. Though she was advised to commence a cross training program, which she was not able to do so due to lack of facilities in the vicinity.
Assessment after four weeks of relative rest, revealed only a moderate improvement. Although she did not participate in running training, she had practiced some volleyball. Due to the only moderate improvement of the load reduction she was prescribed Sodium Alendronate 10mg daily with supportive Calcium lactacte 600mg daily for three months.

During the first three weeks she did not take part in any sports activities. Assessment of her condition at three weekly intervals, showed a significant improvement of her condition. She was advised to start brisk walking in week six and jogging in the 8th week and moderate speed running in the 9th week. She could perform her normal running training at the 10th week after initiating the Alendronate therapy. There were no side effects reported from the medication.

DISCUSSION

Few treatment options for MTSS exist at present despite of the high incidences found in athletes [18]. Most likely, new treatment strategies should be focussed on bony overload instead of a traction induced periostitis since the nature of the MTSS condition [4]. Bisphosphonates are currently used for osteoporosis, transient osteoporosis and stress fractures [13,14,15]. Treatment with oral bisphosphonates may lead to stomach upset [19], and oesophagus ulcera [20]. Cases of osteonecrosis of the jaw have been described [21], but treatment with biphospanates seems safe even in the long term [20,21].
This report aimed at describing the additional effect of bisphosphonates in patients with MTSS added to our usual care. Normally standard treatment consists of rest followed by graded activity [22]. The two cases described were able to practise and compete in their sports, rugby and running, 10-11 weeks after starting bisphosphonates. Worth mentioning is that the second patient did have an altered loading pattern after the initiation of the bisphosphonates. She decreased the volume of her volleyball activities, although she was a runner. This could have influenced the time to return to sport. However, we think this influence was minimal, because the volume of volleyball was low and the running volume was not changed after the bisphosphonates. In the literature few reports adequately described the time to return to sport. In the randomized trial by Andrish et al. [2] military personnel was treated for MTSS after 1-4 days of shin pain. They reported an average of 10 days lost to running. The second randomized trial was also conducted in the military. Follow-up in this study was only 14 days [5]. The third most recent randomized study was conducted by Johnston et al. in the US Army [6]. Their criteria for completion of the study was to run 800 meters (0,5 mile). Half of the subjects that started the study did complete the study. On average the treatment group completed the 800 meters after 14,4 days and the control group after 17,2 days.
These data can hardly be compared to the athletes in this case report. The two cases reported here had a much longer duration of symptoms prior to the start of treatment. One other MTSS treatment study (a retrospective controlled study) reported follow-up better and was conducted among athletes [23]. They compared exercise therapy (stretching and strengthening of the calves) and shockwave therapy with exercise therapy. The shockwave therapy in addition to the standard care improved a Likert activity scale more than the control group. However, after

4 months none of the control group were completely recovered and only 24% of the combined treatment group. Preliminary data of Moen et al. (2010) revealed in the follow-up of 50 MTSS patients that in different treatment groups the time to return to sport (being able to train at the desired level) was 90-100 days. When compared to the athletes reported here, they were able to train at their desired level after 10-11 weeks (=70-77 days). This seems promising but the fact that it is a case report means no solid conclusions can be made. This case report raises the possibility that bisphosphonates could decrease the time to return to sport in MTSS patients. To gain more information on the possible effect size of the bisphosphonates therapy and assess possible complications a larger prospective case series should be performed. After this a double blinded prospective randomised controlled clinical trial can be considered . The duration and dosage of the treatment is not yet known and should also be studied further.

CONCLUSION

This case report described two patients with MTSS treated with bisphosphonates after other conservative treatment failed. The results seem promising, but further research is needed.

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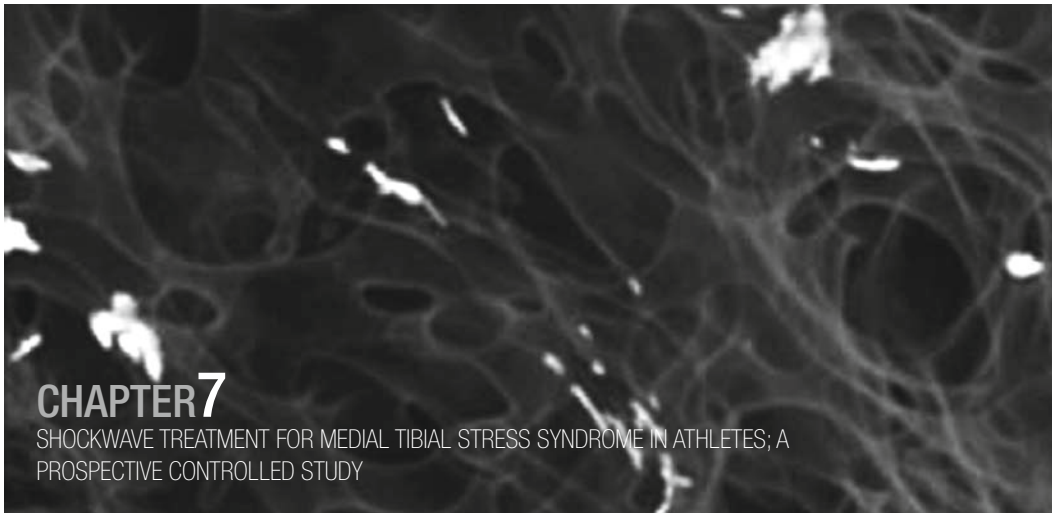

CHAPTER 7

SHOCKWAVE TREATMENT FOR MEDIAL TIBIAL STRESS SYNDROME IN ATHLETES; A PROSPECTIVE CONTROLLED STUDY

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ABSTRACT

***Objective*: The purpose of this study was to describe the results of two treatment regimens for medial tibial stress syndrome (MTSS); a graded running program and the same running program with additional shockwave therapy (ESWT). *Design:* Prospective observational controlled trial. *Setting:* Two different sports medicine departments. *Participants:* 42 athletes with MTSS were included. *Intervention:* Patients from one hospital were treated with a graded running program, while patients from the other hospital were treated with the same graded running program and focused ESWT (5 sessions in 9 weeks). *Main outcome measurements:* Time to full recovery (end point was being able to run 18 consecutive minutes without pain at a fixed intensity). *Results:* The time to full recovery was significantly faster in the ESWT group compared to the patients that only performed a graded running program, respectively 59.7 ± 25.8 days and 91.6 ± 43.0 days (*p*=0.008). *Conclusions:* This prospective observational study showed that MTSS patients may benefit from ESWT in addition to a graded running program. ESWT as an additional treatment warrants further investigated in a prospective controlled trial with the addition of randomisation and double blinding.**

INTRODUCTION

Medial tibial stress syndrome (MTSS) is one of the most common complaints of the lower leg in the athletic population.[1] Incidences between 4 and 35% have been reported in both military and athletic studies.[2,3,4] Different aetiological mechanisms have been proposed for MTSS. For years MTSS was thought to be due to traction induced periostitis.[5,6,7] Another aetiological theory is that overloaded bone remodelling causes MTSS.[8,9] Recent studies showed that with overloaded remodelling the cortex appears osteopaenic on computer tomography (CT) scans and that dual energy x-ray absorptiometry (DEXA) scans reveal decreased bone density.[10,11] When MTSS symptoms subside the bone density returns to normal values,[12] suggesting that MTSS is related to mechanical overloading of the bone.

In the treatment of MTSS, a therapy in which bone cells are up regulated would possibly enhance bone density and thus decrease symptoms. Studies that tried to enhance the number of bone cells in the treatment of stress fractures and non-union of fractures provided evidence for the plausibility of this theory.[13,14] In these studies ESWT was used to stimulate the bone.

At the time of planning the study there were no studies published on the use of ESWT in MTSS. As some idea of effect size is necessary to perform an adequate power analysis for the proper planning of a randomised controlled trial it was decided to perform a prospective observational controlled study which could be simply realized in the local area. In two regional hospitals the treatment protocol

used was different and this situation lent itself to performing this observational study. The effect on time to full recovery after ESWT and a graded running program was compared with a group of MTSS patients that performed only a running program. The aim of this study was to describe the results of two different treatment regimens on MTSS. One group rehabilitated with a running program, while the other group rehabilitated with the same running program in combination with ESWT.

METHODS

Subjects
Patients were included in two separate sports medicine departments of large general district hospitals by one sports medicine specialist. For inclusion in the study the Yates et al. criteria from 2004 were used :[4]
Pain History. The pain was induced by exercise and could last for hours or days after exercise. Pain was located on the postero-medial border of the tibia. There was no history of paraesthesia or other symptoms indicative of other causes of exercise induced leg pain.

Location. The patients identified pain along the postero-medial border of the tibia. The site had to be spread over a minimum of 5 cm.

Palpation. Palpation of the postero-medial border of the tibia produced discomfort that was diffuse in nature and confined to the postero-medial border of the tibia. Complaints had to be present for at least 21 days for patients to be included.

Exclusion criteria. Patients were excluded if there was a past history of a tibial fracture and when ESWT had been used previously for MTSS complaints.

Procedure
Patients were included in two different sports medicine clinics by the same investigator. In one clinic, patients were advised to start ESWT in combination with a running program. In the other clinic, as therapy, patients were advised to perform the same running program.
At inclusion various baseline parameters were measured; sex, weight, height, body mass index (BMI), kind of sport in which the patient is involved, centimetres of pain on palpation of the postero-medial border of the tibia, side of the complaints and number of days with complaints (see table 7.1). The study was performed in compliance with the Helsinki Declaration.[15]

Table 7.1: Baseline values for the treatment groups.

	Running program (N=20)	Running program + focussed ESWT(N=22)	*p*-value
Sex (% males)	35%	73%	0.029
Weight (kilograms)	68.5 (SD 8.6)	74.2 (SD 10.1)	NS
Length (centimeters)	175.1 (SD 6.5)	178.5 (SD 10.3)	NS
BMI (kilograms / (length in centimeters)2)	22.2 (SD 1.9)	23.2 (SD 2.2)	NS
Age (years)	22.7 (SD 7.2)	30,0 (SD 12.5)	0.027
Days with complaints	189.3 (SD 339.8)	629.2 (SD 761.1)	0.022
Centimeters palpation pain on tibia	11.7 (SD 4.5)	11.3 (SD 6.4)	NS
Meters run on treadmill without pain	744.8 (SD 417.1)	1329.6 (SD 562.9)	0.001

(Abbreviation: SD = standard deviation, NS=not significantly different ($p > 0.05$), ESWT=extracorporeal shockwave therapy)

Running test
Before starting the treatment, all patients performed a running test. The test consisted of running on a treadmill at a fixed speed, while wearing running shoes. Before the test, the patient was shown a visual analogue pain scale (VAS, 1-10). It was explained that a four on the analogue scale was associated with complaints and pain that started to become annoying. With the onset of such leg complaints by pointing at the four on the analogue scale, the running test would be stopped. The test started at 7.5 km/hour for two minutes. After this initial phase of warming-up, the distance was registered that could be run at 10 km/hour until a four on the VAS scale was indicated by the patient. The distance ran at 7.5 km/hour was subtracted from the total meters run and was called “meters run on a treadmill without pain”.

Treatment
The treatment consisted of focused ESWT in combination with a graded running program or a running program only (see table 7.2).

Running program
All patients performed a graded running program as part of the treatment.[16] The program consisted of 6 phases. In the first two phases the patient ran on a treadmill while in the following phases the patient ran outdoors. A starting point in the running program was established using the results from the running test. If "meters run on a treadmill without pain" was between 0-400 meters, the patient was told to start the running program in phase one. If 401-800 meters could be run, the patient started in phase two. With 801-1200 meters, the patient started phase three. If 1201-1600 meters could be run, the patient started phase four. At 1600 meters or more, patients started with phase five. The running program was not started if the patient experienced pain during walking. In that case, the patient was advised to avoid complaints by reducing loading of the leg. Only after two consecutive days without pain during walking, they were allowed to start the program in the first phase. The program was performed three times per week. Instructions were given not to run on consecutive days.
A new phase of the running program could be commenced if the previous one could be finished without a pain score of four or higher on the 1-10 VAS pain scale. Also, with pain (four or more on the VAS scale) experienced immediately after the session of the running program or one day after the session, the next phase was not commenced. In that case, the next running session started in the same phase with two minutes less to run. When phase six was finished, we advised patients to gradually start their own sport. They were instructed to practise sport and to adjust the intensity and duration to keep their pain score at four or lower on the 1-10 VAS pain scale.

ESWT and running program
In addition to the running program, one group of patients was treated with focused ESWT. All treatments were performed by one of the authors (S.R.) without local anaesthesia. A focused ESWT device (Storz Medical, Duolith SD1, Tägerwilen, Switzerland) was used in all patients. Five treatment sessions were scheduled in the weeks 1,2,3,5 and 9 after inclusion. At the first session, 1000 shocks were administered with an energy flux density of 0.10 mJ/mm^2 with the patient supine and the knees flexed at 30 degrees. The treatment frequency was 2.5 shocks per second. Before each treatment session, contact fluid was applied over the length of the posteromedial tibia. At the start of the first session, the part of the tibia that was painful on palpation was treated with the ESWT device and also highlighted with a waterproof marker. The zone that was highlighted with the marker was also treated in the consecutive sessions. At the second session (in the second week of treatment), 1500 shocks were applied with an energy flux density of 0.15 mJ/mm^2 and 2.5 shocks per second. The third session took place in the third week of treatment. 1500 shocks were applied with an energy flux of 0.20 mJ/mm^2 and 2.5 shocks per second. At the fourth session (in week 5 of the treatment), again 1500 shocks were applied with an energy flux density of 0.25 mJ/mm^2 and 2.5 shocks per second. The last session was in week 9 of the treatment. In this session, 1500 shocks were applied with an energy flux density of 0.30mJ/mm^2 and 2.5 shocks per second.
The treatment was performed along the painful area on the postero-medial border of the tibia. No restrictions after the treatment sessions were given. The running program started in the week of the first treatment with ESWT.

Outcome measurement
The number of days from inclusion to completion of phase six of the running schedule (=full recovery) was used as primary outcome measurement. When a patient did not fully recover according to the graded running program, the Likert scale was used to assess the status of the patient.[17] Scores varied on a scale from one to six : 1 = completely recovered, 2 = much improved, 3 = somewhat improved, 4 = same, 5 = worse and 6 = much worse.

Statistical analysis
After blinded, double, data entry, all analysis were carried out using SPSS version 17.0 (SPSS Inc., Chicago, Illinois, USA). To compare data between groups and explore for possible confounding factors, Chi-square analysis and ANOVA were used. Variables with a significant difference between treatment groups using univariate analysis of variance or Chi-square analysis were considered as potential confounders. Their univariate relation with the outcome parameter, "days to full recovery" was expressed by the (corrected) amount of variance explained using univariate analysis of variance in the case of ordinal or nominal confounders, or by means of univariate regression analysis in the case of scale confounders.
All confounders were tested together in a multivariate analysis of variance, with scale confounders as covariate and nominal or ordinal confounders as a random factor. All confounders were also tested in interacting with the treatment status. Statistical significance was set at $p \leq 0.05$.

RESULTS

In total 42 athletes were included in the study. The athletes participated most frequently in recreational running (19.1%) and soccer (13.2%). Other sports that athletes practiced were field hockey, tennis, basketball, athletics and dancing. The baseline characteristics of the athletes are displayed in table 7.1.

One patient in the running program group and two patients in the running program with focused ESWT did not finish the last phase of the running program due to persisting complaints. The patient in the running program group scored a 3 on the Likert scale (somewhat improved) on quitting the study. In the running program with ESWT group two patients scored 4 on the Likert scale (same) on quitting the study. In total 39 athletes finished the running program.

Time to recovery
In the group of the running program with ESWT the duration to full recovery was 59.7 (SD 25.8) days. In the group with the running program only, the duration was 91.6 (SD 43.0) days. The means were significantly different between the groups (p=0.008), with treatment explaining 17.5% of the total variance in the number of days to full recovery.

Multivariate risk factor analysis
Some baseline characteristics were different between the treatment groups: sex (p=0.029), age (p=0.027), days with complaints (p=0.022) and meters run on a treadmill without pain (p=0.001).
Apart from sex (p=0.039), no confounder could explain a significant percentage of the variance (corrected R^2) in the number of days to full recovery: age: <1%; days with complaints: <1%; meters run on a treadmill without pain: 3%. Females needed more days to complete phase 6 then males: 88.8 days (SD 38.4 days) versus 63.6 days (SD 35.1 days). With treatment used as fixed factor in a multivariate analysis of variance on the number of days to full recovery, none of potential confounders mentioned above influenced the outcome parameter 'number of days to full recovery'. The use of ESWT was the only variable that explained the difference between the two groups.

DISCUSSION

This prospective observational controlled study described the time to full recovery for two different treatment protocols. The protocol in which ESWT was added to the running program showed a significantly quicker recovery. This study is limited as it was observational and no randomisation or blinding was used. There are significant differences in the baseline characteristics between the groups, although on analysis these did not significantly affect the outcome. These results provide support for the hypothesis that the treatment of MTSS with a running program combined with ESWT may be faster than the treatment with a running program alone.

The results of this study are in keeping with a recently published retrospective trial by Rompe et al. who studied the effect of ESWT on MTSS retrospectively.[18] They compared this treatment with a control group that performed a home training program. They found that the group receiving ESWT did recover faster, and more patients recovered than the control group. No studies were found that investigated ESWT for MTSS prospectively.

Other prospective studies on the treatment of MTSS could not find a significant difference comparing different treatment options. Three randomised controlled trials were performed in which the following interventions were investigated: ice massage with ice massage and aspirin, ice massage and fenylbutazone, ice massage and heel-cord stretching and a walking cast, active laser and placebo laser and a leg orthosis.[2,19,20] It should be noted that the mentioned studies had serious methodological shortcomings such as small numbers or the lack of blinding. ESWT was only used for MTSS in one retrospective study by Rompe et al..[18] The ESWT device used in this study was radial. One group was treated with ESWT, while the other group received a home exercise program (calf stretches, heel raises and toe raises). As primary outcome measure they used a 6 point Likert to assess recovery (1=completely recovered, 6=much worse). They found that after 1,4 and 15 months the group that was treated with ESWT had significantly better Likert scores (p<0.001). Rompe et al. did not structurally report the time to return to sport. They stated that time to return to sport ranged from 6 weeks to 6 months. After 15 months 85.1% of the athletes treated with ESWT had returned to their pre-injury sport, while 46.8% of the athletes in the exercise group returned to their pre-injury sport.

This study did not measure time to return to sport, so a comparison with the study by Rompe et al. is difficult.[18] The primary outcome measure in the current study was days to complete a running program (termed full recovery). This was used to have an outcome measure that was the same for all athletes, regardless of the type of sport and level of sport. The time to full recovery in the running program with ESWT group was 59.7 (SD 25.8) days. Rompe et al. reported that only

64% of their athletes with MTSS treated with ESWT were completely recovered or much improved after four months.[18]

The difference in outcome may be explained by the differing outcome measures. In the present study the patients had to complete a running program while in the Rompe et al. study the patients had to have made a full return to sport which, for most athletes, would possibly involve more tibial loading than the running program.[18] The difference between the studies may also possibly be due to the fact that the present study used a focused ESWT instead of the radial ESWT by Rompe et al.. One study was found that compared radial and focused shockwave while treating bone. Differences in microcrack density and microcrack length were found.[21] What these differences mean for the clinical practice is not clear. The difference in outcome between our study and the study by Rompe et al.[18] could also be explained by the fact that our study added a running program to the ESWT. Waldorff et al. showed a significant decrease in microdamage in tibiae over time following weight bearing or intermittent weight bearing compared to limb suspension.[22]

Finally, baseline characteristics for age and duration of symptoms were not the same between this study and the study by Rompe et al..[18] This could have influenced the outcome as well. However, Moen et al. showed that days with complaints (and meters run on a treadmill without pain) were not prognostic factors to predict time to full recovery.[23]

Several recent studies investigated the impact and consequences of ESWT on cortical bone.[13,14,24,25,26,27] These studies showed an increase in osteoblast activity and an increase in bone matrix deposition in vitro.[26,27,28] Promising clinical results of ESWT on bone healing were found in studies involving humans.[13,14,24,25] In this study, at baseline, several baseline characteristics were different between the groups, so these were considered possible confounding factors (age, days with complaints and meters run without pain on a treadmill and sex). Univariate analysis of variance with sex as a random showed only a weak relationship with days to full recovery. This could have possibly influenced the results in this study, since more males were present in the running program with ESWT group. However, after multivariate analysis of variance and chi square analysis, no significant relationship was found between these parameters and days to full recovery.
This study has several limitations. First, although the study had a prospective design, it was not a randomised study. This explains the difference in baseline characteristics. With a randomised study the chance of unequal distributions of these characteristics would be lower. The prospective observational design of this study was chosen because of the limited availability of focused shockwave devices and the fact that the pre-existing protocols were well suited to this observational design to assess the possible effect size for future study planning. Also, the control group did not have contact with a physical therapist, while the patients in the

treatment group did. This could have influenced time to complete the running program. The physical therapists who performed the ESWT were instructed to advise the patients as little as possible. Still, the treatment in itself could have lead to a placebo effect. In the future blinding would help eliminate this shortcoming. Another limitation of the study is its relatively small number of participants. However, even with the limited amounts of participating athletes a significant difference between the two treatment groups was found. This allows for a good estimation of effect size of the treatment which can now serve to perform a good power analysis for designing a randomised, blinded trial.

CONCLUSION

The time to full recovery in athletes with MTSS with a running program and focused ESWT was significantly (p=0.008) faster in the running program and ESWT group (59.7 days (SD 25.8) and 91.6 days (SD 43.0) respectively). These results from this study provide a base for further research of the treatment of MTSS with ESWT combined with a running program for the treatment for MTSS in a prospective, randomised, blinded study.

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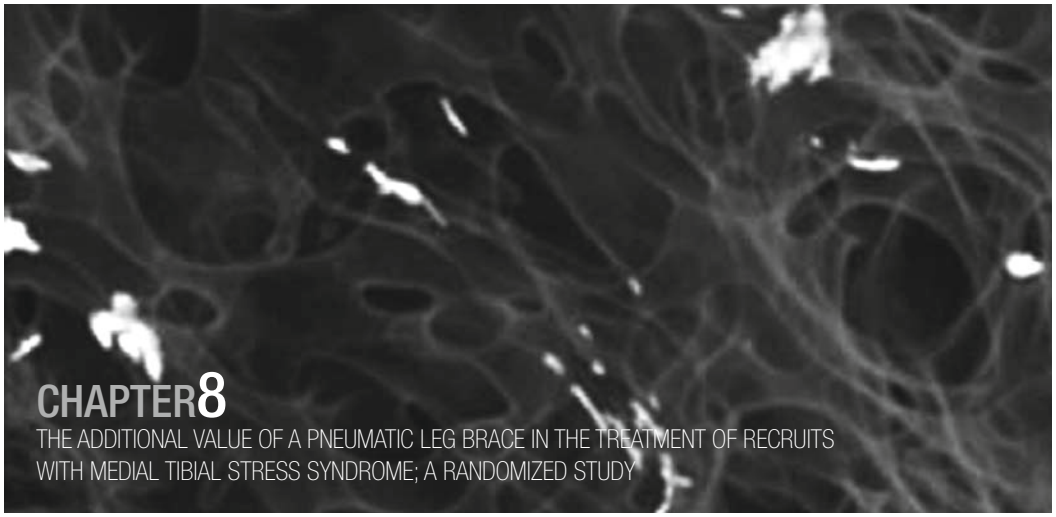

CHAPTER 8

THE ADDITIONAL VALUE OF A PNEUMATIC LEG BRACE IN THE TREATMENT OF RECRUITS WITH MEDIAL TIBIAL STRESS SYNDROME; A RANDOMIZED STUDY

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ABSTRACT

Objective: To study the additional effect of a pneumatic leg brace with standard rehabilitation for the treatment of medial tibial stress syndrome (MTSS) in recruits. Methods: In a randomized study, 15 recruits (age 17-22) followed a rehabilitation program consisting of leg exercises and a graded running program. Recruits performed daily exercises and ran three times a week. The running program consisted of 6 consecutive phases. One group was, after randomization, additionally provided with a pneumatic leg brace. Follow-up was provided every other week. Days to completing the running program was the primary outcome measure, the Sports Activity Rating Scale (SARS) score and satisfaction with the treatment were secondary outcome measures. Results: In total 14 recruits completed the rehabilitation program. No differences were found in the number of days until phase six of the running schedule was finished between the brace and the control group (Brace 58.8 ± 27.7 (mean ± SD) vs Non-Brace 57.9 ± 26.2 (mean ± SD, p = 0.57). Also no differences were found in the SARS scores between the groups. Overall satisfaction with the treatment was 6.4 ± 1.1 (mean ± SD) on a 1-10 scale for the brace group and 7.1 ± 0.7 (mean ± SD) for the control group (p = 0,06). Comfort of the brace was assessed as 4.8 ± 1.3 (mean ± SD) on a 1-10 scale. Conclusions: No additional large effect of the pneumatic leg brace could be found in recruits and wearing of the brace was not feasible, since the wearing comfort was low.

INTRODUCTION

Medial tibial stress syndrome (MTSS) is one of the commonest causes of exercise-induced leg pain [1]. Incidences varying from 4-35% are reported, with both extremes being derived from military studies [2-4]. The most commonly accepted definition is that provided by Yates and White [4]: "*exercise induced pain in the leg on the posteromedial side of the tibia and in addition pain on palpation of the posteromedial tibia for at least five centimetres*", and despite incidences of up to 35% a recent systematic review reported a lack of good quality studies on the treatment of MTSS [5]. All three studies reviewed were performed in a military setting and were of poor quality [2,6,7]. The review reported that no treatment has been shown to be superior to rest alone and it was suggested that clinical trials should be performed on the treatment of MTSS. The same review proposed that MTSS is a problem of bony overload [5]. There are four important findings that support the theory that bony overload forms the primary patho-physiological basis for MTSS. Firstly, on triple phase bone scans the last phase is abnormal, showing that the bone and periosteum are involved [8,9]. Secondly, on high resolution CT-scans, although rarely performed for this indication clinically, the tibial cortex is found to be osteopenic, as can be seen in patients as well as in asymptomatic athletes

as a sign of bone remodeling [10]. On MRI images bone marrow oedema as well as a signal along the periosteum can be seen [11,12]. Fourthly, in patients with MTSS bone mineral density is reduced when compared to controls [13]; when symptoms improve the bone density returns to normal [14]. These findings suggest that the pathology of MTSS may be similar to tibial stress fractures where a similar but wider signal can be seen on bone scans and MRI images [11,15].
Since bony overload is believed to be the underlying problem in MTSS, treatment options for stress fractures, such as a pneumatic brace, could also be useful in MTSS. Since the 1980's two case series and three randomized controlled trials, some of which were conducted in the military setting [16-20], have been published. All except for Allen et al [16], showed a promising effect of the pneumatic leg brace in the treatment of tibial stress fractures. A 2005 Cochrane review concluded that rehabilitation of bony overload injuries may be aided by the use of a pneumatic leg brace [21]. The present study examined the role of a pneumatic brace in addition to a standard rehabilitation protocol in recruits with MTSS, with the working hypothesis that the addition of the brace would significantly reduce the time taken to complete a standard rehabilitation programme and produce a faster functional recovery.

METHODS

Following local medical ethical committee approval, male soldiers (age 17-22 years) were recruited from two bases of the Royal Dutch Army between October 2008 and June 2009. All subjects had previously been withdrawn from basic army training and placed into a remedial platoon and referred by an army physician to our trained investigator with a suspected diagnosis of MTSS. Patients were included by the investigator if they fulfilled the inclusion criteria and gave their informed consent. The inclusion criteria were: exercise induced pain in the leg on the posteromedial side of the tibia and pain on palpation of the posteromedial tibia for at least five centimetres [4] for at least two weeks. Patients were excluded if there was suspicion of a tibial stress fracture, compartment syndrome or tibial fracture in the past. When X-rays showed tibial stress fracture or compartment pressure measurements revealed compartment syndrome patients were excluded.

Procedure
Patients were randomly assigned by sealed envelope selection, to one of the two available treatment arms: standard rehabilitation programme or standard programme plus the use of a pneumatic leg brace. Individuals were always kept in different rehabilitation groups to other trial participants to ensure they were blinded to the recovery of other participants. Baseline demographic and comorbidity data was obtained as well as a baseline measurement of outcome parameters.

Running test
At baseline all patients performed a running test to assess severity of MTSS and determine the starting point of the rehabilitation program. Before the test, the researcher explained that significant pain was defined as more than ten consecutive strides whereby the pain was rated at 4 or more on a 0-10 pain scale. The test consisted of 2 minutes walking on a treadmill at 7.5km / hour before increasing to 10km / hour at which point running commenced. The patient stopped running when the specific 'MTSS' pain was felt in the leg on the posteromedial side. The distance run without pain at 10km / hour was recorded. No running test was performed, when pain was present during walking.

Standard Rehabilitation Program
The starting point of the rehabilitation protocol (Table 8.1) was determined by the results of the treadmill running test (Table 8.2). When pain was present already during walking no running test was performed and the subject started with the exercise schedule. Supervised running on the treadmill was performed three times a week with at least one day rest in between.; when symptoms improved, running outside was no longer supervised. Recruits were instructed to run until they experienced leg pain ≥ 4 / 10 on the 1-10 pain scale. When a rehabilitation phase was completed without pain and there was no pain both immediately after running and on the following day, the recruit move dup to the next rehabilitation phase. When Phase six was completed without pain, the recruit was considered to be recovered. When pain was present (≥ 4 / 10) during running or shortly thereafter, the running was stopped and the next run was started at the start of the same phase. When the recruit had just started a new phase and pain was experienced during running, the recruit was returned to the previous phase.

Table 8.1: The running program; (*); Intensity 1: running speed; light jogging, Intensity 2: running speed: jogging while able to speak, Intensity 3: running speed; jogging while speaking becomes difficult.

Phase	Surface	Minutes								Total	Speed / intensity
1	Treadmill	2	2	2	2	2	2	2	2	16 min	2 is running 10 km / hour 2 is walking 6km / hour
2	Treadmill	2	2	2	2	2	2	2	2	16 min	2 is running 12 km / hour; 2 is walking 6 km / hour
3	Grass	3	2	3	2	3	2	3	2	20 min	Intensity 1-2 (*) 3 is running; 2 is walking
4	Road	3	2	3	2	3	2	3	2	20 min	Intensity 2, 3 (*) is running; 2 is walking.
5	Road									16 min	Intensity 2 (*).
6	Road									18 min	Intensity 2/3 (*).

Table 8.2: baseline characteristics of the recruits with MTSS.

Groups	Brace (N=8)	No brace (N=7)	*p*-value
	Mean ± SD	Mean ± SD	
Age (years)	19,1 ±1,9	18,6 ±1,2	0,62
Body mass index (BMI)	24,5 ± 2,0	23,1 ± 2,0	0,25
Meters on treadmill before developing pain	854,3 ± 490,4	734,8 ± 626,9	0,96
Duration of symptoms (days)	32,9 ± 20,2	35,1 ± 16,9	0,83
Sports Activity Rating Scale (SARS) score	75,7 ± 21,3	74,3 ± 10,2	0,44

Figure 8.1: The pneumatic leg brace worn by the recruits.

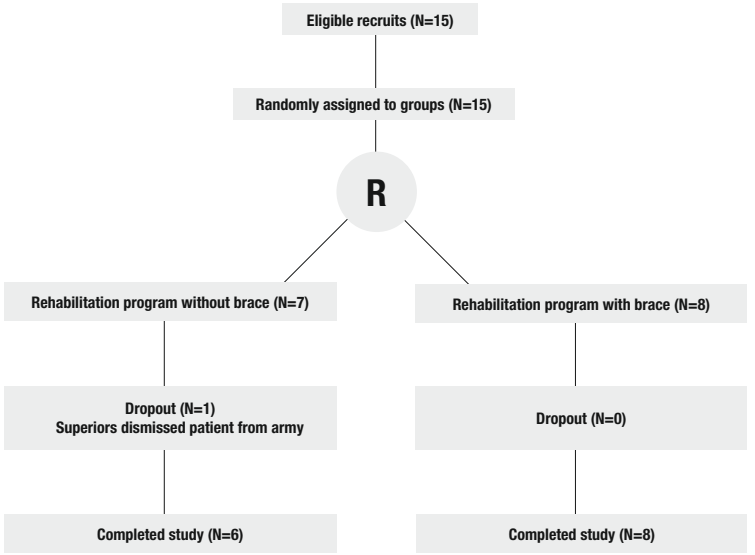

Figure 8.2: Flow diagram presenting the progress of the recruits in the study, including withdrawal from the protocol. R = random assignment to study groups.

Apart from running, the patients performed exercises five times a week, supervised by a military instructor. These exercises consisted of stretching, strengthening and ankle stability exercises. Five different phases of the exercises existed, which were increasingly tough to perform. When one phase of the exercises was finished without pain (≤4/10) the next phase could be commenced the next day. The exercises were first demonstrated by a therapist and printed instructions given to the patients. The patients conducted the exercises with an army supervisor present, who was trained and instructed for this task.

Both groups followed the same rehabilitation protocol, the only difference being that one group also received a pneumatic leg brace (Aircast Inc., Summit, New Jersey, USA) (Figure 8.1) to wear during running. The size of the brace was fitted to the length and width of the patients lower leg. The patients were instructed to wear the brace while performing the running schedule. When pain was present during ambulation patients were instructed to wear the brace all day, but not dur-

ing the night. Additional information was provided by the investigator in order to prevent blisters and friction wounds which could occur while wearing the brace.

Outcome measurements
The recruits were assessed every two weeks by an investigator - the primary outcome measure was the time from beginning rehabilitation to completing Phase 6 of the running program without pain. Secondary outcome measures were the Sports Activity Rating Scale (SARS) score [22] in which functional activity is expressed on a 0-100 scale, where 0 = severe complaints in daily activities and 100 = no complaints during heavy sport activity, overall satisfaction with the treatment and comfort of the brace to wear. The overall satisfaction with the treatment and the wear comfort of the brace were expressed on a 1-10 score (1= very low, 10= very high). A score of 7 or higher was assessed as feasible. Compliance was looked at by the investigator, who checked compliance diaries that the patients kept.

Statistical analysis
Based on previous studies using a pneumatic brace for stress fractures in the leg [16-20] we believed we would find a large effect of the brace. Based on a 80% power to detect a significant difference ($p = 0.05$) 7 patients were required in each study group. The researchers analyzing the data (MM and EB) were blinded to the treatment allocation and had no contact with the patients. Data were analyzed using SPSS version 15 (SPSS Inc, Chicago, Illinois, USA). Groups were compared using the Independent Samples T-Test or, in case of skewed distributions, the non-parametric Mann–Whitney U Test. For loss to follow-up the intention-to-treat principle was used.

RESULTS

From October 2008 until June 2009 15 military recruits were included in the study. The progress of the patients in the study, including withdrawals from the protocol, is shown in Figure 8.2. One patient in the brace group was excluded from the study; thus data from 14 patients were available for the intention-to-treat analysis.
Baseline values for age, body mass index, distance in meters on the running test, SARS score and duration of symptoms at inclusion were not statistically different between the control group and the brace group (Table 8.3).
No significant difference was found in the primary outcome measure, the number of days to complete the running schedule between the brace and the control group (Brace 58.8 ± 27.7 days (mean ± SD) vs non-brace 57.9 ± 26.2 $p = 0.57$).
No significant difference was found in the secondary outcome measures. The SARS scores were not significantly different between the two groups at baseline ($p = 0.44$) and after the rehabilitation running schedule ($p = 0.17$). Both groups showed a significant improvement in SARS score after completing the running schedule (brace group $p = 0.02$, no-brace group $p = 0.0004$). The other secondary outcome measure, overall satisfaction with the treatment, was not significantly different either (6.4 ± 11 on a 1-10 scale for the brace group and 7.1 ± 0.7 for the control group ($p = 0.06$)). Wear comfort of the brace was assessed as 4.8 ± 1.3 (mean ± SD). At follow-up after six months no recruit reported having developed symptoms of MTSS again after they were free of symptoms.

Complications / compliance
All but one recruits (86%) wearing the pneumatic leg brace mentioned complaints while wearing the brace, consisting of pain around the ankle. On follow-up small wounds and shafting were regularly seen around the lateral and medial malleolus. The complaints could only partly be solved by filling the brace with more air and by applying tape on the edges of the brace where it could be sharp. Nonetheless, compliance of wearing the brace was good.

DISCUSSION

This study showed that for recruits, there was no additional value in using a pneumatic leg brace in the treatment of MTSS as measured by days to completion of a running program. In addition, the wearing comfort and thus the feasibility of the brace for the recruits, was low. Our power calculation was based on data from trials of pneumatic leg brace in tibial stress fractures [16,18,19], two of which showed a reduction in time to completion of rehabilitation of more than 55 days [18,19]. We assumed a comparable but lesser reduction of 30 days to complete our rehabilitation programme using the brace, therefore the study was only powered to detect a large difference in outcome and was planned as a potential pilot study – further, larger studies would be needed to demonstrate smaller treatment effects of the brace on MTSS.
The theory underlying our trial is the belief that MTSS forms part of a spectrum of disease with tibial stress fractures [5] and that there is evidence [24,25] that a pneumatic brace is of value in treating fractures, confirmed in a Cochrane review [21]. Dickson and Kichline studied ten female athletes with tibial stress fractures, diagnosed with radiographs or bone scans [17]. The athletes received a pneumatic brace and were immediately able to compete at the same level as before the onset of symptoms. All were asymptomatic in less than one month. Whitelaw et al. [20] also used a pneumatic brace for the treatment of tibial stress fractures. Seventeen men and women were included, after establishing the diagnosis with radiographs and bone scan. These patients were able to perform intensive training after 3.7 weeks (range 3-6 weeks) and were able to return to competition at the pre-injury level after 5.3 weeks (range 4-7 weeks). A randomized controlled trial by Swenson and colleagues in 1997 studied 18 athletes with tibial stress fractures [19]. All patients, men and women, had positive bone scans correlating to the painful site

and after 12 weeks, 94% of the radiographs showed positive signs of a stress fracture. After random selection, one group received a pneumatic leg brace while the control group did not. The median number of days until the start of light activity was significantly lower in the brace group (p =0.017) compared to the control group (7 versus 21 days). The median number of days from treatment initiation to recovery was 21 ± 2 (SD) for the brace group and 77 ± 7 (SD) for the control group (p =0.0005). It is of note that this study was small and that in the control group more women were present. An Australian military study included 60 patients and allocated them randomly to an pneumatic brace group or a six weeks convalescent leave group. The last group was given non-impact exercise advice. After either wearing the brace or convalescent leave, both groups joined a standardized rehabilitation protocol. A significant difference was found in the number of lost training days (12.3 ± 21.1 days vs 72.4 ± 45days; p <0,0001) in favour of the use of the brace [18]. The most recent randomized study was performed in the military and showed no difference in the time taken to be able to run 1 mile pain free (p = 0.24). Of the 31 included patients only 20 of them completed a rehabilitation program (10 with pneumatic leg brace, 10 without brace) [16]. Recently, in a randomized trial, Johnston et al. studied the effect of a non-pneumatic brace on the recovery of MTSS in a military population [6]. They could not find an aided effect of their brace compared to a control group.
One proposed mechanism by which a brace may be useful is by increasing the resistance to torque, as was shown in an animal study with canine tibial fractures by Dale et al. [24]. In this way less bowing of the tibia may be the result as other studies have shown that increased bowing leads to increased microdamage of the bone [26,27] .

One limitation of our study is that subjective assessment of leg pain was used throughout baseline testing and rehabilitation to decide starting rehabilitation phase and phase progression through the rehabilitation schedule. Consequently, not all patients progressed to a next phase of the running schedule having the same sensation in the legs. Furthermore no validated score is available for MTSS, so progress or worsening of symptoms is hard to measure. The development of such a score would greatly add the study of MTSS in the future. It is also of note that in our study recruits were not supervised beyond Phase 2 of the running schedule which may have reduced recruit compliance.

CONCLUSION

This randomized study failed to show the predicted large benefit of adding a pneumatic leg brace to the standard rehabilitation protocol in the treatment of MTSS in military recruits. Reported comfort levels with the brace were low. Despite these negative findings we would recommend further research with a pneumatic brace in the treatment of MTSS, given the better results found in other randomized studies in the treatment of leg related bony overload conditions.

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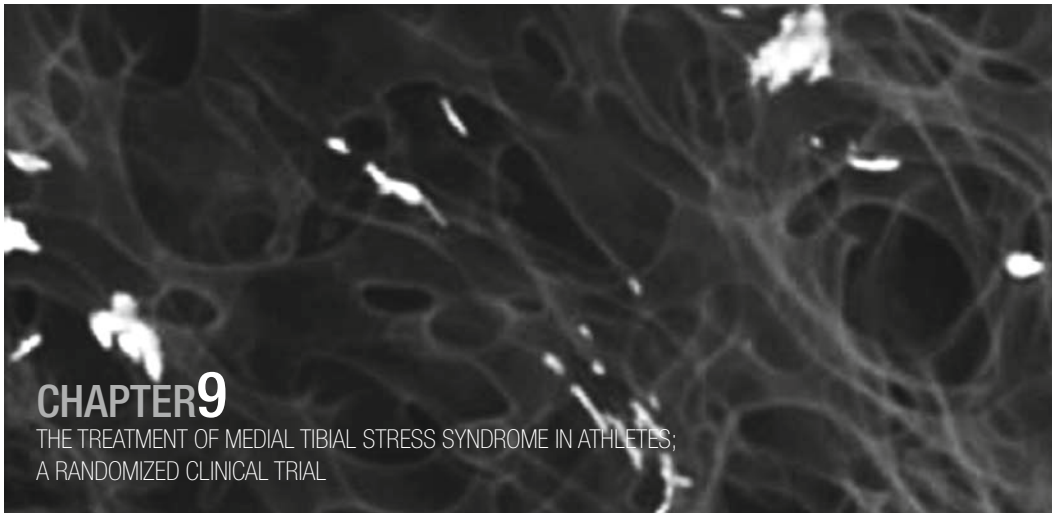

CHAPTER 9

THE TREATMENT OF MEDIAL TIBIAL STRESS SYNDROME IN ATHLETES; A RANDOMIZED CLINICAL TRIAL

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Sports Med Arthrosc Rehabil Ther Technol (2012; 4(1):12)

ABSTRACT

Background: The only three randomized trials on the treatment of medial tibial stress syndrome (MTSS) were all performed in military populations. The treatment options investigated in this study were not previously examined in athletes. The study investigated if functional outcome of three common treatment options for MTSS in athletes in a non-military setting was the same. Methods: This study design was randomized and multi-centered. Physical therapists and sports physicians referred athletes with MTSS to the hospital for inclusion. 81 athletes were assessed for eligibility of which 74 athletes were included and randomized to three treatment groups. Group one performed a graded running program, group two performed a graded running program with additional stretching and strengthening exercises for the calves, while group three performed a graded running program with an additional sports compression stocking. The primary outcome measure was: time to complete a running program (able to run 18 minutes with high intensity) and secondary outcome was: general satisfaction with treatment. Results: 74 Athletes were randomized and included of which 14 did not complete the study due a lack of progress (18.9%). The data was analyzed on an intention-to-treat basis. Time to complete a running program and general satisfaction with the treatment were not significantly different between the three treatment groups. Conclusion: This was the first randomized trial on the treatment of MTSS in athletes in a non-military setting. No differences were found between the groups for the time to complete a running program.

INTRODUCTION

One of the most common causes of overuse leg injuries is medial tibial stress syndrome (MTSS) with incidences varying between 4 and 35% in athletic and military populations [1,2,3]. In the past the etiology of this syndrome was not clear, and several possible causes were described e.g. increased intracompartimental pressure or a traction induced periostitis [4,5]. Recently, different imaging techniques have demonstrated that the tibial cortex is probably involved in MTSS. With dual energy x-ray absorptiometry (DEXA) scanning Magnusson et al. showed that decreased bone density was present in the symptomatic part of the tibia [6]. High resolution computer tomography (CT) scans revealed osteopenia in the involved tibial cortex [7]. However, histological studies are needed in which the bone overload theory is confirmed. Until then, bone overload as a cause of MTSS remains a hypothesis.

Despite the high incidence of MTSS, a recent systematic review of the literature only identified three randomized controlled trials in the treatment of MTSS, all performed in military population [8]. In the study by Andrish et al. five different interventions (ice application, aspirin and ice application, phenylbutazone and

ice application, heel cord stretching and ice application, walking cast) were compared. The outcome measure was being able to run 500 meters comfortably [1]. The study by Nissen et al. studied if the application of gallium-arsenic laser treatment compared to sham laser treatment shortened the time to return to duty [9]. Johnston et al. investigated if a leg brace added to a rehabilitation program influenced the time to complete 800 meters of running pain free [10]. None of these studies found that the intervention group recovered significantly faster than the control group [1,9,10]. Besides these three RCTs there were two non-randomized controlled studies [11,12], and a few lower quality studies found [13,14,15,16,17]. In these treatment studies many different outcome measures were used. There is no recognized validated outcome measure for MTSS.

In clinical practice, graded running, strengthening and stretching exercises for the calf muscles are frequently prescribed for MTSS [18,19]. Graded running in itself could strengthen the tibial cortex [20,21,22]. Waldorff et al. showed that physiological loading allowed increased remodeling of the tibiae and increased resorption of micro-damage [22]. While very few studies have been published on the effect of stretching for MTSS [1,12], stretching is frequently included in treatment programs. Some research has been published on the effect of muscles in protecting the cortex. Animal and human studies showed that diminished muscle force negatively influences the bone adaptation process. Weaker muscles that oppose tibial bending allow an increase in bending to occur [23,24,25,26]. A recent military study showed that tibial strain, measured with strain gauges, increased after performing fatiguing long distance marches [27].

Sports compression stockings are used frequently in the Netherlands to treat MTSS [28]. A sports compression stocking might provide direct compression of the tibia and via the surrounding soft tissues, especially during intermittent loading. Compression of bony tissue has been shown to promote the expression of bone specific genes [29].

The effects of these interventions have not been previously studied in randomized trials in an athletic population. The aim of this study was to study, in a non-military, athletic population, a graded running program alone or with additional strengthening and stretching exercises or while wearing a sport compression stocking for the leg for the treatment of MTSS in a randomized trial.

METHODS

Subjects

The design of the study was a randomized multi-center trial with three groups. Each athlete was randomly assigned to a treatment group, and all the athletes in the group received an intervention. The multi-center study was announced to physical therapists, general practitioners, sports medicine physicians and orthopedic surgeons. They informed the athletes about the existence of the study. They could all refer an athlete to a sports physician in one of three participating

sports medicine clinics in the Netherlands (two large district and one university hospital). The sports physicians examined the athlete for complaints of MTSS and for suitability for inclusion. If the athlete was suitable for inclusion, the sports physician referred the athlete to one of the investigators for intake. A single sports physician identically trained the investigators for the study. The diagnosis of MTSS was made according to the criteria of Yates et al. (see Table 9.1) [30]. For exclusion criteria the description of symptoms provided by Edwards et al. in their recent review were used to specify stress fractures of the tibia and chronic exertional compartment syndrome (CECS) [31]. Pain in stress fractures is often focal (clinically and with physical examination) and the start of complaints is usually abrupt. Pain initially occurs as a mild ache after exercise, but as the condition progresses pain can be felt early after starting exercise. Athletes with CECS often complain of burning, cramping or pain over the involved compartment with exercise. Pain is progressive with continued exercise and will disappear after cessation of activities [31].

The athletes had to be involved in sport at least once a week. The inclusion was definitive when the diagnosis MTSS by an instructed sports physician was confirmed according to the Yates et al. criteria [30] and the presence of exclusion criteria [31] was excluded (Table 9.1) and informed consent was given.

Table 9.1: Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Pain induced by exercise and present during or after exercise	Tibial fracture in the past
Pain on the postero-medial border of the tibia	History of parestaesia
Diffuse pain on palpation of the postero-medial tibia for at least 5 centimeters	Focal pain on palpation of the posteromedial tibia or stress fracture present on x-ray
Age > 16 years old	Clinical suspicion of exercise induced compartment syndrome or increased intra-compartimental pressure
Active in sport at least once per week	
Complaints for more than 3 weeks	

Randomization

For the randomisation 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 athlete.

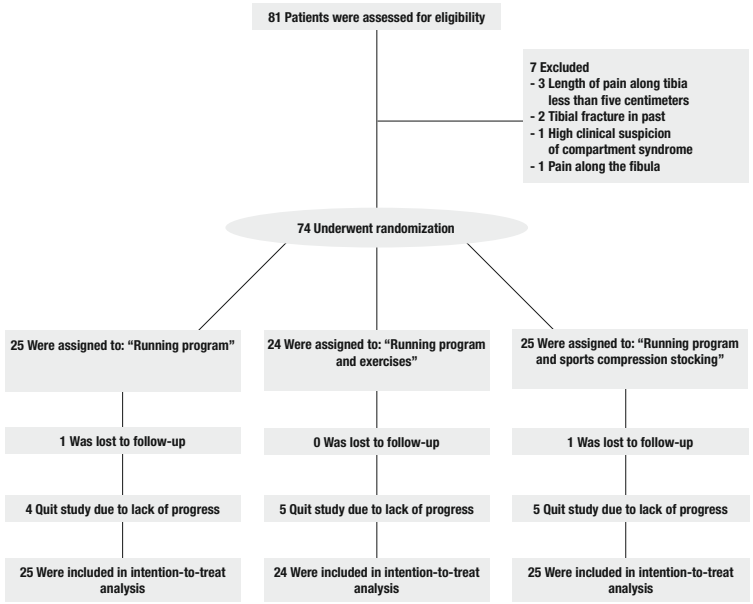

Figure 9.1: Flow of patients through the study.

Intake

At baseline the investigators noted sex, weight, height, body mass index (BMI), kind of sport in which the athlete was involved, centimeters of pain on palpation of the postero-medial border of the tibia, side of the complaints and number of days with complaints. Subsequently, a running test was performed. The running test consisted of running on a treadmill at a fixed speed, while wearing the athlete's own running shoes. Although the running test is not validated for the use in MTSS athletes it has been used previously used in treatment studies on MTSS [32,33]. First, the athlete was shown a visual analogue scale (VAS) for pain by the investigators. Then the athlete was told that when a four (on a 1-10 VAS scale) for MTSS was experienced, defined as an indication that the pain was starting to become annoying, the running test had to be stopped. The running test started at 7,5 km/hour for two minutes. After this initial warming-up phase the distance was noted that could be run at 10 km/hour until a four on the VAS scale was noted. The distance ran at 7,5km/hour was subtracted from the total meters run and was called "meters run at 10km/h".

Graded running program

With the result of the running test the athlete was placed in one of the six phases of the graded running program (see Table 9.2) [32,33]. When "meters run at 10km/hour" was between 0-400 meters, the athlete started the running program in phase one. When 401-800 meters could be run, the athlete started in phase two. When 801-1200 meters could be run the athlete started in phase three. When 1201-1600 meters could be run, the athlete started phase four. When 1600 meters or more could be run, athletes started phase five. When pain was present already during walking no running test was performed. Then the athlete was advised about how to avoid complaints by reducing loading of the leg. When in these athletes pain was not present during walking for two consecutive days, phase one of the running program was started. The running program was performed three times per week, with a day off between each session.
A new phase of the running program could be commenced if a phase was finished without a pain score of four or higher on the 1-10 VAS pain scale during the running. When pain (four or more on the VAS scale) was present immediately after the running or the day after the running the program did not progress and running remained in the same phase and the time run was decreased by two minutes.

Table 9.2: Running program.

Running phase	Surface	Minutes	Total	Speed / intensity
1	Treadmill	2 2 2 2 2 2 2	16 minutes	2 = running at 10km/hour, 2 = walking at 6km/hour
2	Treadmill	2 2 2 2 2 2 2	16 minutes	2 = running at 12km/hour, 2 = walking at 6km/hour
3	Concrete	3 2 3 2 3 2 3 2	20 minutes	Intensity 1-2 (*) 3 = running, 2 = walking
4	Concrete	3 2 3 2 3 2 3 2	20 minutes	Intensity 2-3 (*) 3 = running, 2 = walking
5	Concrete	Continuous running	16 minutes	Intensity 1-2 (*)
6	Concrete	Continuous running	18 minutes	Intensity 2-3 (*)

(*): Intensity 1; running speed: light jogging. Intensity 2; running speed; jogging while able to speak. Intensity 3; running speed: jogging while speaking becomes difficult

Graded running program with exercises

In addition to the graded running, which is described above, athletes performed exercises at home five times per week (see addendum). The exercises consisted of stretching and strengthening exercises of the calves. The investigators practiced the exercises with the athletes until they were familiar enough to perform them

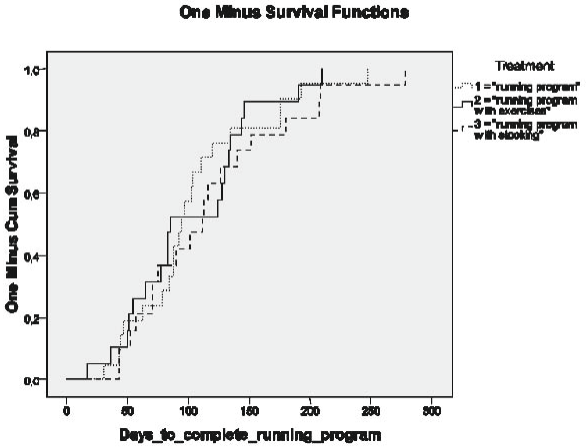

Figure 9.2: Reversed Kaplan-Meier survival curve for days to complete the running program.

at home. The exercise schedule consisted of five phases. When a certain phase could be performed without a four on a 0-10 VAS pain scale, the following phase could be started. When phase five was finished, the athlete kept on exercising with a random mix of exercises from different phases.

Graded running program with a sports compression stocking
In addition to the graded running program, which is described above, a sports compression stocking for the leg (Herzog Medical, Woudenberg, the Netherlands) was worn when the athlete was walking or running. The compression stocking could only be taken off when the athlete was seated or laying down for more than 15 minutes. To supply the right size, the investigators measured the circumference of the calf just below the knee fold, the maximal calf circumference and the circumference just above the malleoli. Based on these measurements a size 1-6 of the stockings was supplied**.**

Follow-up
Follow-up took place at week 2,4,6,8,10,12,16,22,28,34,42,50. To structure and perform follow-up, the investigators were identically trained by one sports physician (MM). Athletes were asked about progress with the running schedule, complaints and compliance with the treatment. Additionally, a physical examination was performed and feedback was provided.

Compliance
A commonly used method to measure compliance is self-reported adherence to the treatment [34,35]. At follow-up athletes were asked to choose from the following sentences: “I stuck to the prescribed activities”, “most of the time I stuck to the prescribed activities”, “I stuck to the prescribed activities at the beginning, but not anymore”, or, “I did not follow the prescription at all” (adapted from Kallings et al., 2009) [34]. The athletes that answered “I stuck to the prescribed activities” and “most of the time I stuck to the prescribed activities”, when asked about the adherence of the prescribed activities, formed the group that adhered.

Blinding
The athletes and investigators were not blinded. The data analyst (EB) was blinded to the chosen therapy. The athlete was not blinded to the treatment, because it was not possible to perform blinding. The investigators were not blinded, because the investigators had to give feed-back to the athlete about the intervention. The investigators also asked about compliance of the prescribed treatment.

Outcome measurement
Primary outcome: the number of days from inclusion to the completion of phase six (being able to run 18 consecutive minutes outdoors at a speed in which speech becomes difficult) of the running schedule was used as primary outcome measurement. Although this outcome measurement was used in previous studies on the treatment of MTSS [32,33], this outcome measurement has not been validated. Unfortunately, no validated outcome measurements for MTSS exist. When an athlete was not able to finish the running program and quit the study, the Likert scale was used to assess the status of the athlete [36]. This scale was scored as: 1 = completely recovered, 2 = much improved, 3 = somewhat improved, 4 = same, 5 = worse and 6 = much worse. When a athlete did not have progress anymore and wanted to quit the study the Likert score was collected. The Likert scale was shown by the investigator and the investigator asked how the athlete was doing at the moment of quitting the study compared to baseline. The athlete choose a number. Satisfaction with the treatment in general on a 1-10 scale was used as secondary outcome measurement, in which 1 = very dissatisfied with treatment and 10 = highly satisfied with the treatment in general.

Data analysis
Data was entered using SPSS 17.0 (SPSS Inc, Chicago, Illinois, USA). To compare the outcome between groups Analysis of Variance (ANOVA) with post-hoc analysis according to Games-Howell was used. For dichotomized variables Chi-Square analysis was used. The athletes were analyzed by intention-to-treat. For athletes that were lost to follow-up a worst and best case scenario was calculated. For athletes that withdrew from the study due to a lack of progress, the time to complete the running program was entered as missing data in the database. Kaplan-Meier analysis was used to obtain reversed survival curves.

The local medical ethical committee agreed with the study beforehand (reference number for the study; NL23471.098.08). The committee agreed to include athletes who were 16 years of age and older. Informed consent was received from each participant.

Power analysis
Previous studies on the treatment of MTSS reported a maximum time to recovery of 17.2 days and a standard deviation of 9,5 days [1,9,10]. Based on these findings, we considered a reduction of 50% in time to recovery would be clinically relevant. Sample size calculation indicated that 22 athletes (including an expected 10% lost to follow-up) per treatment group were needed to detect such difference with a power of 80% at a significance level of 0.05.

RESULTS

Between October 2008 and February 2010 athletes were included in the study. 81 athletes were assessed for suitability for inclusion and 74 fitted the criteria and were randomized. The flow of athletes through the study is shown in Figure 9.1. The baseline characteristics for all athletes groups are presented in Table 9.3. No significant differences in baseline characteristics were found between the treatment groups. Most athletes (69%) started in phase 1 or 2 of the running program. No significant differences were found for the starting phase between the groups. The follow-up period ended in June 2010. The athletes were involved in different kind of sports. The most prevalent were soccer (24%), running (15%) and field hockey (10%). The mean number of hours that the athletes were involved in sport was 5,1 (SD 3,2) hours / week (range 1-21 hours / week). No significant differences in hours / week involvement in sport were found between the groups.
No differences were found between the groups for primary and secondary outcome measures after intention-to-treat analysis (Table 9.4). The mean number of days to complete the running program was 105.2 days (SD 54.6) for the group with the running program, 117.6 days (SD 64.2) for the group with the running program and exercises and 102.1 days (SD 52.3) for the group with the running program and the sports compression stocking ($p > 0.05$).The reversed survival curve is presented in figure 9.2. No significant differences were found in the number of meters able to run on quitting the study in athletes that withdrew between the groups.
For satisfaction with the treatment in general (secondary outcome measurement) no differences were found between the groups ($p > 0.05$). Satisfaction in the running program group was 6.5 (SD 1.3), in the running program with exercises group 5.9 (SD 1.6) and 6.8 (SD 2.0) in the running program and sports compression stocking.
No significant differences were found in the number of athletes that quit the study due to subjective lack of progress with the injury or that were lost to follow-up (see figure 9.1). The Likert score for these athletes was not significantly different between the groups and ranged from 3 to 4. In a worst case / best-case scenario for the intention-to-treat analysis (the lost athletes were calculated as fastest recovery (17 days) or slowest recovery (278 days)) still no significant differences between groups could be found in days to complete the running program.
No athletes were excluded from the study due to a lack of compliance. All athletes reported, "I have stuck to the prescribed activities" or "most of the time I have stuck to the prescribed activities". No complications were reported after the treatments.

Table 9.3: Baseline characteristics for the three treatment groups.

	Running program (SD) N=25	Running program + exercises (SD). N=24	Running program + compression stocking (SD) N=25	*p*-value
Length (centimeters)	175,4 (4,9)	171,6 (5,1)	177,0 (9,9)	NS
Weight (kilograms)	68,7 (8,1)	68,3 (7,7)	70,4 (11,2)	NS
BMI (kilograms / (length)^2)	22,2 (1,8)	22,9 (2,6)	22,3 (2,6)	NS
Age (years)	22,2 (6,8)	20,7 (6,4)	23,0 (8,2)	NS
Sex (percentage females)	65,2%	72,7%	53,5%	NS
Side with complaints (percentage both sides)	87,0%	77,3%	96,4%	NS
Centimeters of pain on palpation	12,2 (4,9)	11,6 (5,1)	16,1 (8,8)	NS
Days with complaints	178,0 (319,2)	174,0 (274,1)	213,7 (363,8)	NS
Meters run without pain on treadmill	7408,7 (423,9)	572,6 (419,2)	591,8 (427,2)	NS

Abbreviations; NS: not significant ($p>0.05$)

Table 9.4: Primary and secondary outcome measures.

	Running program (SD, 95% CI)	Running program and exercises (SD, 95% CI)	Running program and compression stocking (SD, 95% CI)	*p*-value
Days to complete the running program	105.2 (54.6, 80.4-130.1)	117.6 (64.2, 86.7-148.6)	102.1 (52.3, 76.9-127.2)	NS
Satisfaction with treatment in general on 1-10 scale	6.5 (1.3, 4,5-8,6)	5.9 (1.6, 4.6-7.3)	6.8 (2.0, 5,7-8,0)	NS

Abbreviations: NS: not significant ($p>0.05$), SD = standard deviation, 95% CI = 95% confidence interval

DISCUSSION

This is the first randomized study on the treatment of MTSS in athletes outside the military . No significant differences for time to complete a running program and athlete satisfaction were found between the treatment groups. The interventions in this study were implemented for both sexes, a wide range of different sports and ages between 16-51 years old. This means that the results from this study can be generalized to a broad athletic population. The results from this study are in keeping with the only three other published RCTs on the treatment of MTSS [1,9,10].
Prior to the start of treatment a running test was performed, which is not validated. The running test, although not validated, was used in previous studies on MTSS [32,33]. The results of the running tests in these studies were more or less comparable to the findings in this study. For the future, the running test should be validated.
In the literature no validated outcome measure for MTSS is available and therefore several outcome measures are used. The development of validated outcome measures is a priority in this research field to increase the quality of treatment studies on MTSS. The previous randomized studies were all conducted in a military population and used different outcome measures. Andrish et al. used no reported tenderness or being able to run 500 consecutive meters as outcome measure [1]. In the study by Nissen et al., days to return to active duty was the primary outcome measurement [9]. The study by Johnston et al. used the time to run 800 meters without pain as outcome measure [10].
This study used time to complete a running program (defined as running continuously at a pace when speech becomes difficult) as the primary outcome measure. This is similar to the studies by Andrish et al. and Johnston et al. [1,10]. In a pilot study conducted by our research group, a lot of athletes were able to run further than 800 meters during the running test at intake. That is why the decision was made to lengthen the running program compared to these studies.
No significant differences between the groups for primary and secondary outcome measures were found. Therefore, if MTSS is treated with a running program, no large additional effect of the two interventions can be expected. It should however, be noted that a graded running program has not been compared with a control group that rested in any study. Now, only assumptions can be made that the graded running program improves the density and strength of the tibia, and that rest does not have this effect. This is why no conclusions can be drawn from this or other studies that a graded running program is superior to rest. While setting up the study, it was tried to include a control group that rested. However, several physical therapists, sports physicians and orthopedic surgeons did not want to participate in the study if the control group rested, because they believed then they couldn't offer anything to the athletes. This was the reason that the control group performed a graded running program.
Self- reported adherence to the treatment was used to quantify compliance. This method of quantifying adherence carries a potential risk of bias, including social desirability [34]. Nevertheless, self-reported adherence has been found to be accurate and reliable when compared to objective quantification of physical activity [34,35].
No gold standard for quantifying adherence to physical activity or physical activity levels exist [37].
In all three groups athletes quit the study due to a lack of progress. These athletes were included in the analysis and this did not affect the outcome. With a relatively high dropout percentage (18,9%), this is a shortcoming of the study. The number of athletes that quit was not significantly different, with a dropout percentage varying between 16,0 and 20,8%.
Another limitation of this study is the lack of blinding of the athletes and the investigators. The studied treatment modalities were so different, that it was very hard to apply blinding to the athletes. The investigators were not blinded, as they had to give feedback to the athletes on the treatment received.
One of the weakness of this study is the power analysis used. At the start of the study, based on the available information from military studies [1,9,10], we assumed that 22 athletes per treatment group were needed to find a clinically relevant reduction of 50% in time to recovery, i.e. from 17 days to 8-9 days, with alpha set on 0.05 and a power of 0.8. However, recent studies [12,32,33] indicated that a time to recovery of 60-100 days is likely to be more realistic in athletes with MTSS. The current study was therefore able to detect a large effect of the interventions. For future studies, with the data from these studies and the data from this study a more precise power analysis could be possible [12,32,33].

CONCLUSION

This is the first randomized controlled study on MTSS in athletes outside a military setting. No significant differences were found between the three treatment groups in days to complete a running program (primary outcome measure) and satisfaction with the treatment (secondary outcome measure). This study does provide insight in recovery of MTSS in athletes with an average time to complete a running program of 102.1 (SD 52.3) – 117.6 days (SD 64.2). Further RCT's should be performed to test the hypothesis that a graded running program leads to a favorable outcome compared with rest. In future studies validated outcome measures should be developed and new interventions can be tested by comparing their effectiveness to a graded running program.

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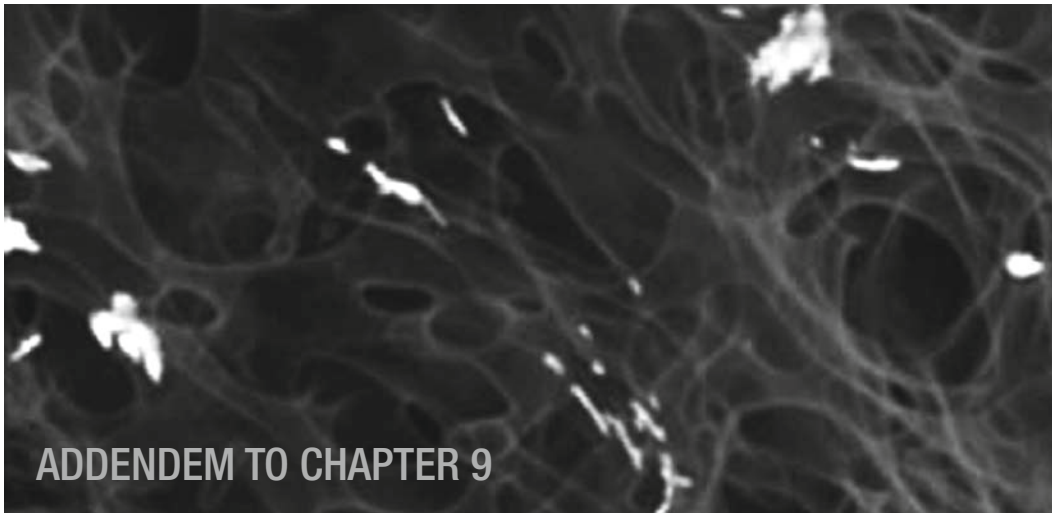


ADDENDEM TO CHAPTER 9

PHASE 1

1. Seated on a chair, maximally flex and bend the ankle. Keep the foot down for five seconds and then keep the foot up for five seconds. Do this 10 times in three series. Between the series take a 30 seconds break.
2. Seated on a chair, write the alphabet with the foot on your injured side. Perform this one time.
3. Seated on a chair, roll up a towel with the foot on your injured side. Perform this three times with a 30 seconds break in between.
4. Seated on a chair with your feet on the ground, raise your heels as high as possible and hold for five seconds. Repeat this for 10 times. Perform three series of repeats with a 30 seconds break in between.
5. Stand between two chairs and put your hands on them. Then, bend your knees until 120 degrees and then slowly get up. Repeat this for ten times. Perform three series of repeats with a 30 seconds break in between.

PHASE 2

1. Stand on the foot of the injured leg with the knee slightly bend. Hold the other leg above the floor and hold this position for 30 seconds. Repeat three times with a 30 seconds break in between.
2. Stand on the foot of the injured leg with the knee slightly bend. Move the other leg, which should be held in the air, next, in front and behind this leg. When no complaints are evoked, practice this exercise on an uneven surface. Perform the exercise for 30 seconds and repeat three times with a 30 seconds break in between.
3. Stand on the foot of the injured leg with the knee slightly bend and the foot of the other leg in the air. Hold your arms straight in front of your body. Then, without moving the knee, move your arms to the right and the left. Move them slowly for 30 seconds and take a 30 seconds break. Repeat the exercise three times.
4. Stand on the foot of the injured leg three meters in front of a wall, the other foot in the air. Throw a ball 20 times to the wall and catch it. Perform three series and in between rest for 30 seconds.
5. Stand on the foot of the injured leg and bend the knee slightly. Stand maximally on the toes and hold for two seconds. Repeat this in three series of 10 repetitions. Take a 30 seconds break between the series.

PHASE 3

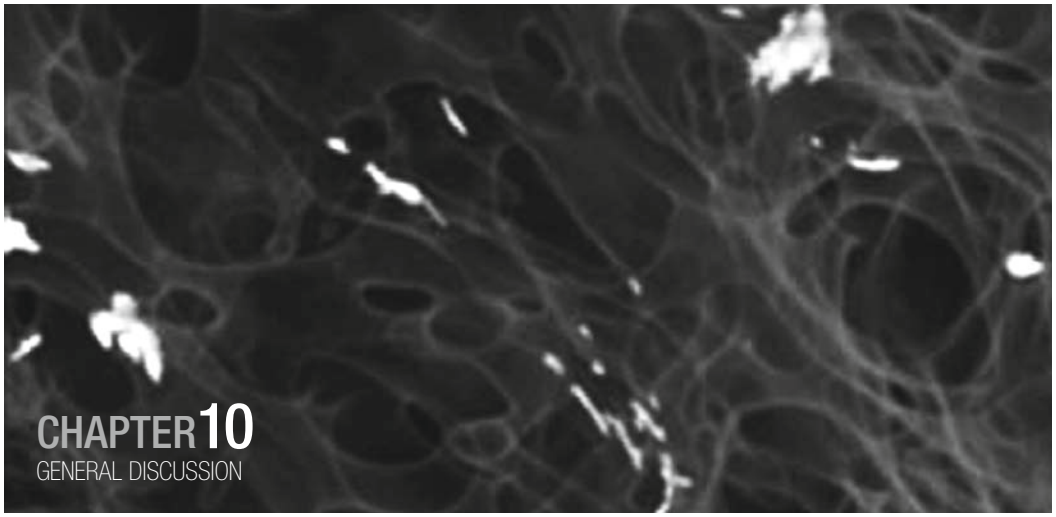
1. Stand on a low bench with both feet. Then stand on the toes of both feet and slowly lower your heel below the level of the bench. Repeat 15 times in three series. Between the series take a 30 seconds break.
2. Stand with both feet on the ground. Walk on your heels for 30 seconds. Perform this three times with a 30 seconds break in between.
3. Stand with both feet on the ground. Walk on your toes for 30 seconds. Perform this three times with a 30 seconds break.
4. Stand 30 centimeters in front of a wall. Place one foot a step behind and keep the leg straight with the hands against the wall. The front leg is bend in the knee. Then press the hips foreword until a tension is noticed in the hind leg. Keep the position for 10 seconds, take a 30 seconds break and perform two more times. Both legs should be stretched in this manner.
5. Stand 30 centimeters in front of a wall with the hands pressed against this wall. Place one foot a step behind and bend this knee. The front leg is also bent in the knee. Then, bend the hind leg further until a tension is noticed. Keep the position for 10 seconds, take a 30 seconds break and perform two more times. Both legs should be stretched in this manner.

PHASE 4

1. Stand on both feet. Jump a little bit in to the air and after a jump stand still for two seconds. Repeat this for 30 seconds in total. Take a 30 seconds break and perform two more series.
2. Stand on both feet. Perform a little jump to the front and back and stand still for 2 seconds. Repeat this for 30 seconds in total. Take a 30 seconds break and perform two more series.
3. Stand on both feet. Perform a little jump to the left and then to the right. After this, stand still for two seconds. Repeat this for 30 seconds in total. Take a 30 seconds break and perform two more series.
4. Stand with both feet and the floor and jump on a 25 centimeters high bench. Land on both feet and jump back to the floor, landing on two feet. Perform this 10 times. Repeat this in three series total with a 30 seconds break in between.
5. Stand on both feet and jump foreword with one foot as if you were skating. Repeat this 20 times and after each jump stand still on one leg for two seconds. Take a 30 seconds break and perform two more series.

PHASE 5

1. Stand on one leg. Perform a jump to the left and then to the right. After each jump stand still on one leg for two seconds. Perform 20 jumps in total, then take a 30 seconds break. Perform 3 series in total.
2. Stand on the foot of the injured leg. Perform small jumps for 30 seconds, then take a 30 seconds break. Repeat this in two more series.
3. Perform small jumps with the foot of the injures leg. After 10 jumps make a left turn in the air and stand still for 2 seconds. Repeat this until you turned left for 10 times. Take a 30 seconds break and perform two more series.
4. Perform small jumps to the left, right, front and back and rest for 5 seconds. Repeat this for 5 times and take a 30 seconds break. Then perform two more series.
5. Stand on the foot of the injured leg. Jump on a 25 centimeter high bench and jump back to the floor landing on the foot of the injured leg. Repeat 10 times and take a 30 seconds break. Then perform two more series.



CHAPTER 10
GENERAL DISCUSSION

In this thesis the aetiology, imaging and treatment of medial tibial stress syndrome (MTSS) was studied. Throughout the years, much controversy existed on the aetiology of MTSS. Nowadays, still no consensus is reached, although most of the evidence seems to favour the bone overload theory. In the ideal situation, a known aetiology guides the treatment of overuse injuries. That is why clarifying the exact aetiology of MTSS remains of clinical significance. In this Chapter, the two main aetiological theories of MTSS are discussed. Thereafter, it is examined how the diagnosis MTSS could or should be established. Later on, the different available treatment options for MTSS are summarized. Finally, practical conservative and surgical treatment advice as well as preventive interventions for MTSS are discussed.

AETIOLOGY

The past decades many theories on the aetiology of MTSS have been postulated. Of all these theories, described in **Chapter** 1, two main aetiologies remain.

Bone overload

In this theory it is assumed that MTSS is caused by overload of the tibial cortex. Several studies have shown that MRI images of symptomatic legs can depict bone marrow and periosteal oedema as a sign of bone remodelling. CT scan studies showed osteopenia on the postero-medial side of the tibia in symptomatic legs (Gaeta et al., 2006). Magnusson et al. performed DEXA scans in athletes, which showed decreased bone density in symptomatic legs compared to their controls (Magnusson et al., 2001) .

In addition to the observations described above, in **Chapter 5**, it has been shown that even in asymptomatic legs of athletes bone marrow oedema and periosteal oedema can be present (Batt et al., 1998; Bergman et al., 2004; **Chapter** 5). Bergman et al. performed a study in which an MRI scan was performed in 21 asymptomatic runners who ran 50-70 miles each week (Bergman et al., 2004). 43% of them showed findings on MRI scans (five unilateral findings and four bilateral findings). The findings varied from mild to moderate periosteal oedema to periosteal oedema and bone marrow oedema on T1 and T2 images. None of the runners developed complaints in the 48 months follow-up period. **Chapter 5** and the study by Batt et al. also showed bone marrow and periosteal oedema in asymptomatic legs of athletes with MTSS (Batt et al., 1998 ; **Chapter 5).** These MRI findings raise the question if bone marrow oedema does represent normal remodelling of the bone after loading. Possibly, bone marrow oedema in athletes represents a normal sign of bone remodelling, which may become symptomatic once the loading exceeds a certain threshold.

Loading can affect remodelling of the bone in different manners. Loading applied by muscle forces and axial loading transferred through the joint can deform the bone tissue and thereby creating strains that influence cellular processes in

the cortex. This concept was placed in a theoretical framework by Frost (Frost, 1998; Frost, 2004) who called it "Mechanostat Theory" (see figure 10.1). When the load is minimal and below a genetically derived threshold the bone becomes weaker (disuse threshold, MESy), by resorbing trabecular or endocortical bone. When the load is higher than the disuse threshold and below a second threshold (maintenance threshold, MESm) the bone remains its strength. When load is between the maintenance threshold and a threshold above which cortical microdamage occurs (damage threshold, MESp), the bone strengthens. Loads above this last threshold lead to microscopic fatigue damage (microdamage) that accumulates because the loads and microdamage are too great to recover from.

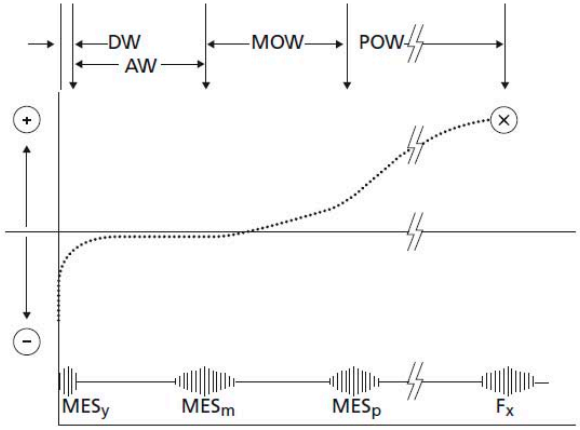


Figure 10.1: Remodelling graph of load bearing bones adapted from Frost, 2004. Abbreviations; DW: disuse window, AW: adapted window (as in normally adapted young adults), MOW: mild overload window, POW: pathologic overload window. MESy: disuse threshold, MESm: maintenance threshold, MESp: damage threshold, Fx stress fracture or MTSS (Reprint permission granted by Allen Press and Angle Orthod).

Increasing evidence is gathering that osteocytes play a key role in the processes of sensing the strains by axial loading or muscular contraction (Hughes & Petit, 2010). The osteocyte's cytoskeleton, ion channels and cilia appear to play a role in sensing the mechanical signal and the transduction of the mechanical signal into a biochemical signal used by the cell (Bonewald, 2006; Scott et al.,2008).

For example, the release of prostaglandins and nitric oxide by osteocytes due to loading leads to recruitment of osteoblasts from the marrow (Turner et al.,2004). However, the biochemical processes inside the bone following mechanical loading are just starting to become evident. More studies will give us insight in understanding the mechanotransduction into biochemical processes in more detail.

Bone pain mechanism

When the bone is overloaded and microdamage accumulates, complaints may occur. The pain mechanism of overloaded bone has only recently been established. The prevailing opinion was that bone pain arises from the densely innervated periosteum (Mundy, 1999). However more recent studies showed that sensory nerve fibres also innervate the mineralized bone and bone marrow (Mach et al., 2002; Gajda et al., 2005). Several studies suggested that these nerve fibres are stimulated by mechanical distortion (Mundy, 1999; Alder, 2000). Other studies suggested that sensory nerve fibres could be activated by protons, which are released by osteoclasts when resorbing bone. That is because osteoclasts form a highly acidic compartment between themselves and mineralized bone. The acidic environment is sensed by afferent nerves that innervate the mineralized bone and induces a pain signal (Iba & Yamashita 2010; Mach et al., 2002; Niiyama et al., 2007). Furthermore, microcracks could also provide direct sensory input to intracortical nerves. When the crack disrupts the nerve, signalling is interrupted that can potentially lead to (referred) pain (personal communication Weinans, 2011).

For the future, more studies which examine the microstructure of the tibial cortex are required to obtain proof that MTSS is caused by bone overload. This could be performed by high-resolution (in-vivo) CT scanning or micro-CT scanning of (in-vitro) bone samples. These imaging modalities could provide more insight in the definite aetiology of MTSS by revealing intra-cortical lesions and trabecular damage in detail. Cortical tissue biopsies have the potency to show the existence of microcracks in MTSS. So far, these have only been shown in animal studies. For this, approximately a 0,3 x 0,3 centimeter deep samples of the cortex should be obtained. These should be analyzed for microdamage and ideally be compared to cortex samples of exercising individuals without complaints.

Traction

The other aetiological theory on MTSS is that the syndrome is caused by traction. In the past it was generally accepted that the tibial posterior muscles caused traction on the periosteum and periostitis. But, significant evidence for periostitis was lacking, as was shown in studies that performed histological research (**Chapter** 2). Furthermore, the location of the tibial posterior muscles (latero-proximal) does not resemble the location of complaints in patients with MTSS (Beck et al., 1994; **Chapter** 2).

Two articles were published that provided some evidence for the possibility of the traction theory. Stickley et al. showed in an anatomical study with 16 cadav-

ers that the crural fascia was present along the entire postero-medial border of the tibia in all but three specimens (Stickley et al., 2009). They propose that traction on the crural fascia could produce complaints along the postero-medial tibial border. Fibres of the flexor digitorum, posterior tibial and soleus muscles were not found along the distal tibia. In 2006 an interesting study was published by Bouche and Johnson (2006). In this study three fresh frozen cadaver limb specimens were disarticulated at the knee and vertically aligned in a frame. The posterior tibial, flexor digitorum longus and soleus muscles were connected to cables, which could pull in an upward direction, simulating muscle pull. Four strain gauges were inserted in the crural fascia at its insertion on the posterior side of the tibia at 3, 6, 9 and 12 centimeters from the medial malleolus. Load was applied to the different muscles via the cables and strain was measured in the gauges. The result was that increased load to the muscles, led to increased strain, recorded in the three and six centimeter strain gauges, in a linear manner. The data from the nine and 12 centimeter strain gauges was variable and inconsistent (Bouche & Johnson, 2006). Bouche and Johnson suggested that with dynamic loading the crural fascia is under tension and through traction this may lead to complaints of MTSS.
With the Bouche and Johnson study, the traction theory cannot be ruled out. But more comparable studies are needed to obtain firm evidence for the traction theory. Currently, the evidence is based on just three cadavers. Furthermore, it is not clarified how traction could lead to bone marrow oedema as seen on MRI, osteopenia as seen on CT scans and decreased bone density as seen with DEXA scans.

Pain mechanism
The mechanism of pain for the traction theory is not fully understood. Hardly any studies investigated the crural fascia histologically. Johnell et al. found some evidence for inflammation of the crural fascia in the minority of patients (Johnell et al., 1982). No further studies examined crural fascia tissue in MTSS, so it remains unclear what exactly could cause pain symptoms according to the Bouche and Johnson theory. According to them the aetiology of MTSS is the same as for plantar fasciitis. In this field, some more and larger histological studies have been performed. These studies showed that seldomly inflammatory cells could be found and that probably collagen degeneration and mucoid degeneration lead to complaints (Lemont et al., 2003; Snider et al., 1983; Schepsis et al. 1991; Tountas & Fornasier, 1996). The crural fascia also consists of collagen fibres and could degenerate as well (Stecco et al., 2009). If this is the case, free nerve endings at osteoligamentous attachment sites can be activated mechanically by strain or chemically and transmit electrical signals with subsequent neurotransmittors leading to pain (Stecco et al., 2006; Stecco et al., 2007). Findings in plantar fasciitis, however, were not investigated in patients with MTSS. If the mechanism of pain for MTSS (according to the aetiology proposed by Bouche and Johnson) and plantar fasciitis are comparable remains to be investigated.

HOW TO ESTABLISH THE DIAGNOSIS MTSS / IMAGING

In the literature, most studies describing inclusion criteria established the diagnosis of MTSS clinically (Andrish et al., 1974; Callisson et al., 2002; Johnston et al., 2006; Nissen et al., 1994; Rompe et al., 2010), and when published after 2004, according to the criteria by Yates et al. (2004). However, many reviewers of MTSS related articles ask for imaging data as inclusion criteria to prove the diagnosis of MTSS.
In the literature, radiographs, CT-scans, bone scans and MRI scans have been used to establish the diagnosis. Radiographs performed in MTSS patients have almost always showed normal images, so they are not useful to confirm MTSS (Anderson et al., 1997; Aoki et al., 2004; Magnusson et al., 2001). Two studies from the same study group investigated the role of CT-scans. These studies showed osteopenia in the tibial cortex in most of the patients (Gaeta et al., 2005; Gaeta et al., 2006). However, in 45% of the tibiae in asymptomatic runners, osteopenia was also found. This makes establishing the diagnosis using CT-scans at least difficult, if not impossible.
For bone scans and MRI scans a vast number of false positive and negative cases have been described (Bergman et al., 2004; **Chapter** 5; Drubach et al., 2001). Bergman et al. showed that 43% of runners who ran between 64-112 kilometers per week, showed findings on MRI which can be compared to the findings in athletes with MTSS (Batt et al., 1998; Bergman et al., 2004; **Chapter** 5). On follow-up these runners did not develop leg complaints. In the study by Drubach et al., 100 young athletes referred for a bone scan because of low back complaints, were analysed for asymptomatic bone scan abnormalities in the legs. They found that in 34% of the legs abnormalities in the asymptomatic legs could be found (Drubach et al., 2001). In 57% of the MRI's of athletes with longstanding MTSS complaints no abnormalities on MRI could be found (**Chapter** 5). Due to these figures, it is recommended to establish the diagnosis of MTSS clinically.

Practical advice on establishing the MTSS diagnosis:
To establish the diagnosis of MTSS use the criteria adapted from Yates et al. (2004):

Pain history. The pain is induced by exercise and may last for a few hours or days after exercise. Pain is located on the posteromedial border of the tibia. There is no history of paraesthesia or other symptoms indicative of other causes of exercise induced leg pain.

Location. The patients identify pain along the posteromedial border of the tibia. The site is spread over a minimum of 5 cm. Focal areas of only 2 to 3 cm are typical of a stress fracture.

Palpation. Palpation of the posteromedial border of the tibia produces discomfort that is diffuse in nature and confines to the posteromedial border of the tibia. In the areas of discomfort, the bone surface may feel uneven.

Treatment

According to the facts described above, more evidence is available for bone overload causing MTSS compared to the traction theory, suggesting that interventions for MTSS should be aimed mainly at the bone. However, in the past, most interventions seem to be aimed at periostitis. Five randomized controlled trials (RCT's), three controlled trials and several case series and case reports were published on the treatment of MTSS. The five RCT's could not find significant differences between the groups. Andrish et al. examined whether differences could be found in the recovery time between several interventions (rest and ice; rest, ice and asperin; rest, ice and phenylbutazone; rest, ice and heel-cord stretching exercises; rest, ice and a cast) (Andrish et al., 1974). Each intervention aimed at periostitis as stated in the article. Nissen et al. treated MTSS (defined as traction induced periostitis) patients with active or inactive laser therapy. They studied in a military population if the time to return to active duty or Visual Analogue Scale (VAS) pain scores could be influenced by the treatment (Nissen et al., 1994). No significant differences were found between the groups. In 2006 Johnston et al. studied if a neoprene leg brace with an aluminium bar aided the recovery of MTSS (due to bone stress as stated by the authors) (Johnston et al., 2006). No difference in time to complete 800 meters of running pain free, was found between the groups. Johnston et al. did not provide any rational for the chosen treatment, except that they chose to study the therapy because of a claim made by the manufacturer of the brace. In **Chapter 8**, a pneumatic leg brace was used to treat MTSS, because it was thought that the brace would minimize bending moments occurring in the tibial cortex . But also in this study, no differences were found between the intervention and the control group.
The last RCT described in **Chapter 9** studied common interventions for MTSS (running program; running program with strengthening and stretching exercises; running program with a compression sleeve) (**Chapter** 9). No differences in time to complete a graded running program between the groups was present. The interventions were all aimed at bone overload via different pathways.
In controlled studies, Rompe et al. treated MTSS with radial shockwave and compared the intervention to home based exercises of the leg (Rompe et al., 2010). They found that the shockwave group was more likely to be completely recovered on the short term (one month) and on the long term (15 months). In the article no statement was provided that could explain the reported effects. They do state that MTSS can be caused by traction induced periostitis or tibial stress injury. In the study in **Chapter 7** the effect of focused shockwave in addition to a running program versus a running program alone was studied. The shockwaves were aimed at the bone. The shockwave group recovered significantly faster than the group with the running program alone (59.7 ± 25.8 days v 91.6 ± 43.0 days). Callisson et al. suggested that MTSS was caused by the tibial posterior muscle and pronation of the midfoot and aimed the therapy (acupuncture) at the site where "microtearing of the suspected involved muscles" occurred (Callison, 2002). Acupuncture was compared to exercise of the leg muscles and acupuncture with exercises combined. The groups in which acupuncture was involved recovered the fastest over a three week period. Recovery was measured using pain scores during activity and in rest.
Overstressing the anterior and posterior tibial muscle was thought the cause of MTSS is a case series by Delacerda (Delacerda, 1982). He therefore treated MTSS with iontophoresis (a technique using a small electric charge to deliver a medicine through the skin) using xylocaine and hydrocortisone. The pain decreased after xylocaine treatment, but returned quickly and after hydrocortisone the pain subsided after an average of three treatment sessions. Eickhoff et al. treated MTSS with prescribed foot orthoses (Eickhoff et al., 2002). They thought that pronation resulted in traction of the already stressed muscle tendon unit on the medial side of the tibia. In their retrospective study using questionnaires, 88% of the respondents recovered completely after 4 weeks wearing the orthosis. Another study, examining the effect of orthoses in the treatment of MTSS, was performed by Loudon and Delphino (Loudon & Delphino, 2010). Most patients noticed a decrease in pain after three weeks wearing the orthoses. The authors suggested that MTSS could be caused by traction on the medial side of the tibia or by a stress reaction of the bone. Curtin et al. performed a pilot study treating MTSS with dextrose injection under the periosteum (Curtin et al., 2011). This resulted in a decrease in the VAS scores of pain during sports. The indication for the injections was not clear, since the study was only presented as an abstract of a presentation.
A case report by Schulman described that provided acupuncture was aimed at the Wei-Qi meridian which is thought to flow at the fascial-muscle interface on the medial side of the leg (Schulman, 2002). The patient reported that after a single acupuncture session, his complaints were resolved in two days. A report by Morris treated MTSS with electric current, but the reason was not clear (Morris, 1991). The exact time to recovery was not described in the paper. Another case report by Krenner used chiropractic interventions and anti-inflammatory supplements to counter suspected periostitis in MTSS (Krenner, 2002). No time to recovery was described in the article. **Chapter** 6 described a case report in which athletes were treated with bisphosphonates (**Chapter** 6). The athletes were able to compete at their pre-injury level after 70 and 77 days respectively. The bisphosphonates were used because they are known to inhibit bone resorption.

Conservative treatment

From the above it is apparent that most studied interventions aimed at reducing pain. Most studies stated the hypothesis that traction caused complaints in MTSS. Fewer studies suggested that treatment should be aimed at bone. Of all

the treatment studies, just a few non-randomized ones found a treatment effect. The interventions that can thus be advised for clinical practise are therefore derived from these studies.
Rompe et al. and **Chapter 7** showed that, when shockwaves (either radial or focused) were added to a treatment protocol, the recovery was enhanced (**Chapter** 7; Rompe et al., 2010). In **Chapter 7** a running program was added in addition to the focused shockwaves. With one retrospective study (Rompe et al.) and one prospective controlled study (**Chapter** 7) according to the Institute for Quality of Healthcare [Centraal Begeleidings Orgaan] classification, this would provide moderate evidence for shockwave (and a running program) as an intervention. To gain more evidence for shockwave for the treatment of MTSS randomized controlled studies are needed.
The other intervention that was studied in a controlled trial and showed a treatment effect,was acupuncture (Callison, 2002). Only one controlled study could be found which studied this, leading to limited evidence (CBO-classification) for the intervention. Acupuncture for the treatment of MTSS should also be investigated further, although it is hard to understand how acupuncture would interfere with processes in the tibia. Also, limited evidence is available for orthoses as an intervention for MTSS with two non-controlled trials available (Eickhoff et al., 2000; Loudon & Dolphino, 2010).

Practical advice on conservative treatment:
For the treatment of MTSS with shockwave therapy, level II evidence is present. Based on **Chapter 7** of this thesis, we advice to treat MTSS with shockwave combined with a graded running program. Shockwave therapy is starting to become more available in recent years, however, is unfortunately not present in every physical therapy practise. When this intervention is ineffective, acupuncture or orthoses can be prescribed, but for these interventions, only level III evidence exists.

Surgical treatment
In some patients despite having tried multiple conservative treatment options, complaints persist. In these patients a surgical intervention for MTSS might be an option, however evidence is limited due to the lack of controlled trials. Several studies have been published on the surgical treatment of MTSS and all are of poor methodological quality (Abramowitz et al., 1994; Detmer, 1986; Holen et al., 1995; Jarvinnen & Niittymaki, 1989; Wallenstein, 1983; Yates et al., 2003). Surgical treatment is believed to be sufficiently adequate for pain control (69-92% of the patients report good or excellent results (Abramowitz et al., 1994; Detmer, 1986; Wallenstein, 1983; Yates et al., 2003)). However, most studies report a low percentage of patients who return to sport at their pre-injury level (29-41% (Abramowitz et al., 1994; Holen et al., 1995; Yates et al., 2003)).

The reason why a surgical intervention for MTSS might work is not clear, because in most surgical methods the periosteum is stripped from the tibia. Perhaps this leads to disruption of the already hyperstimulated nerves which are abundantly found in the periosteum. But, due to the bone pain mechanism described above, this can only partly explain the decrease in pain in most patients.

Practical advice on surgical treatment:
If all conservative treatment options failed, surgical treatment by specialized orthopaedic surgeons can be proposed to patients with MTSS (Level III evidence). It does not seem to matter which method of operation is used, with all methods reporting a reasonable outcome for pain.

Future treatment
For the future, studies should focus on performing interventions that are aimed at either reducing the amount of bending of the tibia or interfering with cellular processes in the cortex mechanically or pharmacologically. Possibly, treatment options that are now used or developed for osteoporosis and stress fractures could be applied to the treatment of MTSS.
Future studies could aim at adapting the loading of the tibia. If strains on the tibia seem too low, loading of the tibia could be stimulated to induce more microdamage and remodelling below the second threshold on purpose. If strains on the tibia seem too high, causing microdamage to accumulate, the load on the tibia should be reduced. Bracing might increase the resistance to torque and reduce bending in the tibia (Dale et al., 1993). However**, Chapter 8** studied the effect of a pneumatic brace and found no effect, but the study was small and larger studies are needed to draw definite conclusions on pneumatic bracing for MTSS. Pulsed electromagnetic field (PEMF) and capacitively coupled electric field stimulation are both being used for a variety of bone disorders such as fracture, pseudarthosis and stress fractures (Schmidt- Rohlfing et al. , 2011). These interventions could also be tested for MTSS treatment. Currently, a randomized controlled study using PEMF for MTSS is underway, but no results are available yet (personal communication; Bredeweg et al., 2011).
Several options are available to influence cellular processes in the cortex pharmacologically. These interventions are currently used or studied for the treatment of osteoporosis in which a misbalance between osteoblasts and osteoclasts exists as well. These medications are administered systemically, and therefore have the potency to cause side-effects.
Bisphosphonates (having an inhibitory effect on osteoclasts) should be studied in prospective trials, since now only one case report on the treatment of MTSS with biphosphonates is available (**Chapter** 6). Another pharmacological option would be parathyroid hormone (for example hPTH 1-34 or hPTH 1-84), which promotes the proliferation and differentiation of osteoblasts (Datta &

Abou-Samra, 2009; Jilka, 2007). Parathyroid hormone should be administered subcutaneously. New forms of parathyroid hormone that can be taken orally are being developed currently (John et al., 2009; Lane & Silverman, 2010). Some evidence exists that strontium ranelate enhances replication and differentiation of osteoblasts (Lyritis et al., 2010). In addition strontium ranelate also possesses antiresorptive capacities (Brennan et al., 2009; Ferrari, 2010).
For the future a little bit further ahead of us, perhaps calcilytics can play a role in the treatment of MTSS. These calcilytics block the Ca^{2+} sensing receptor and this may result in a pulse of secreted parathyroid hormone, which has an anabolic effect on osteoblasts (Kumar et al., 2010). Perhaps MTSS could be treated with antibodies such as anti-sclerostin or anti-Dickkopf, which are both new drugs that are very potent bone anabolic stimulators and are designed for the treatment of osteoporosis. Both sclerostin and Dickkopf proteins are negative regulators of bone formation by inhibiting proliferation of osteoblasts and promoting apoptosis (Geoghegan et al., 2004; Wang et al., 2008). In addition, statins, also possess antiresorptive actions, and have shown to possibly enhance bone density (Tang et al., 2008). The exact mechanism by which this occurs remains to be elucidated.

Prevention
Several preventive strategies for MTSS were studied in the past decades. Of these, only for a shock absorbing insole level I evidence exists (**Chapter** 2). Shock absorption may lead to less strain per impact in the tibia while the leg is axially loaded. Less strain and less bending of the tibia result in less microdamage above the second threshold as described by Frost (Frost, 2004). No further preventive measures have proven its benefit (**Chapter** 2).
For the future attempts to prevent MTSS could be aimed at risk factors known to be associated with MTSS. One of the most commonly described risk factors is pronation of the midfoot at rest or during exercise (Bandholm et al., 2008; **Chapter** 2; Tweed et al., 2008). No studies investigated if an anti-pronation insole could prevent the development of MTSS. Other risk factors that were described in the literature are more difficult if not impossible to focus on, such as female gender, decreased internal range of motion of the hip joint and increased plantar flexion of the ankle.
It can be postulated that in the future MTSS could be prevented by having athletes, in particular the more susceptible women, participate in whole body vibration. An effect of whole body vibration on bone mineral density was shown in animal bones (Rubin et al., 2001). Several human studies showed that vibration training increased bone mineral density (BMD) in postmenopausal women (Rubin et al., 2004; Verschueren et al., 2004). Another study showed that younger women with a lowered BMD improved BMD after daily treatment with whole body vibration during a year (Gilsanz et al., 2006). A recent study in young women with normal bone density status showed that after two weekly sessions of whole body vibration during 16 weeks the local bone density in the femur and vertebrae increased significantly compared to a control group (Humphries et al., 2009). The tibia was not investigated in this study. Although more research is needed, whole body vibration could be promising as a preventive measure in the future.
Another strategy to prevent MTSS could be to provide athletes with feedback of the amount of tibial loading. Less axial loading would lead to less bending of the tibia and as a result less microdamage would occur. Several studies showed that live feedback of tibial loading lead to reduced impact loading using a monitor which displayed forces on the tibia. This effect sustained for at least a month after the feedback was provided (Crowell et al., 2010, Crowell et al., 2011).
To prevent MTSS it would be useful to be able to measure BMD in athletes. If the BMD reduces, the training load could be adapted. Usually, BMD is measured using dual x-ray absorptiometry (DEXA) scans. This method does not seem practical for athletes, since measurements have to be performed in the hospital. Qualitative ultrasound has been used to measure BMD in athletes (Foldes et al., 1997; Falk et al., 2003; Falk et al., 2010). Although this more practical method of measuring BMD seems promising, more studies should be undertaken to recommend the technique in practise yet.

Future directions
Many studies can and should be undertaken in the MTSS field the coming years. The following suggestions for future studies are herewith proposed:
1. A validated outcome score is essential for objective quantification of the symptoms and to compare interventions and study groups. Currently, such a validated outcome score is unavailable and should therefore be developed.
2. The high suspicion that MTSS is caused by bony overload has never been thoroughly investigated. For this, a study could be performed in which biopsies of the tibial cortex of MTSS patients are studied for microcracks. Also, cortex material of a matched athletic control group, operated on the lower leg for a non-MTSS reason, should be studied and compared to the MTSS group. If significantly more microcracks are found in the MTSS group, the bone overload theory has become far more likely.
3. An MRI study could be undertaken to compare findings in the legs of athletes with MTSS and matched athletic controls. Such a study could provide insight on the consequences on MRI of loading of the tibia.
4. More treatment studies are needed in the future, since none of the randomized treatment studies so far showed an effect of an intervention compared to a control group. In future randomized controlled treatment studies a graded running program could be compared with a group of MTSS patients that only rest. In the MTSS treatment studies so far, a true control group is lacking.
5. Shockwave treatment for MTSS has now been studied retrospectively and in a prospective controlled trial design. For the future, a randomized controlled trial with a double-blind design could be started, in which shockwave treatment is compared to sham-shockwave.
6. Bisphosphonates have only been described in a case report. A larger series is needed to establish if controlled trials should be started.

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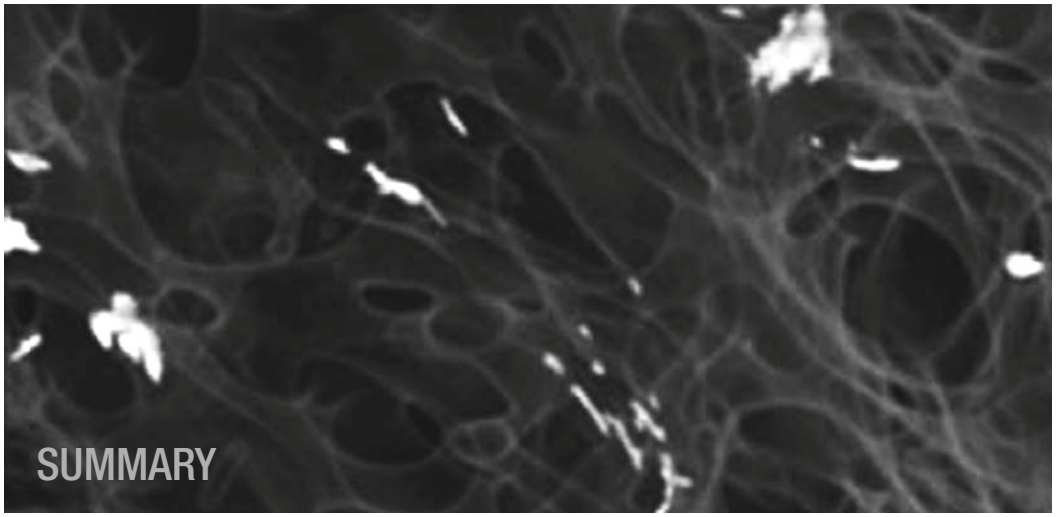


SUMMARY

Although MTSS is one of the most common causes of leg complaints, in the past decades few studies have looked at medial tibial stress syndrome (MTSS). The available studies on MTSS most often focused on investigating risk factors and less on imaging or treatment. Until this thesis just a few controlled treatment studies were present in the literature. Not much research has been conducted on the aetiology of MTSS, although this topic has been the subject of much debate. This thesis aimed at studying the aetiology, imaging and treatment of MTSS.

Chapter 1 provides an overview of historical perspectives in MTSS. From the nineteen forties onwards, various mechanisms were described that could cause MTSS. Nowadays, some authors still refer to these older mechanisms. The first chapter also describes the aims of the content of the different chapters in this thesis.

As there had not been a recent review of the literature, the available studies on MTSS were summarised in **Chapter 2**. This chapter discusses different aspects of MTSS; aetiology, histology, physical examination, imaging, risk factors, treatment and prevention. Concerning aetiology, no definitive evidence was found that confirmed one of the aetiological theories. It is most likely that bone overload is the chief cause of MTSS and not periostitis, as was thought for years. Different methods of imaging have been described in the literature of which the use of bone scans and MRI scans were investigated most frequently. It is not clear whether or not these modalities should be used in clinical practise, due to the high numbers of false positive and false negative scans. Only three randomised clinical treatment trials could be identified. None of these studies showed an effect of an intervention when compared to a control group. Several studies investigated preventive measures, in which a shock absorbing insole reduced the number of athletes / recruits with MTSS significantly.

A case-control study in 35 military recruits examined risk factors for MTSS in **Chapter 3.** Fifteen recruits with MTSS were included with the control group comprising 20 healthy recruits. In these recruits the following parameters were recorded: internal and external rotation of the hip, knee flexion and extension, dorsal and plantar flexion of the ankle, subtalar inversion and eversion, maximal calf girth, standing foot angle and navicular drop test (tests to quantify pronation of the foot). Recruits with MTSS showed significantly less internal rotation of the hip, increased plantar flexion of the ankle and a positive navicular drop test compared to the control group. A higher Body Mass Index (BMI) was a prognostic factor for a longer time to recovery.

Chapter 4 is a case-report of a patient who developed MTSS, without obviously overloading the tibia. After excluding different possible causes of his complaints, it was concluded that the use of methotrexate for psoriatic arthritis was the probable reason for the leg complaints. One of the known additional effects of

methotrexate is osteopathy. This chapter showed that methotrexate can be a rare cause of MTSS.

Fifty two athletes with MTSS were investigated using an MRI scan in **Chapter 5** and the findings were described. Additionally, this chapter studied whether prognostic factors for time to recovery could be established. The MRI scans showed periosteal or bone marrow oedema in 43,5% of the athletes. When periosteal or bone marrow oedema was present, the time to recovery was significantly decreased compared to the group in which no oedema was seen. When oedema was seen on MRI, the time to recovery was 52.4 ± 42.1 days, compared to 80.1 ± 48.6 days, when oedema was not seen. Of all the clinical parameters, the SARS and LEFS scores (both functional scoring systems) were associated with the time to recovery, explaining 54% of the variance.

Two athletes with MTSS who were treated with bisphosphonates are described in **Chapter 6**. This novel treatment for MTSS has not been described in the literature before. The rational for treating MTSS with bisphosphonates was that bisphosphanates are known to inhibit osteoclasts. In this way remodelling of the bone could be influenced and complaints could be reduced. The two athletes used the bisphosphonates for three months, after which the use of the medication was ceased. The athletes were recovered from their complaints after 70 and 77 days, which is shorter than some of the recovery times described in the literature. Larger prospective studies on the treatment of MTSS with bisphosphonates are needed, before this treatment can be recommended.

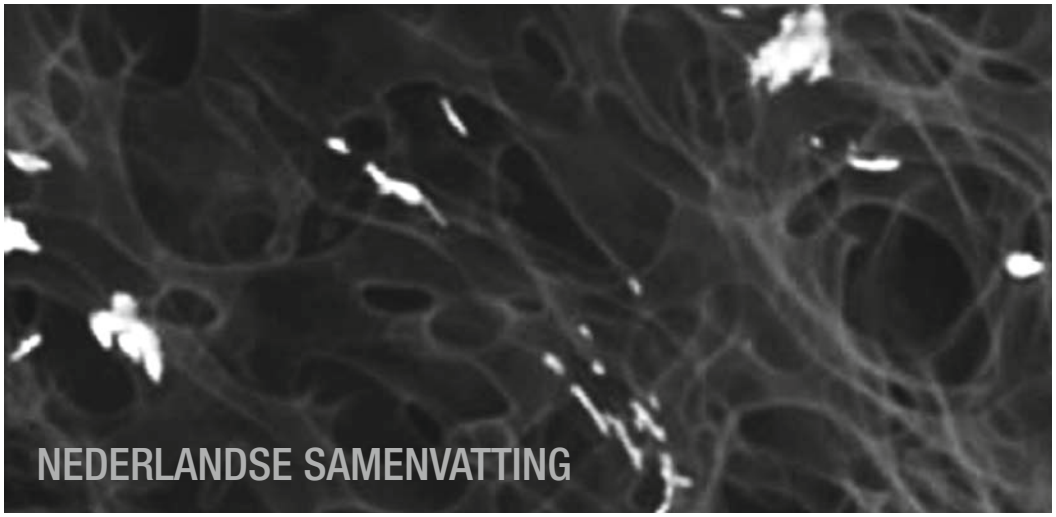
In **Chapter 7**, 42 athletes with MTSS were studied in a prospective controlled treatment trial. One group was treated with focused shockwaves (five sessions) in addition to a graded running programme, while the control group was treated with a graded running programme alone. The primary outcome measure used was the time to complete a graded running programme. The athletes who were treated with the focussed shockwaves and the graded running programme were recovered in 59.7 ± 25.8 days, while the athletes in the control group recovered in 91.6 ± 43.0 days. With this, the athletes in the focussed shockwaves and graded running programme group recovered significantly faster. No other factors, other than kind of treatment, were found that influenced the time to recovery.

A small group of fifteen recruits with MTSS was studied in a randomised trial in **Chapter 8.** One group of recruits rehabilitated with a pneumatic brace in combination with a graded running programme. The other group (control group) was treated with a graded running programme alone. No significant differences were found in time to recovery between the groups (with brace 58.8 ± 27.7 days, without brace 57.9 ± 26.2 days) . The comfort of the brace was reported to be poor by most of the recruits.

Seventy four athletes were treated with three different interventions which were allocated after randomisation in **Chapter 9.** Group one was treated with a graded running programme, group two was treated with a graded running programme and exercise for the calves (stretching and strengthening exercises) and group three was treated with a graded running programme and an additional sports compression sleeve. The primary outcome measure used was the time to complete the running programme (= time to recovery). No significant differences were found for time to recovery between the groups, which varied from 100 to 120 days. No significant differences between the groups were found for satisfaction with the treatment.

The last chapter in this thesis is **Chapter 10.** In this chapter the two main aetiological theories on MTSS are discussed. One theory is that MTSS is caused by bone overload, while the other theory is that MTSS is caused by traction (on the crural fascia). The possible pain mechanisms for the two aetiological theories are also discussed. Additionally, suggestions are made on how to establish the diagnosis of MTSS, which treatment options are available for MTSS and which of these treatment options to apply currently and which are possibly relevant for the future. Several preventative options are highlighted as well. Finally, suggestions are provided on possible future studies on MTSS.

For the future, a validated outcome measure for MTSS is very much needed. Without it the different outcomes of treatment studies cannot be easily compared. So far, no randomised controlled treatment trial, including the studies from this thesis, was able to show a significant difference in outcome between treatment groups. More high quality studies are needed to make the treatment strategy for MTSS patients more evidence based.



NEDERLANDSE SAMENVATTING

De afgelopen decennia is er relatief weinig onderzoek gedaan naar mediaal tibiaal stress syndroom (MTSS), terwijl MTSS bij sporters een vaak voorkomende oorzaak is van onderbeensklachten. Het onderzoek dat werd gepubliceerd richtte zich met name op risicofactoren en in mindere mate op de diagnostiek en behandeling van MTSS. Tot deze promotie werden slechts enkele gecontroleerde behandelstudies beschreven. Betreft de etiologie van MTSS waren tevens weinig studies verschenen, maar theorieën over de ontstaanswijze waren er des te meer. Dit proefschrift richt zich op het verhelderen van de etiologie, de diagnostiek en de behandelwijze van MTSS.

In **Hoofdstuk 1** wordt een overzicht gegeven van de historie van MTSS. Vanaf de jaren 40 van de vorige eeuw werden vele verschillende ontstaanswijzen geformuleerd, die tot de dag van vandaag in meer of mindere mate nog steeds opduiken in de literatuur. Naast dit overzicht van de historie t.a.v. de ontstaanswijze van MTSS werden de doelen en hypothesen van de afzonderlijke hoofdstukken van dit proefschrift geschetst.

Gezien het gebrek aan een recent literatuuroverzicht over MTSS werd de literatuur hieromtrent samengevat en gepubliceerd in **Hoofdstuk 2**. Er werd ingegaan op verschillende aspecten, namelijk: ontstaanswijze van MTSS, histologie (weefselonderzoek), lichamelijk onderzoek, aanvullend onderzoek, risicofactoren, behandeling en preventie. Betreft de ontstaanswijze werd duidelijk dat er nog geen definitief bewijs is voor een van de theorieën. Wel werd duidelijk dat botoverbelasting en niet ontsteking van het scheenbeenvlies de meest waarschijnlijk oorzaak van MTSS is. Er werden verschillende vormen van aanvullend onderzoek gevonden, waarbij de MRI-scan en de botscan het meest werden gebruikt. De waarde van het gebruik van de scans staat voor de praktijk nog niet vast gezien het aantal fout negatieve en fout positieve resultaten. Slechts drie gerandomiseerde onderzoeken, gericht op de behandeling, konden worden geïdentificeerd. Deze studies lieten geen verschil zien tussen de groep met interventie en een controlegroep. Qua preventie werden verschillende studies gevonden die het nut aantoonden van schokdempende zooltjes.

Bij 35 soldaten werd in **Hoofdstuk 3** gekeken naar risicofactoren voor MTSS. Bij 15 soldaten met klachten en een controle groep van 20 soldaten zonder klachten werden verschillende parameters vergeleken. Dit waren: endo- en exorotatie van de heup (naar binnen- en buiten draaien), knie flexie en extensie (buigen en strekken van de knie), dorsaal en plantair flexie in de enkel (buigen en strekken van de enkel), hallux flexie en extensie (buigen en strekken van de grote teen), subtalaire eversie en inversie (het naar binnen en buiten bewegen van de enkel), maximale omtrek van de kuit, standing foot angle en de navicular drop test (beide testen voor het bepalen van de maat van pronatie (naar binnen zakken) van de voet). Uiteindelijk bleek dat soldaten met MTSS minder endorotatie van de heup, een versterkte plantair flexie van de enkel en een positieve navicular drop test hadden

in vergelijking met de controle groep. Een hogere Body Mass Index (BMI) bleek een voorspeller voor een langere duur van het herstel van de klachten.

In een case-report in **Hoofdstuk 4** wordt een persoon beschreven die zonder overmatige belasting van de tibia toch klachten van MTSS ontwikkelde. De waarschijnlijke reden van zijn klachten was, na uitsluiten van andere oorzaken, het gebruik van Mexthotrextaat voor zijn artritis psoriatica (gewrichtsklachten door psoriasis). Bekend van Methotrexaat is dat het soms kan leiden tot osteopathie (botklachten). Dat het medicament ook kan leiden tot MTSS toonde dit hoofdstuk aan, maar blijft een zeldzame reden van de klachten.

In **Hoofdstuk 5** werd een groep sporters (N=52) met MTSS onderzocht door middel van een MRI-scan. Ook werd onderzocht of er factoren te vinden waren, die een voorspellende waarde voor de herstelduur hadden. Bij 43.5 % van de sporters met MTSS was er op de MRI een afwijking (periostaal en / of beenmergoedeem) te vinden. Wanneer er periostaal of beenmergoedeem werd gezien betekende dit dat de duur van het herstel korter was, dan wanneer er geen oedeem op de MRI scan werd aangetoond. De herstelduur van de sporters was bij aanwezigheid van periostaal of beenmergoedeem op de MRI 52.4 ± 42.1 dagen, terwijl bij afwezigheid van oedeem de hersteltijd langer was (80.1 ± 48.6 dagen). Verschillende klinische parameters (SARS score en LEFS score) bleken tevens voorspellend voor het duur van herstel, aangezien 54% van de variantie van de herstelduur hierdoor kon worden verklaard.

Hoofdstuk 6 beschrijft een tweetal sporters, die op een niet eerder beschreven methode voor MTSS werden behandeld met bisfosfonaten. Het idee achter deze manier van behandelen was, dat bisfosfonaten ingrijpen op de botstofwisseling op een manier waarbij de activiteit van de osteoclasten (botafbreekcellen) werd geremd. De sporters gebruikten de bisfosfonaten gedurende drie maanden, waarna ze de behandeling stopten. De twee sporters waren na respectievelijk 70 en 77 dagen hersteld. Deze duur van het herstel is korter dan die in de meeste wetenschappelijke artikelen betreft behandeling van MTSS wordt beschreven. Grotere prospectieve studies zijn echter nodig voordat sporters met MTSS op grotere schaal met bisfosfonaten kunnen gaan worden behandeld.

Door middel van een prospectief gecontroleerd onderzoek (**Hoofdstuk** 7) werd onderzocht of sporters met MTSS (N=42) die werden behandeld met gefocusseerde shockwave therapie (5 behandelingen) en een opbouwend loopschema sneller waren hersteld van hun klachten dan een groep sporters met alleen een opbouwend loopschema. De uitkomstmaat die werd gebruikt was de duur in dagen tot het afronden van een loopprogramma. De groep die het loopschema combineerde met de shockwave behandeling was een stuk sneller hersteld dan de controle groep (59.7 ± 25.8 vs 91.6 ± 43.0 dagen). Buiten het type behandeling werden geen factoren gevonden die de duur van het herstel konden verklaren.

In **hoofdstuk 8** wordt een kleine groep soldaten met MTSS beschreven (N=15), die in een gerandomiseerde studie werden vergeleken. De interventie die werd onderzocht was een pneumatische brace, die gedragen werd om het onderbeen. Deze werd door groep een gedragen in combinatie met een opbouwend loopschema, terwijl groep twee (de controle groep) werd behandeld met alleen een opbouwend loopschema. Er werden geen verschillen gevonden in de hersteltijd tussen beide groepen (met brace 58.8 ± 27.7 dagen, zonder brace 57.9 ± 26.2 dagen). Verder bleek het draagcomfort van de brace voor de meeste soldaten laag.

Een groep sporters met MTSS (N=74) werd in **Hoofdstuk 9**, na randomisatie, behandeld met een van drie verschillende interventies. Groep een werd behandeld met een opbouwend loopschema, groep twee werd behandeld met een opbouwend loopschema en oefeningen voor de kuiten (rekken / krachtsoefeningen), terwijl sporters in de derde groep behandeld werden met een opbouwend loopschema en een sportcompressiekous. Als uitkomstmaat werd de duur in dagen tot het afronden van een loopprogramma gebruikt. Er werden geen significante verschillen gevonden tussen de duur van het herstel in de drie groepen, waarbij het herstel varieerde tussen de 100-120 dagen gemiddeld. Ook voor tevredenheid met de behandeling werd geen verschil gevonden tussen de groepen.

Hoofdstuk 10 geldt als laatste hoofdstuk van dit proefschrift. In dit hoofdstuk wordt ingegaan op de twee voornaamste etiologische mogelijkheden betreft het ontstaan van MTSS (MTSS door botoverbelasting en MTSS door trekkrachten van spieren / fascie). Daarnaast wordt het pijnmechanisme van deze twee etiologische theorieën besproken. Ook wordt bediscussieerd hoe de diagnose MTSS te stellen is, welke behandelingsmogelijkheden er zijn beschreven en welke in aanmerking komen voor de behandeling momenteel en voor de toekomst en wordt ingegaan op preventie van MTSS. Uiteindelijk worden aanbevelingen gedaan voor toekomstige studies op het gebied van MTSS.

Voor de toekomst is het erg belangrijk dat er een gevalideerde uitkomstmaat komt voor MTSS. Tot nu toe heeft elke verrichte therapeutische studie het nadeel geen goede uitkomstmaat te hebben. Het gevolg hiervan is o.a. dat studies niet makkelijk met elkaar te vergelijken zijn. Daarnaast is er tot op heden nog geen enkel gerandomiseerd onderzoek geweest dat een verschil tussen twee behandelopties aantoonde. Vandaar dat er grote behoefte is aan meer studies van hoog niveau om de behandelstrategie van patiënten met MTSS wetenschappelijk nog meer gefundeerd te maken.

CURRICULUM VITAE

"Maarten Hendrik Moen werd op 27 augustus 1978 geboren in Zwolle. Na de middelbare school te Utrecht (Christelijk Gymnasium) startte hij de studie Geneeskunde aan de Universiteit van Amsterdam. Zijn eerste baan als arts was AGNIO orthopedie in het Flevoziekenhuis te Almere. Het vervolg hierop was het begin (en ook het eind; in 2009) van de opleiding tot sportarts in het Medisch Centrum Haaglanden te Leidschendam (hoofdopleider Don de Winter). Na een periode (2009-2011) werkzaam te zijn geweest in het Rijnland Ziekenhuis bij de sportgeneeskunde werd in het UMC Utrecht een nieuwe baan als sportarts begonnen. Tevens werd NOC*NSF zijn nieuwe werkgever (functie: prestatiemanager medisch), zodat vanaf 2011 een duobaan in de agenda stond.
Door de jaren als sportarts (i.o.) heen begeleidde hij op medisch gebied diverse (inter)nationale tennistoernooien, was hij teamarts van verschillende nationale (jeugd) teams van de KNVB, had hij de functie van bondsarts van de squashbond en nam hij de begeleiding van diverse multisport- evenementen via NOC*NSF voor zijn rekening. In 2012 zal hij de rol van teamarts vervullen tijdens de Paralympische Spelen te Londen.
Op wetenschappelijk gebied richtte hij zich m.n. op mediaal tibiaal stress syndroom, maar ook bijvoorbeeld sinus tarsi syndroom, piriformis syndroom, patellapeestendinopathie, schouderklachten en hamstringblessures nam hij onder de loep.

DANKWOORD

Dit dankwoord gaat uit naar vele mensen, waarmee ik gedurende het ontstaan van dit proefschrift prettig mee heb samengewerkt. Wat absoluut duidelijk is en waarschijnlijk een cliche, mocht je meerdere dankwoorden uit proefschriften opslaan (wat ik niet deed overigens, maar het sterke vermoeden bestaat), is dat je een proefschrift maken NIET alleen kan. Glashelder. Graag wil ik dan ook in de komende alinea's een aantal mensen in het bijzonder bedanken:

Prof. dr. F.J.G. Backx, beste promotor, Frank; zeer hartelijk dank om mijn promotiewens kracht bij te zetten door me te laten starten in het UMC Utrecht bij de sportgeneeskunde. Dank voor het bijstaan in het traject naar dit uiteindelijk boekje. Mooi om te zien dat jij echt begint te spinnen als er zaken geregeld moeten worden! Zo was het opstarten van de MRI studie (Hoofdstuk 5 van dit proefschrift) een tijdje lang een probleem, aangezien er wel mooi 50 MRI's Gratis vervaardigd moesten worden. Dankzij jouw interventie bij de collega's van radiologie verdwenen die problemen als sneeuw voor de zon. Ook toen de corona voor de promotie ingericht ging worden had jij binnen no-time een prachtig voorstel klaar liggen, waarmee iedereen vervolgens vlug instemde. In het aantal wetenschappelijke artikelen kan ik nog lang niet aan je tippen; jouw lijst op Pubmed is een stuk groter dan die van mij en groeit ook nog eens met de dag. Dank ook voor de ruimte wetenschappelijk onderzoek te ontplooien (op verschillende gebieden) binnen en buiten de muren van het UMCU.

Dr. J.L. Tol, beste co-promotor, Hans; respect is het eerste wat in me naar boven komt als ik aan je denk. Ik maakte je mee als sportarts i.o. in Leidschendam en hield gelijk van je no-nonsense stijl. Kwalitatief hoogstaand je poli afwerken en daarnaast volle bak de wetenschap induiken (jij m.n. op enkel en achillespeesgebied). De souplesse die je in dat "proces" hebt heb ik proberen na te apen. Maar dat alleen verklaart respect niet genoeg. De scherpte waarmee je artikelen beoordeelt en ze veel beter maakt is grote klasse. Niet verwonderlijk dat je voor een topbaan in Qatar bent gevraagd de wetenschappelijke poot aldaar een doorstart te bezorgen en te groeien naar wereldniveau en misschien wel beter. Jij kan dat. Heel mooi vind ik ook je benadering naar wetenschappelijk "werk" toe: het is leuk. Als het niet leuk is, moet je het ook niet doen. Ik ben het daar hartgrondig mee eens. Ook iets om te kopiëren is je schrijfstijl bij het antwoorden op eerste schetsen van een artikel. Je commentaar, in moeilijk leesbaar Nederlands, dat toch wel, bij Hoofdstuk 2 begon met; "Je vind me na het lezen van deze opmerkingen waarschijnlijk de grootste l** van Nederland, maar…..". Dat was overigens niet zo en ik verwacht ook niet dat dat snel zo zal gaan worden (je zit toch in Qatar).

Beste doctoren paranymfen; zeer hartelijk dank om me op 25 mei 2012 bij te willen staan bij de verdediging van de promotie. Met jullie erbij als wetenschappelijke Superstars kan het haast niet missen (hoop ik)! Wat hebben jullie toch een

prachtige artikelen bij elkaar geschreven. De New York Times en Washington Post gonzen er nog van. Mooi vind ik dat jullie wetenschap als (nerden) hobby benaderen. Daar voel ik me bij thuis!
Adam, na jouw hele mooie promotie, waar ik bij mocht optreden als paranymf, heb je me top geholpen bij de artikelen. Jij bent ook echt iemand die een artikel beter kan maken. Mijn bescheiden mening is: dat kunnen er maar heel weinig. Daarnaast heb ik ook geweldig met je kunnen lachen de afgelopen jaren sinds ik je ken uit Leidschendam. Jammer dat je weg bent uit Amsterdam, wellicht moet ik ook eens (met familie) de kant van Overveen opkruipen. Wat hebben wij kunnen praten en discussiëren over artikelen en wat ken je er veel! Als ik ons hoorde praten, bijvoorbeeld in de trein, gaf me dat wel soms (glimlachend) het idee van: wat moeten de mensen wel denken; wat een wetenschappelijke stakkertjes, maar wij hadden daar altijd plezier in. Door de verleden tijd lijkt het wel een beetje op een grafrede, maar ik ga er vanuit dat dit in de tegenwoordige tijd zal doorgaan!
Robert-Jan, het is toch ongelofelijk bijzonder dat bij vele congressen waar ik kom vaak wel minimaal een artikel van jou wordt geciteerd. En het mooie is: als jij met een artikel komt is dat vrijwel altijd een heel relevant goed stuk. Dat is pure klasse. Natuurlijk blijf jij er hoogst bescheiden bij (lijkt echt zo), maar wat jij neerzet is echt buitencategorie. Je hebt van die mensen he, zijn klasbakken in hun werk en spelen ook nog even Hoofdklasse voetbal en pakken terloops even de Wereldtitel voetbal voor Artsen mee. Ze bestaan echt en jij bent er een van.

Prof. dr. Paul Knipschildt (statisticus, wellicht dat u dit ooit zult lezen); in de opleiding tot sportarts zat onderwijs gericht op epidemiologie en statistiek. Een hopeloos saaie, maar verplichte, cursus had ik mentaal al genoteerd. Dat die cursus mij de ogen zou openen voor de levendige wereld die wetenschap heet had ik nooit kunnen denken. Prachtige beeldende verhalen (over het netjes wetenschappelijk verantwoord afserveren van de rol van irisscopie voor de diagnostiek van galstenen) heb ik graag bij vrienden smeuïg herhaald. Maar naast de smeuïge verhalen ging ik van de cursus weg met honger en plezier in wetenschappelijk onderzoek.

Don de Winter; mooie jaren hebben wij gehad in Leidschendam waar je mijn opleider was. Ik ben blij dat je een van de mede-auteurs bent in dit proefschrift. Maar meer dan dat: dank voor de wijsheid die ik van je mee heb gekregen tijdens de opleiding. We waren het zeker niet altijd eens, maar een ding is duidelijk; jij staat voor je sportarts in opleiding. Dat is bij binnenkomst op dag 1 duidelijk en dat niet alleen, je maakt dat vier jaar lang waar. Je bent meerdere malen gekozen tot sportarts van het jaar en ik kan dat begrijpen. Zelfs mijn moeder zou ik naar je sturen.

Eric Bakker en Sandor Schmikli; wat ben ik blij dat jullie er waren met jullie wetenschappelijk ervaring en vooral kennis en statistische kunde als ik even mentaal in de spagaat zat met de multivariate regressie of chi kwadraat test. Verschillende keren, bijvoorbeeld na lastige vragen van referenten, hebben jullie de buit betreft wel of niet geaccepteerd worden van een artikel, binnengesleept. Onbetaalbaar dus.

Wessel Zimmermann; heel mooi dat er in Nederland nog iemand rondloopt met een passie voor onderbenen en dan in het bijzonder de schenen. Vaak zaten we de afgelopen jaren aan de telefoon om over nieuwe ideeën te brainstormen. De kans is groot dat we in de komende tijd tot mooie nieuwe studies gaan komen!

Zonder Liesbeth Barelds en Esther Dekker (UMC Utrecht) was de kans op een proefschrift als dit een stuk kleiner geweest. Zonder logistieke ondersteuning, die top en strak geregeld is, kan je soepel onderzoek doen wel vergeten. Vele K-tjes (onderzoekspatiënten) prijkten er in mijn agenda de afgelopen tijd en ik heb ze er niet ingezet ;-)

Dank aan alle studenten die mee hebben geholpen aan de studies (m.n. aan Hoofdstuk 9). Al die kilometers in de auto naar de verschillende locaties om weer militairen of ALO-studenten met scheenklachten te vervolgen hebben heel erg zin gehad. Hopelijk hebben jullie er wat van kunnen leren en (voor mij niet onbelangrijk), er is een proefschrift uit voort gekomen! In het bijzonder dank aan Leonoor Holtslag, die bij de belangrijke eerste fase van de studie in Hoofdstuk 9, veel werk heeft verzet. Dank ook aan Timo Bongers voor zijn grote aandeel in de militaire studies in Hoofdstuk 3 en 8.

Veel dank is ook verschuldigd aan de sponsors van dit proefschrift. De kosten van het drukken (ook al had ik een mooie deal) kunnen toch oplopen en ik ben erg blij dat ze me wilden steunen. Dus: NOC*NSF, Medisch Centrum Haaglanden, Vereniging voor Sportgeneeskunde, Rijnland Ziekenhuis, Koninklijke Nederlandse Voetbal Bond, Koninklijke Nederlandse Lawn Tennis Bond, Bergman Kliniek, Sport Medisch Adviescentrum Amersfoort, Universitair Medisch Centrum Utrecht, Medicort Sports & Orthopedic Care en Tulipmed, nogmaals heel hartelijk dank!

Pa en ma, wat mooi dat jullie het promoveren altijd zo positief en zonder poeha hebben benaderd. Als ik dit traject niet had bewandeld, was het ook geen probleem geweest en dat is juist waar het om gaat. Van harte steunen waar nodig en niet teveel van dat opgedring hebben jullie tot een kunst verheven. We hebben toch maar enorme bof met de familie Moen, dat we elkaar zo vaak zien en dat het nog gezellig is ook! Wat gaat het eigenlijk voor de wind, geluk zit blijkbaar toch voor een deel in de genen! Ik hoop dat pakketje genen en vele andere, door te geven aan onze twee zoons; dan moet het haast goed komen!
Ma, jouw sociale gaven spreken boekdelen, volgens mij moet je bijna een tweede telefoon kopen omdat anders je contactgegevens er niet meer inpassen. Wat ken

jij een mensen! En na een gezellig avondje kijk jij nog even een Duitse crimi en sta je de volgende morgen weer met frisse moed op. Dat doen er niet veel je na! Ik heb geprobeerd dat energieke en positieve van je over te nemen en ik denk zeker dat dat erg nuttig was voor het slagen van deze promotie! Dank ook voor het oppassen op onze zoons, ze kijken er iedere keer weer naar uit!
Pa, ik kan niet ontkennen dat ik veel op je lijk, die Moen trekjes heb ik wel, zelfs de haardracht begint enigszins gelijkenissen te vertonen.. Wat ik van jou met name heb geprobeerd te benutten is mensen enthousiast proberen te krijgen voor een project. Wat ik heel vaak van je heb mogen horen is dat er weer een of ander project (zonder denigrerend te willen doen) was opgestart en dat er politieke dan wel menselijke crises weggepoetst moesten worden. Vrijwel kom je altijd weer thuis met het bericht dat het een behoorlijk goede missie was (nooit gehoord dat het fantastisch ging trouwens ;-)). Dat is natuurlijk geen toeval, jij bent er erg goed in om plooien glad te strijken en voor elkaar te krijgen wat er gebeuren moet. Voor bovenstaand en nog heel veel andere goede eigenschappen van jullie (ik kan niet eeuwig door blijven gaan, dat is 1), en per slot van rekening moet er ook wat overblijven voor de Sinterklaas gedichten de komende jaren (reden 2)), heel hartelijk dank!!

Broer en zus, Wouter en Suzanne Moen, maar natuurlijk ook Janneke en Wilco; ook jullie ga ik bedanken vowor het tot stand komen van mijn proefschrift. Geen promotor, geen co-promotor, geen paranymf, die rollen hebben jullie dan wel niet bekleed, maar belangrijk waren jullie absoluut! Ik zie het zo, als het in het leven behoorlijk gaat zoals je wilt dan heb je meer energie over voor dingen als een proefschrift schrijven. Gelukkig gaat het behoorlijk zoals ik wil en daar dragen jullie absoluut aan bij! Je met kerst sociaal slepen naar het jaarlijkse familiaire diner en daar drie dagen van moeten bij komen kost alleen maar energie. Bij jullie is het juist andersom! Hebben we gezellig gegeten, geborreld, gehangen dan levert dat alleen maar wat op! Luxe noem ik dat, helemaal omdat jullie zo dicht bij wonen. Nou ja, Janneke even niet. Die kan ik het proefschrift ook niet even in de pdf versie toesturen, omdat het downloaden teveel van de zonnecel gaat kosten diep in Oeganda (maar dat terzijde). Hardcopies rule wat dat betreft. Ik kan gelukkig zeggen dat ik enorm geluk heb met mijn broer, zus, zwager en schoonzus (al heb ik jullie nog nooit zo genoemd (gewoon Wilco en Janneke toch?). Dat alleen al geeft energie genoeg om nog twee a drie proefschriften op te laten draaien ;-)

Heren 2; oh ja trouwens, ik ga 25 mei promoveren en jullie mogen ook komen. Er is ook een feestje bij. Je wordt niet thuisgebracht. Heren 2, ole ole.

De 4 musketiers klinkt behoorlijk suf, maar je kan toch niet ontkennen dat we vaak met z'n vieren afspreken (Thomas, Sander, Patrick en ik). Jarenlang gaan we al met elkaar om en jullie zijn dan ook onderdeel van de happy few die mee hebben gemaakt hoe er met goede moed gestart werd met een eerste wetenschappelijke aanzet en hoe dat nu eindigt in een promotie. Dat we elkaar al zo lang zien dat zegt toch heel wat (en niet alleen dat we oud beginnen te worden). De avondjes / weekendjes met z'n vieren doen me altijd goed en leiden weer tot frisse moed en bergen energie om er maar weer eens een artikeltje bij te pakken. Sander als professioneel journalist heb je me heel wat tips kunnen geven over schrijven enzo, maar eerlijk is eerlijk; in een cafeetje een biertje met je drinken en oeverloos ouwehoeren over van alles en nog wat, bevalt me stukken beter! Patrick, hoe vaak heb ik jou als huisarts wel niet gebeld over klachtjes van sporters bij toernooien in het buitenland. Daarna even bijpraten over vele zaken, waarbij ik je wel opvallend vaak aan de telefoon in je auto (wel een carkit toch?) bijna de verkeerde kant oprijdend aantrof ;-). Thomas, mede-vader; ondanks je pittige baan en je mooie dochter kan je toch altijd tijd vinden voor een drankje of potje tennis. Zien wij elkaar ben je altijd ontzettend geïnteresseerd in wat ik te vertellen heb (wat onthoudt jij toch veel, je lijkt die olifant uit de Rolo reclame wel…). Ik denk dat de teller van keren vragen hoe het met de promotie stond bij jou het hoogst is geëindigd. Ook met jou is het heerlijk bomen over allerlei zaken, van wielrennen tot vieze luiers, altijd even relaxed! Jullie zien; de gemene deler is: over van alles en nog wat praten kan met jullie ontzettend goed. En dat is fantastisch!

Rooski, waar dank ik je eigenlijk niet voor? Je hebt het schrijven van dit proefschrift enorm ondersteund, je bent vreselijk lief, een heel voorbeeldig vriendinnetje (eigenlijk verloofde, maar dat klinkt zo), een enorm knap moedertje , de kraamkamer voor twee wonderschone zonen (Olivier en Laurens), een pittige tante als het nodig is, een vrouw met heel veel humor en het glas halfvol en je bent nog prachtig ook! Een lot uit de loterij. Wat kan een promovendus zich nog meer wensen. Niets, helemaal niets.