MASTEROPPGAVE I MANUELLTERAPI

"Histological findings and diagnostic imaging features of medial tibial stress syndrome – A systematic review"

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Manuellterapi teori: Emnekode: MANT395

Høst 2022

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Preface

My motivation for choosing this topic comes from my personal experience with treating individuals that have been affected by this condition, many of which have gotten to a point where they struggle to perform their daily activities pain free, including walking for short distances and walking up or down the stairs. More often than not, they have been told that they have an inflammatory condition in their periosteum of their lower leg, by friends, family or a healthcare professional, or they have come to this conclusion by themselves after researching reasons for leg pain online. A great number of patients have attempted to treat the condition using NSAIDS and periods of rest, without success. There is growing evidence in the scientific literature that suggests that the diffuse activity related pain experienced along the medial tibia, is in fact a bone stress injury and not an inflammatory condition. Still, major health-oriented websites in Norway advocate the notion that it is an inflammatory condition. This discrepancy is what has ultimately led me to perform this systematic review.

I want to thank my amazing wife Nava Shahin, for her enormous support throughout the entirety of my master's studies. I am deeply appreciative of the time and energy you have spent on helping me get through my master's, for being such a lovely and caring mother for our soon-to-be 1 year old son, and for looking after him during my travels to Bergen and on the days and nights when I was studying for my exams and writing my thesis. Thank you for being there for me. I love you.

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Abstract

Background: Medial tibial stress syndrome (MTSS) is a prevalent condition in athletic and military populations. The current evidence suggests that MTSS is a tibial overload injury, however the etiology is still not clearly understood. Biopsy and imaging studies could help improve our understanding of the underlying pathology. This study aims to review the histological findings and diagnostic imaging features of MTSS and compare these with asymptomatic legs.

Methods: A systematic search was performed in MEDLINE, EMBASE, AMED, CINAHL, and Web of Science. Observational studies presenting results from a biopsy and/or imaging study on the symptomatic lower legs of individuals with MTSS, were included. Studies were excluded if results could not be isolated to a MTSS-population, if the diagnostic criteria were not fulfilled, or if there were concomitant pathology such as stress fracture. Risk of bias was assessed with the Newcastle-Ottawa Scale. The study was registered in PROSPERO (record number CRD42022338221).

Results: 12 studies with 225 symptomatic individuals were included. They reported findings on three-phase bone scan (n = 5), plain radiographs (n =5), magnetic resonance imaging (n = 4), ultrasound (n = 2), dual x-ray absorptiometry (n = 1), and bone and periosteal biopsies (n = 1). The overall methodological quality was poor. Results were descriptively synthesized. Frequent findings in symptomatic legs included tibial periosteal edema (20,7-96,4 %), bone marrow edema (26,3-50,0 %), and abnormal scintigraphic uptake involving the posterior tibial cortex (55,6-92,9 %). Plain radiographs were normal. Biopsies frequently revealed abnormal periosteum and bone changes, but rarely any inflammatory changes. Data on asymptomatic legs was limited.

Conclusion: Abnormalities in the lower leg are frequently reported in individuals with MTSS. Few studies have compared findings in symptomatic and asymptomatic legs. The limited body of evidence suggests that several of these abnormalities represent normal adaptation to physical stresses, rather than MTSS.

Keywords: Medial tibial stress syndrome; MTSS; shin splints; imaging; biopsy

Sammendrag

Bakgrunn: Medialt tibialt stressyndrom (MTSS) er en hyppig forekommende tilstand blant idrettsutøvere og militært personell. Det nåværende evidensgrunnlaget tyder på at MTSS er en overbelastningsskade i tibia, men etiologien er fortsatt uklar. Biopsi- og bildediagnostiske studier kan hjelpe oss med å forstå den underliggende sykdomsprosessen bedre. Målet med studien er derfor å gjennomgå histologiske og bildediagnostiske funn ved MTSS, og sammenligne dette med funn i asymptomatiske legger.

Metode: Det ble gjennomført et systematisk søk i MEDLINE, EMBASE, AMED, CINAHL, and Web of Science. Observasjonsstudier som presenterte funn fra biopsier eller bildediagnostiske undersøkelser av symptomatiske legger hos personer med MTSS, ble inkludert. Studier ble ekskludert hvis resultatene ikke kunne isoleres til en MTSS-populasjon, hvis diagnosekriteriene ikke var oppfylt, eller hvis det var samtidig patologi som f.eks. tretthetsbrudd. Newcastle-Ottawa-skalaen ble benyttet til å vurdere kvaliteten på studiene. Studien ble registrert i PROSPERO (registreringsnummer CRD42022338221).

Resultater: 12 studier med 225 symptomatiske personer ble inkludert. De rapporterte funn fra beinscintigrafi (n = 5), røntgen (n = 5), magnetisk resonanstomografi (n = 4), ultralyd (n = 2), beintetthetsmåling med DXA (dual x-ray absorptiometry; n = 1), og biopsier av bein og beinhinne (n = 1). Den overordnede kvaliteten på de inkluderte studiene var lav. Resultatene ble presentert i en deskriptiv sammenstilling. Det ble ofte funnet ødem i tibias beinhinne (20,7-96,4 %) og beinmarg (26,3-50,0 %), og unormalt opptak av radioaktive isotoper i tibia i symptomatiske legger (55,6-92,9 %). Røntgenundersøkelser var uten funn. Biopsiene viste ofte forandringer i beinhinnen og det kortikale beinet, men sjelden tegn til inflammatoriske forandringer. Det var lite data om asymptomatiske legger.

Konklusjon: Det sees ofte unormale funn i smertefulle legger hos utøvere med MTSS. Få studier har sammenlignet funn i symptomatiske og asymptomatisk legger. Det begrensede evidensgrunnlaget tyder på at flere av funnene representerer normal tilpasning til fysisk belastning, heller enn MTSS.

Nøkkelord: Medialt tibialt stressyndrom; MTSS; leggsmerter; bildediagnostikk, biopsi

1. Introduction

1.1. Rationale

Medial tibial stress syndrome (MTSS), commonly referred to as shin splints, is a common condition among active individuals, particularly runners and military recruits. This condition is characterized by exercise-induced pain on the inside of the lower leg that is exacerbated by activity, and tenderness of the medial border of the tibia, often in the most distal two-thirds (Yates & White, 2004). The pain is normally at its worst during or right after exercise but may last for days. This condition typically develops after a period of increased activity, exercise intensity, or upon starting a new activity (Kortebein, Kaufman, Basford, & Stuart, 2000). Women are at a significantly greater risk of developing MTSS, with one systematic review reporting a risk ratio of 1,7 (Newman, Witchalls, Waddington, & Adams, 2013) and another systematic review an odds ratio of 2,35 (Reinking, Austin, Richter, & Krieger, 2017). 12 to 20 % of athletes in running sports will develop this condition during one season (Bennett et al., 2001; Plisky, Rauh, Heiderscheit, Underwood, & Tank, 2007; Raissi, Cherati, Mansoori, & Razi, 2009), and similar numbers among military recruits are 8-36 % during their initiation period (Garnock, Witchalls, & Newman, 2018; Newman, Adams, & Waddington, 2012; Sharma, Golby, Greeves, & Spears, 2011; Yates & White, 2004). Out of those, 41-88 % will have bilateral symptoms (Bennett et al., 2001; Bliekendaal et al., 2018; Sharma et al., 2011; Yagi, Muneta, & Sekiya, 2013; Yates & White, 2004).

The etiology of this condition is still not clearly understood. It has previously been proposed that it develops as a result of repetitive traction from the muscles of the lower leg to the periosteum at their sites of origin, leading to a localized tibial periosteal inflammation (Winters, 2017a), or indirectly through traction forces through the crural fascia to its insertion along the medial tibial border (Bouche & Johnson, 2007).

A more recent, and currently the most widely supported theory, is that MTSS is an overuse injury to the medial tibial cortex caused by large and/or repetitive loads and abnormal bending forces, which in turn causes increased compression stress in the posterior tibia. This may lead to a weakening of the medial tibial cortex due to a buildup of microscopic cortical injuries and an imbalance in the osteoblast/osteoclastic activity. This theory proposes that MTSS is a part of a continuum of bony stress reactions of the tibia.

Biopsy and imaging studies can both be helpful to our understanding of the underlying biological disease processes. Depending on the type of examination, we can analyze tissue chemistry, composition (e.g., cell differentiation, blood vessel proliferation), changes in tissue morphology and structure (e.g., lamellar structure, tissue disruption, bone density), and we can depict changes suggestive of abnormal metabolic activity in various tissues, e.g., abnormal cellular uptake of radioactive tracers. The wide spectrum of examinations makes it possible to make inferences about the likely underlying processes, which can be in favor of or contradict the current hypotheses.

There has been published several evidence syntheses on the topic of MTSS (Craig, 2009; Franklyn & Oakes, 2015; Kortebein et al., 2000; Menéndez et al., 2020; Moen, Tol, Weir, Steunebrink, & De Winter, 2009; Winters, 2017) and systematic reviews on its associated risk factors (Hamstra-Wright, Bliven, & Bay, 2015; Newman et al., 2013; Reinking et al., 2017; Singh, 2016). However, there has not been published any systematic review that assesses the histological and/or imaging findings in individuals with MTSS, and as of October 13, 2021, no such review had been registered in the International Prospective Register of Systematic Reviews (PROSPERO).

1.2. Objectives

The aim of this review is to summarize the histological findings and diagnostic imaging features of the lower leg of symptomatic individuals with MTSS, and if possible, to compare those with the imaging diagnostic features of asymptomatic legs, as this may shed further light on the pathology of this condition, and specifically to answer the following questions:

1) What are the imaging features of medial tibial stress syndrome?
2) Is there any presence of inflammatory changes in the tibial periosteum?
3) Are there any changes in the tibial cortex?
4) Are there signs of alterations to bone metabolism?

Primary outcomes of interest include histological findings and morphological changes in the tibial periosteum, tibial cortex and crural fascia, presence and pattern of tibial periosteal edema, tibial bone marrow edema, tibial cortical edema, and scintigraphic uptake in the tibia. Secondary outcomes of interest include relationships between the primary outcomes and clinical features, such as symptom severity, duration, and location.

2. Methods

2.1. Study protocol registration

The study protocol for this review has been registered in PROSPERO with record number CRD42022338221, prior to performing the systematic literature search and study selection process. PROSPERO is a database where study protocols for systematic reviews can be published, with the purpose of making the research transparent to minimize risk of bias, and to avoid duplicate studies.

2.2. Research design

In order to get a complete overview of the histological and imaging findings in individuals with MTSS, I will perform a systematic review of the literature. A systematic review aims to identify, evaluate, and summarize selected outcomes from all studies relevant to a particular topic (Gopalakrishnan & Ganeshkumar, 2013). Performing a systematic search using pre-defined inclusion and exclusion criteria and outcomes of interest, is thought to allows for a less biased and more transparent review, than if the study was performed in a non-systematic way, e.g., a narrative review (Greenhalgh, Thorne, & Malterud, 2018). In addition, performing a systematic review requires fewer resources than performing original research.

2.3. Literature search

2.3.1. Electronic searches

A systematic search for relevant publications will be performed by a single researcher in the following databases: MEDLINE (Ovid), EMBASE (Ovid), AMED (Ovid), CINAHL (CENTRAL), and Web of Science, from their inception to their last update. The search in Web of Science will be limited to meeting abstracts, which are not indexed in the other databases. Relevant nouns will be truncated to locate singular and plural forms (injur* to locate injury and injuries) and relevant suffixes (tibia* to locate tibia and tibial). Duplicate titles between MEDLINE, EMBASE, and AMED, will be removed with the «remove duplicates» option in Ovid. A preliminary search located a significant number of titles unrelated to this syndrome. Based on this search, titles with the following words will be excluded: systematic review, case report, case study, osteoarthritis, arthritis, meniscus, cartilage, and knee. The detailed search strategy can be seen in Table I.

I will also search ClinicalTrials.gov for ongoing or unpublished studies, using diagnosis terms, including medial tibial stress syndrome, shin splints, and lower leg pain.

Table I. Detailed search strategy in MEDLINE, EMBASE, AMED, CINAHL, and Web of science.

#	Search	Fields
1	(mtss or medial tibia* or tibia* stress or tibia* pain or leg stress or shin splint* or shin pain or shin soreness or lower leg pain or ERLLP or exercise related leg pain or ERLP or traction periostitis or soleus syndrome or running injur*).mp.	All fields
2	(MRI or magnetic resonance or CT or tomograph* or DXA or DEXA or bone density or densitometry or x-ray or radiograph* or roentgenograph* or scintigraph* or radionuclide* or ultrasound or ultrasonograph* or sonograph* or biops* or histolog* or specimen* or imag* or scan*).mp.	All fields
3	(systematic review or case report or case study or osteoarthriti* or arthriti* or menisc*).m_titl.	Title
4	(1 and 2) not 3	

MTSS, medial tibial stress syndrome; ERLLP, exercise related lower leg pain; ERLP, exercise related leg pain; .mp, searching for keywords in all fields; MRI, magnetic resonance imaging; CT, computed tomography: DXA/DEXA, dual x-ray absorptiometry; m.titl., searching for keywords in the title.

2.3.2. Other sources

I will screen for relevant titles in reference lists of relevant systematic reviews and articles.

2.4. Study selection

Observational studies that present results from a biopsy or imaging study on a group of individuals with MTSS, will be included. In this study, I will use the commonly used definition of MTSS as «pain along the posteromedial border of the tibia that occurs due to exercise, excluding pain from ischemic origin or signs of stress fracture» (Yates & White, 2004). Furthermore, according to Yates and White (2004), pain has to be spread over a minimum of 5 cm, as «Focal areas of only 2 to 3 cm are typical of stress fracture». There is also a characteristic finding that «Palpation of the posteromedial border of the tibia produced discomfort», that is «diffuse in nature and confined to the posteromedial border of the tibia».

Since focal areas of pain are indicative of a stress fracture, studies that does not specify the tenderness span will only be included if the participants have been assessed with either an MRI or TPBS, which both have high sensitivities in detecting stress fractures (Hopper & Robinson, 2010; Tins et al., 2015). The MRI features of a tibial stress fracture is defined according to Fredericson, Bergman, Hoffman, and Dillingham (1995) as a low-signal fracture line on all sequences, with changes of severe bone marrow edema on T1 and T2-weighted images. On TPBS, a stress fracture can be seen as a very large focal region of highly increased activity (Beck et al., 2012). The sensitivity of plain radiographs in detecting stress fractures is low, especially in the early phase of the injury when up to 85 % of stress fractures are overlooked (Moran, Evans, & Hadad, 2008). Therefore, if studies have excluded stress fractures with a negative radiograph it will not be considered sufficient for this review.

Studies that do not present results from individuals with MTSS in isolation (e.g., mixed-population studies that combines the results of several conditions such as individuals with MTSS and individuals with Achilles tendinopathy), will be excluded. Studies that include individuals with suspected or confirmed stress fractures or with suspected pain of ischemic origin (e.g., chronic exertional compartment syndrome (CECS) or popliteal artery entrapment syndrome (PAES)), will be excluded, unless results can be isolated for individuals with MTSS. Articles written in other languages than English, Norwegian, Swedish, or Danish, will be excluded. Single case studies and cadaver studies will not be included.

The selection of studies will be performed by a single author, based on the inclusion and exclusion criteria.

The results from the literature search and the study selection process will be presented in a PRISMA flow diagram (Moher, Liberati, Tetzlaff, Altman, & Group, 2009). The dates for completion of the electronic searches will be reported. A list of excluded titles with reasons for exclusion will be presented. This list will compile titles that could not be excluded based on its title or abstract but was later excluded based on the content of the full text.

2.5. Data collection

Relevant data will be extracted by a single researcher. The data will be compiled in an excel spreadsheet prior to synthesis. In the case of missing data, attempts will be made to contact the authors of the paper in question. There will not be made attempts to extract data from uncompleted studies, however, in accordance with the recommendations of the Cochrane Collaboration, these titles will be referenced, so that future studies – or an update of this study - might locate and include data from these studies (Li, 2021). If multiple reports include results from the same study, data will be extracted individually from all reports separately, and collated afterwards.

2.6. Risk of bias assessment

The Newcastle-Ottawa-scale will be used to assess the risk of bias in the included studies. It is a tool developed to evaluate the internal validity of observational trials in systematic reviews (Wells et al., 2000). This tool is one of the most widely used to evaluate case-control studies and cohort studies (Ma et al., 2020), and is recommended by the Cochrane Collaboration as one of the most useful tools in evaluating the quality of non-randomized trials (Higgins et al., 2021). This tool can be modified to be used in the assessment of the quality of cross-sectional studies (Herzog et al., 2013).

In the Newcastle-Ottawa-scale, studies are evaluated against three quality parameters (see Table II): 1) Study selection; 2) Comparability; and 3) Exposure (case-control studies) or Outcome (cohort studies and cross-sectional studies). For every item that is satisfied, the study is awarded one star, except for the item in the «comparability» parameter, which can award one or two stars. A higher score represents a higher methodological quality. Case-control studies and cohort studies can be awarded a maximum 9 stars. The modified version of the Newcastle-Ottawa scale for cross-sectional trials has one less item in the outcome parameter, and therefore awards a maximum of 8 stars. The coding manuals for assessing the individual items in case-control, cohort, and cross-sectional studies in this review, can be found in Appendices C through E.

Table II. Newcastle-Ottawa Quality Assessment Scale.

Parameter	**Case-control studies**	**Cohort studies**	**Cross-sectional studies**	**Possible points**
Selection	Is the case definition adequate?	Representativeness of the exposed cohort	Representativeness of the sample	★
	Representativeness of the cases	Selection of the non-exposed cohort	Sample size	★
	Selection of Controls	Ascertainment of exposure	Ascertainment of the exposure	★
	Definition of controls	Demonstration that outcome of interest was not present at start of study	Non-respondents	★
Compara-bility	Comparability of cases and controls on the basis of the design or analysis	Comparability of cohorts on the basis of the design or analysis controlled for confounders	The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled	★★
Exposure)	Ascertainment of exposure			★
	Same method of ascertainment for cases and controls			★
	Non-Response rate			★
Outcome*		Assessment of outcome	Assessment of outcome	★
		Was follow-up long enough for outcomes to occur	Statistical test	★
		Adequacy of follow up of cohorts		★/0

*A maximum of two stars can be awarded in the modified scale for cross-sectional studies; ★ = one point.

The Newcastle-Ottawa scale does not include any explicit guidelines as to how the quality of individual studies should be interpreted based on the points awarded. Systematic reviews by Farsad-Naeimi et al. (2020), Veronese et al. (2015), and Smithson and Mitchell (2018) used different thresholds of ≥6, ≥7, and ≥8, to distinguish high-quality from low-quality studies. Only Veronese et al. (2015) provided a justification for this threshold, which was set to ≥ 7 points based on the median Newcastle-Ottawa score in their included trials. In such a division, each item is weighted equally. For this review, I will use the conversion thresholds proposed by Penson, Krishnaswami, Jules, Seroogy, and McPheeters (2013), which considers the points awarded in each of the selection, comparability, and exposure/outcome parameters:

- *Good*: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- *Fair*: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- *Poor*: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

My reasoning for employing these conversion thresholds is that because it considers the importance of meeting criteria in all the parameters, it seems to better represent the framework of the Newcastle-Ottawa scale.

Normally, two researchers should assess the risk of bias of the included studies, to reduce mistakes and to reduce the possibility of a biased assessment (Boutron et al., 2019). However, due to the limitations of this thesis, the risk of bias assessment will only be performed by the author of this review.

2.7. Data synthesis

2.7.1. Study characteristics

A table that summarizes the included studies will be presented. This table will include information on the study population (number of participants, gender, age, symptom duration, symptom severity, and their activity level), study design, selection criteria, examination type, and histological or imaging diagnostic outcomes relevant for this review.

According to the protocol uploaded in PROSPERO, results were originally planned to be synthesized by outcome. However, in order to simplify the reporting, histological and imaging diagnostic findings will be synthesized by type of examination (e.g., MRI, plain radiographs, biopsy).

2.7.2. Quantitative analyses

A great deal of heterogeneity is expected between examinations and outcomes, and quantitative analyses might not be possible. However, if the data from the included studies can be pooled, meta-analyses will be performed on both dichotomous data (e.g., risk ratios on the prevalence of bone marrow edema on MRI in symptomatic vs. asymptomatic legs) and continuous data (e.g., bone density reported as g/cm2), using the RevMan 5 software.

If results are reported in different units (e.g., metric and imperial, or centimeters and millimeters), they will be computed to a single unit for the analyses. As the quantitative reporting is expected to be homogenous, results from quantitative synthesis of continuous data will be presented as mean differences with confidence intervals. If a study present means without standard deviations, standard deviations will be computed from available data. If the available data do not allow for such computations, values will be imputed, preferably by using appropriate data from the other studies included in this review.

Radiographic findings, such as periosteal elevation or uneven bone surface, are commonly used as evidence of the presence of a stress fracture. This makes it difficult to attribute such radiographic findings to the MTSS diagnosis. To mitigate this, only radiographic findings from individuals in which MRI or TPBS have excluded a stress fracture, will be included for this analysis.

2.7.3. Descriptive synthesis

Histological and imaging diagnostic findings will be synthesized by type of examination (e.g., MRI, plain radiographs, biopsy). Depending on the available data, the results will be summarized for each study, in the following sequence:

1) Symptomatic legs, compared with asymptomatic legs of the same individuals
2) Symptomatic legs, compared with asymptomatic legs in a control group.
3) Symptomatic legs, without asymptomatic controls

2.8. Reporting

The reporting for this systematic review will be performed according to the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al., 2009). In addition, the AMSTAR 2 checklist, which is a tool for evaluating systematic reviews that includes randomized and non-randomized studies (Shea et al., 2017), will also be used to guide the reporting. Any significant deviation from the published study protocol in PROSPERO will be reported.

2.9. Ethical considerations

Ethical considerations are not commonly included as a subject matter in guidelines on perform systematic reviews. Many ethical issues typically encountered in primary research does not apply to systematic reviews, such as informed consent from participants and patient confidentiality. Still, there are many ethical issues related to performing systematic reviews.

Systematic reviews are commonly viewed as being on top of the evidence hierarchy (Murad, Asi, Alsawas, & Alahdab, 2016), and they are for this reason frequently used to guide health practices. Results of systematic review might therefore have serious practical implications, e.g., by dictating best practice guidelines and guiding financial decisions, such as which studies receives funding, what medical equipment is purchased, and which medical procedures are being offered. For this review, depending on the results, certain medical examinations might be more or less likely to be recommended for individuals with MTSS.

An important ethical consideration in this review was therefore related to the accuracy of the MTSS diagnosis. With a strict definition of MTSS, more studies with possibly relevant participants might be excluded from the review due to bad reporting, which might in turn make it difficult to reach relevant conclusions. On the flipside, if the diagnostic criteria for MTSS is less strict, e.g., by including all studies where participants have a clinical diagnosis of «shin splints» or «medial tibial stress syndrome» without specifying these conditions further, this might influence the accuracy of the results by possibly including studies with patients that do have this clinical entity. For this study, it was decided that the accuracy on the diagnostic criteria was more important, because of the potential bias of including patients with tibial stress fractures and circulatory deficits were would have been a great limitation to the trustworthiness of the results and the conclusions drawn from these.

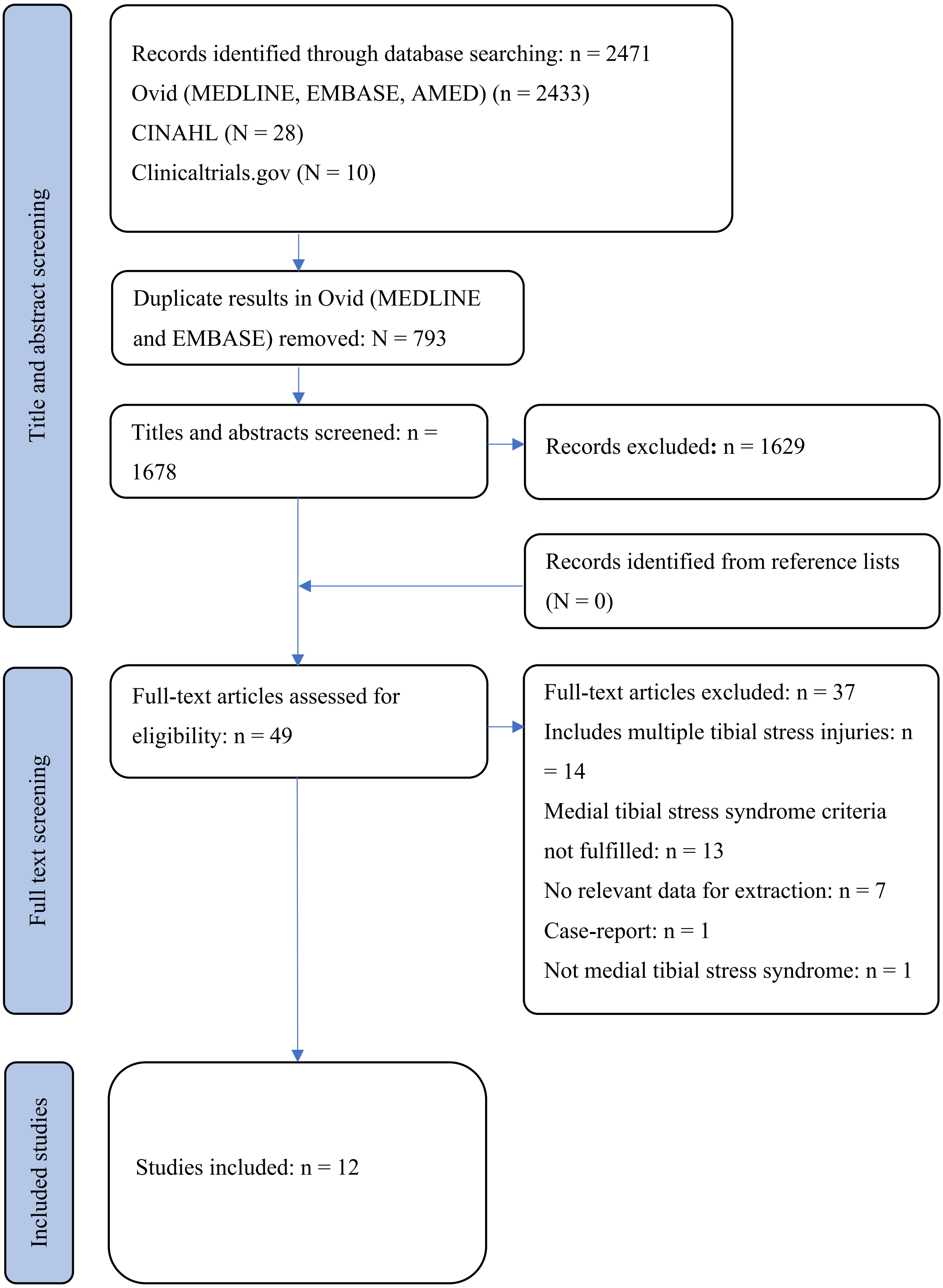
3. Results

3.1. Study selection

The systematic search in MEDLINE (1946 to August 22, 2022), EMBASE (1974 to Week 32, 2022), AMED (1985 to August 2022), CINAHL (inception to august 23, 2022), and Clinicaltrials.gov located 2471 citations. After removing duplicates between MEDLINE, EMBASE and AMED (n = 793), the titles and abstracts of 1678 citations was screened. Of the remaining 45 articles, 12 studies matched the inclusion and exclusion criteria and was included for this review (Allen, O'Dwyer, Barnes, Belton, & Finlay, 1995; Anderson, Ugalde, Batt, & Gacayan, 1997; Aoki, Yasuda, Tohyama, Ito, & Minami, 2004; Bhatt, Lauder, Finlay, Allen, & Belton, 2000; Holder & Michael, 1984; Mattila, Komu, Dahlström, Koskinen, & Heikkilä, 1999; Moen et al., 2014; Wallensten & Karlsson, 1984; Winters, Bon, Bijvoet, Bakker, & Moen, 2017b; Winters et al., 2019; Zhang et al., 2022; Özgürbüz et al., 2011). A flowchart of the selection process can be seen in Figure 1.

The most common reasons for exclusion were that the MTSS-criteria were not fulfilled, particularly missing information on palpation tenderness spanning > 5cm with no MRI or TPBS to exclude stress fractures, or that the study included multiple lower leg stress injuries in their analyses. A list of the excluded studies and reasons for exclusion can be found in Appendix A. One study was initially included for the review, but later excluded due to multiple discrepancies in their data (Batt, Ugalde, Anderson, & Shelton, 1998). These discrepancies did not allow data to be extracted with confidence in regard to symptom status (symptomatic or asymptomatic). Upon personal communication with Mark Batt, he was unable to provide a clarification. A more detailed description of the rationale for excluding Batt et al. (1998) can be found in Appendix B.

Figure 1. PRISMA flowchart of the study selection process.



3.2. Study characteristics.

Study characteristics can be seen in Table III. 6 case-control studies, 4 cross-sectional studies, and 2 prospective cohort studies were included for this review. The number of symptomatic cases ranged from 6 to 92 lower legs in 6 to 52 symptomatic individuals. The duration of symptoms ranged from 3 weeks to 84 months. All participants had tenderness along the posteromedial border of the tibia, of which 7 of the studies specified that the tenderness spanned > 5 cm along the posteromedial tibial border (Anderson et al., 1997; Mattila et al., 1999; Moen et al., 2014; Winters et al., 2017b; Winters et al., 2019; Zhang et al., 2022; Özgürbüz et al., 2011). The studies that did not specify the length of tenderness, assessed the presence of stress fractures on TPBS (Allen et al., 1995; Bhatt et al., 2000; Holder & Michael, 1984; Wallensten & Karlsson, 1984) or MRI (Aoki et al., 2004) and presented results from the participants with MTSS. The studies presented results from the following exams: TPBS (n = 5), plain radiographs (n = 5), MRI (n = 4), biopsy (n = 3), ultrasound (n = 2), and Dual X-ray Absorptiometry (DXA; n = 1).

6 studies included asymptomatic lower legs as controls (Mattila et al., 1999; Moen et al., 2014; Wallensten & Karlsson, 1984; Winters et al., 2017b; Zhang et al., 2022; Özgürbüz et al., 2011), of which only 3 studies blinded the assessors (Mattila et al., 1999; Moen et al., 2014; Winters et al., 2017b).

Table III: Study characteristics.

Study	Cases and controls[a,b]	Inclusion/exclusion criteria	Relevant examinations and outcomes
Allen et al. (1995) Case-control	MTSS: 32 (m/f NS) individuals with "medial tibial syndrome". Age, activity level, symptom duration/severity NS. Controls: Chronic exertional compartment syndrome.	MTSS: Exercise-induced lower leg pain and tenderness along the inner border of the distal third of the tibia.	TBPS: Scintigraphic uptake pattern Plain radiographs: Normal/abnormal.
Anderson et al. (1997) Cross-sectional	MTSS: 19 (8 m; 11 f) competitive high-school, collegiate, and professional athletes (n = 12), and recreational athletes (n = 8). Age: 34,4 (17-54) years. Symptom duration: 23,8 (2-84) months. Symptom intensity: NS.	MTSS: Exercise-induced lower leg pain, diffuse tenderness along the posteromedial tibia spanning > 5 cm, and no clinical evidence of compartment syndrome or muscle herniation.	MRI: Classification of findings into grades 1-4. (1) Normal (2) Periosteal edema. (3) Bone marrow edema and periosteal edema. (4): Stress fracture. Plan radiographs: Normal/abnormal.
Aoki et al. (2004) Case-control	MTSS: 14 (m/f NS) athletes involved in various sports, with "shin splints". Symptom duration: 19 (7-42 days). Age, symptom duration/severity, and activity level and NS. Controls: 8 athletes with tibial stress fractures, involved in various sports.	MTSS: Chronic medial tibial pain in the distal 2/3 of the tibia, during or after sports activities, with moderate or severe tenderness along the posteromedial tibial border. Exclusion criteria: Abnormal findings on radiographs taken at the initial examination, history of acute trauma to the tibia, or a disease predisposing to a stress fracture.	MRI: Tibial periosteal and bone marrow edema. TBPS: Scintigraphic uptake pattern. Radiographs: Normal/abnormal.
Bhatt et al. (2000) Cross-sectional	MTSS: 20 (14 m; 6 f) individuals undergoing surgery for "medial tibial syndrome". Age: 29 (22-46) years. Symptom duration: 15-22 months. Symptom severity and activity level NS.	MTSS: Clinical diagnosis of medial tibial syndrome, including diffuse tenderness along the inner border of the distal tibia, and radiographs and compartment pressures were normal in all patients.	Biopsy: Tibial periosteal abnormalities and bone abnormalities. TBPS: Scintigraphic uptake pattern. Plain radiographs: Normal/abnormal.

Holder and Michael (1984) Cross-sectional	MTSS: 10 (5 m; 5 f) individuals with "shin splints", involved in various sports. Age: 25,1 (16-31) years. Symptom duration: 2-36 months. Symptom severity and activity level NS.	MTSS: Exercise-induced medial tibial pain, initially relieved by rest and exacerbated by exercise, with tenderness along the posteromedial tibial border of the distal 2/3 of the tibia, described as deep, longer, and less focal than with stress fracture, abnormal heel valgus, and excess forefoot pronation.	TBPS: Scintigraphic uptake pattern. Plain radiographs: Normal/abnormal.
Mattila et al. (1999) Case-control	MTSS: 15 (m/f ratio NS) military recruits (n = 12) and athletes (n = 3) with "medial tibial pain". Age: 21 (17-25) years. Symptom duration: 4,8 (3-12) weeks. Symptom severity: Onset of pain within the 500 m of marching. Activity level NS. Controls: Asymptomatic legs of 9 (m/f NS) 9 individuals including young trauma patients (n = 7) with tibial fracture, and asymptomatic leg of the MTSS group (n = 2). Age: 17-40 years (mean 25). Activity level NS.	MTSS: Inclusion criteria: Onset of pain within the first 500 m of marching, with tenderness spanning > 5 cm along the medial tibial shaft. Exclusion criteria: Signs of stress fracture on plain radiographs.	MRI (with contrast): Tibial periosteal and bone marrow edema.
Moen et al. (2014) Prospective cohort	MTSS: 52 (19 m; 33 f) athletes with "medial tibial stress syndrome" involved in various sports. Age: 26.,8 ± 1,6 (SE) years. Symptom duration: 449,2 ± 62,2 (SE) days. Symptom severity: Running distance on treadmill without pain: 985 ± 149 (SE) meters. SARS-score: 72,9 ± 3,5 (SE). LEFS-score: 55,2 ± 2,1 (SE). Controls: Asymptomatic legs from the same individuals (n = 12). Characteristics NS.	MTSS: Athletes with a clinical diagnosis of MTSS, defined as exercise-induced posteromedial tibial pain, with tenderness spanning > 5 cm along posteromedial tibial border. Exclusion criteria: Clinical suspicion of compartment syndrome, tibial stress fracture, or a previous tibial fracture.	MRI: Tibial periosteal and bone marrow edema, graded by severity.

Wallensten and Karlsson (1984) Case-control	MTSS: 8 male individuals with "medial tibial syndrome". Age: 24 (17-32) years. Symptom duration: 20 (6-36 months). Symptom severity: NS. Activity level NS. Control group 1: 8 healthy male individuals. Age 25 (20-34). Activity level: 4-3 times per week, mainly running, while one was an elite athlete. Patient demographics presented was described in a different study (Wallensten & Eklund, 1983). Control group 2: 8 individuals with "chronic anterior compartment syndrome" in the lower leg.	MTSS: Inclusion criteria: Posteromedial lower leg pain, tenderness along the posteromedial edge of the lower middle and upper distal tibia. Exclusion criteria: Signs of circulatory or neurological deficits. Controls: Inclusion criteria: Healthy subject.	TBPS: Scintigraphic uptake pattern Plain radiographs: Normal/abnormal.
Winters et al. (2017b) Case-control	MTSS: 15 (1 m; 14 f) college dance athletes with "medial tibial stress syndrome". Age: 20,3 ± 2,4. Activity level: 12,5 ± 10,6 hours/week. Symptom duration: Median 5 (0,75–66) months. Symptom severity: MTSS-score: 4,21 ± 1,58. Activity level: 12,5 ± 10,6 hours/week. Controls: 27 (7 m; 20 f) college athletes from the same population, without a lower leg injury in the last 6 months. Age: 21,1 ± 3,4 years. Activity level: 18,7 ± 8,2 hours/week.	MTSS: Inclusion criteria: Exercise-induced medial tibial pain ≥ 3 weeks, with tenderness spanning > 5 consecutive cm along the posteromedial tibial border. Exclusion criteria: Current sporting injury, crural fracture, chronic compartment syndrome or stress fracture, or tibial stress fracture or MTSS in the last 6 months. Controls: Inclusion criteria: Age ≥16 years and exercising ≥ 5 hours/week. Exclusion criteria: Injury in the previous 6 months.	Ultrasound: Periosteal abnormalities (edema, at painful spots, periosteal thickening, vascularization); bone abnormalities (edema, irregular surface)
Winters et al. (2019) Cross-sectional	MTSS: 6 (5 m; 1 f) athletes involved in various sports. Age: 22,7 (16-29) years. Symptom duration: 1,5 to multiple years. Symptom severity and activity level NS.	MTSS: Inclusion criteria: Exercise-induced medial tibial pain, with tenderness spanning > 5 consecutive cm along the posteromedial tibial border. Exclusion criteria: Current sporting injury, crural fracture, chronic compartment syndrome or stress fracture, or tibial stress fracture or MTSS in the last 6 months.	Bone biopsy: Presence of diffuse microdamage, microcracks and signs of remodeling.

Zhang et al. (2022) Prospective cohort	23 male individuals with that developed "medial tibial stress syndrome" during participation in a 1-month long-distance running-program. Age: 21,8 ± 1,5 years. Symptom duration: < 1 month. Symptom severity NS. Activity level: NS. Control 1: 20 healthy male individuals from the same cohort, that participated in a 1-month long-distance running program. Age: 22,2 ± 2,6 years. Activity level NS. Control 2: 20 non-injured male individuals with no athletic history. Age: 23,6 ± 1,2 years.	MTSS: Inclusion criteria: A clinical diagnosis of MTSS, as described by Winters et al. (2018), which includes exercise-induced medial tibial pain, with tenderness spanning > 5 consecutive cm along the posteromedial tibial border. Exclusion criteria: Involvement in continuous strength exercising, history of muscle or skeleton injury, running recreationally or competitively.	Ultrasound: Periosteal thickness
Özgürbüz et al. (2011) Case-control	MTSS: 11 athletes (7 m; 4 f) with "medial tibial stress syndrome". Age: 21,0 ± 1,9 years. Symptom duration: 5,0 (3 – 10) weeks. Activity level: Mean 16,9 ± 17,8 hours/week. Controls: 11 healthy athletes (7 m; 4 f), participating in various sports. Age: 23,3 ± 3,0 years. Activity level: 16,5 ± 15,9 hours/week.	MTSS: Inclusion criteria: Age 18-23 years, no systemic disease, clinical diagnosis of MTSS including medial tibial pain at the junction of the distal 2/3 of the tibia, diffuse tenderness spanning > 5 cm along the posteromedial tibial border, and a positive one leg hop test. Exclusion criteria: Other concomitant pathology. Controls: Exclusion criteria: Lower-extremity ligament injury, history of lower extremity surgery, fracture or MTSS, concurrent neurological or vascular pathologies in the lower extremities, and amenorrhea.	DXA: Bone density at the most painful spot.

MTSS, medial tibial stress syndrome, m, male; f, female; NS, not stated; TPBS, Three-phase bone scan; n, number; SD, standard deviation; LEFS, Lower Extremity Functional Scale (0-80); SARS, Sports activity rating scale; [a]Participant demographics are only presented from MTSS and asymptomatic controls; [b]Age and symptom duration is reported as range, or mean (range), or mean ± SD.

3.2. Risk of bias assessment

The results of the risk of bias assessment can be seen in Table IV. 3 studies were graded as «good», 1 study was graded as «fair», and 8 studies were graded as «poor», which make the overall quality of the included studies «poor».

3.3. Statistical analyses

No statistical analyses were performed, as data could not be pooled for any outcome.

Table IV. Newcastle-Ottawa Scale (NOS) for assessing the quality of observational trials, including a modified version for assessing cross-sectional studies. The coding manuals used in this review can be found in Appendices C through E.

Study design	Study	Selection				Comparability		Exposure/Outcome			Score*	
		1	2	3	4	1	2	1	2	3		
Case-control study	Allen (1995)	★						★	★	★	4/9	Poor
	Aoki (2004)	★	★	★		★			★	★	6/9	Good
	Mattila (1999)	★	★					★	★	★	5/9	Poor
	Wallensten (1984)	★					★		★	★	4/9	Poor
	Winters (2017a)	★	★	★	★		★	★	★	★	8/9	Good
	Özgürbüz (2011)	★			★		★		★	★	5/9	Fair
Cohort study	Moen (2014)	★	★	★	★			★	★		6/9	Poor
	Zhang (2022)			★		★	★			★	4/9	Poor
Cross-sectional study	Anderson (1997)	★		★	★	★	★	★	★	N/A	7/8	Good
	Bhatt (2000)			★	★			★	★	N/A	4/8	Poor
	Holder (1984)			★	★			★		N/A	3/8	Poor
	Winters (2019)			★	★			★		N/A	3/8	Poor

Case control studies: Selection: 1) Is the case definition adequate? 2) Representativeness of the cases; 3) Selection of the controls; 4) Definition of the controls. Comparability: 1 and 2) Comparability of cases and controls on the abasis of the design or analysis. Exposure: 1) Ascertainment of exposure; 2) Cases and controls: same ascertainment method; 3) Cases and controls: Same non-response rate. **Cohort studies**: Selection: 1) Representativeness of the exposed cohort; 2) Selection of the non-exposed cohort; 3) Ascertainment of exposure; 4) Demonstration that outcome of interest was not present at the start of the study. Comparability: 1 and 2) Comparability of cohorts on the basis of the design or analysis. Outcome: 1) Assessment of outcome; 2) Was follow-up long enough for outcomes to occur; 3) Adequacy of the follow-up of cohorts. **Cross-sectional studies:** Selection: 1) Representativeness of the sample; 2) Sample size; 3) Non-respondents; 4) Ascertainment of the exposure. Comparability: 1 and 2) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled. Outcome: Assessment of outcome; 2) Statistical test. N/A: Not applicable. *A maximum of 9 stars can be awarded for case-control studies and cohort studies, and 8 stars for cross-sectional studies.

3.4. Data synthesis

3.4.1. Magnetic Resonance Imaging

The literature search identified 4 studies reporting on Magnetic Resonance Imaging (MRI) findings in symptomatic lower legs of individuals with MTSS (Anderson et al. (1997), Aoki et al. (2004), Mattila et al. (1999), Moen et al. (2014). The quality of the trials was «poor» in two, and «good» in two.

Moen et al. (2014) compared the occurrence and severity of tibial periosteal and bone marrow edema in 92 symptomatic lower legs from 52 athletes (mean symptom duration 64 weeks) to 12 asymptomatic legs from the same athletes. The severity of periosteal edema was graded "none", "mild-moderate", "moderate-severe", and bone marrow edema was graded "none", "seen on T2 images", and "seen on T1 and T2 images". They found no statistically significant differences on the occurrence or severity of periosteal edema (see example in figure 2) a, bone marrow edema (see example in figure 3), or both, between the symptomatic and asymptomatic leg of athletes with unilateral pain or between all symptomatic and asymptomatic legs (see Table V). Periosteal and/or bone marrow edema was found in 40/92 (43 %) symptomatic legs and 7/12 (58 %) asymptomatic legs. Periosteal edema was found predominantly on the anteromedial tibial border (70 %). 35 % of athletes with bilateral pain had no abnormal MRI findings. They found no statistically significant association between MRI findings 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" (Lower Extremity Functional Scale). They did, however, find that the absence of bone marrow edema, periosteal edema, or both, was associated with *longer* time to recovery ($p = 0.01$, $p = 0.03$, and $p = 0.02$, respectively).

Mattila et al. (1999) reported on the occurrence of tibial periosteal edema and bone marrow edema in 28 and 14 symptomatic legs, respectively. Periosteal edema was found in 96,4 % of symptomatic legs (n = 27; se example in Figure 4B-4E), of which 6 were graded as "severe". Bone marrow edema was found in 4/14 symptomatic legs (28,6 %; see example in Figure 5), all of which had severe periosteal edema. These changes were only visible on the STIR-sequences, suggesting a grade 2 stress reaction according to Fredericson et al. (1995).

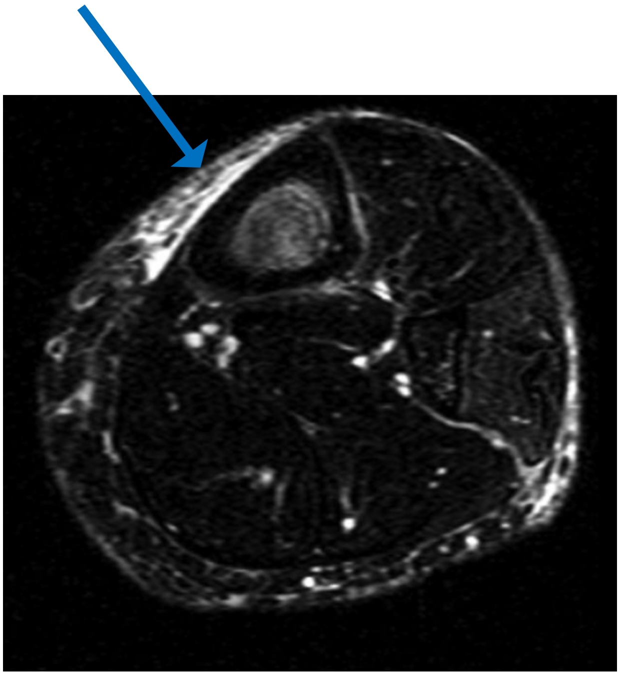


Figure 2. «Axial T2-weighted image of an athlete with medial tibial stress syndrome (MTSS) showing periosteal edema on the anteromedial side of the tibia». From Moen et al. (2014). Reused with permission.

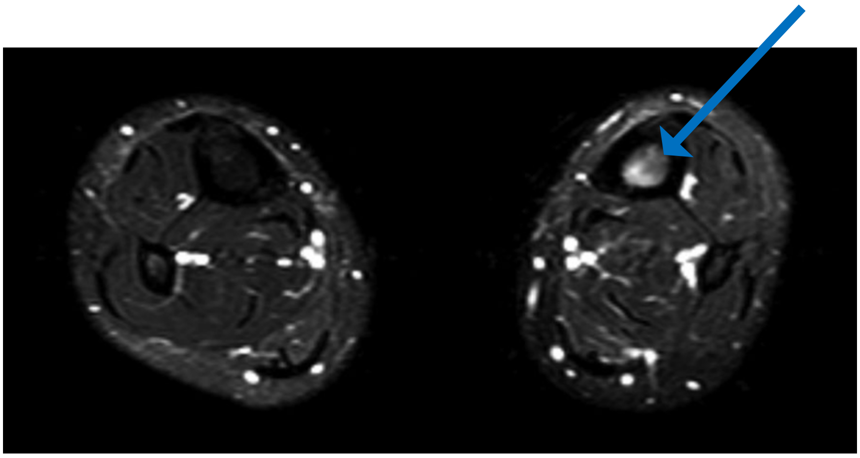


Figure 3. «Axial T2-weighted image of the legs, showing bone marrow edema in the left leg of an athlete with medial tibial stress syndrome (MTSS)». From Moen et al. (2014). Reused with permission.

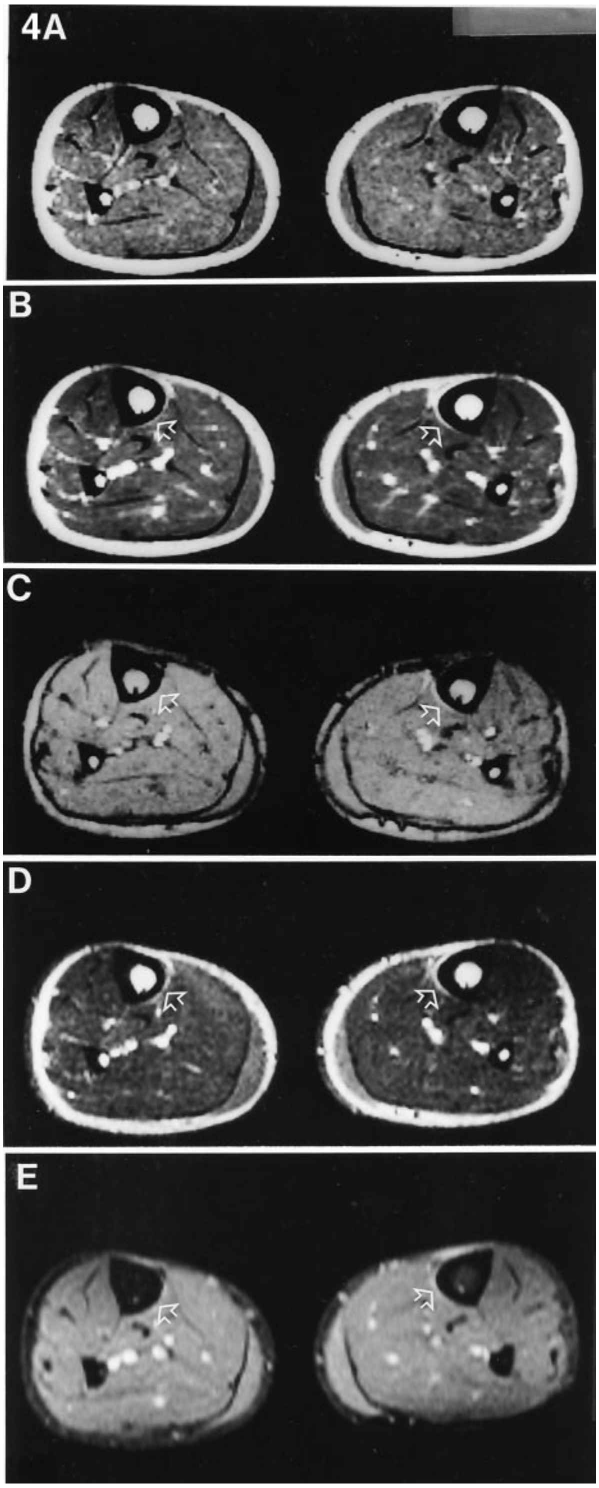


Figure 4. «Axial images of a patient with bilateral symptoms. No pathology is detectable on T1w pre-contrast SE image (500/17) (A), while static phase post-contrast SE image (500/ 17) (B), dynamic post-contrast image (obtained 150 s post- injection) (2D FLASH 30/12) (C), as well as conventional T2w SE (2750/80) (D) and STIR images (1900/20/150) (E) depict bilateral periosteal edema (open arrow). Pre-tibial fat is best differentiated from edema on STIR images». From Mattila et al. (1999). Reused with permission.

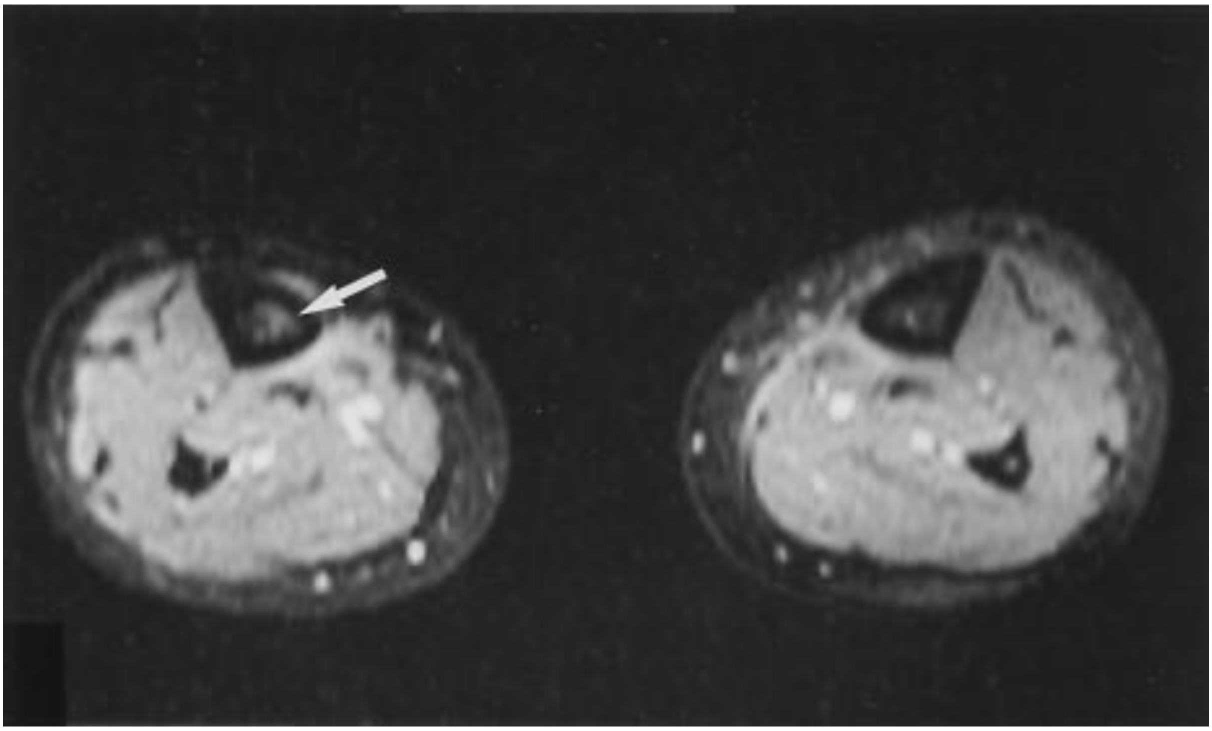


Figure 5. «A patient with grade 2. Bone stress reaction in the right tibia. Intraosseal bright signal is detectable on STIR (1900/20/ 150) (arrow) … ». From Mattila et al. (1999). Reused with permission.

Aoki et al. (2004) reported on the occurrence of tibial periosteal edema and bone marrow edema in 14 symptomatic athletes (symptom duration ≤ 6 weeks). They found that periosteal edema was present in 85,7 % (n = 12), bone marrow edema was present in 50 % (n = 7), and 35,7 % (n = 5) of athletes had both. The periosteal edema was located along the posteromedial surface of the tibia, and the bone marrow edema extended linearly along the medial aspect of the bone marrow, but never through the entire marrow. Five athletes had a follow-up MRI after 4 weeks, in which the abnormally high signal seen had been reduced. They found no statistically significant relationship between MRI findings and the duration of symptoms.

Anderson et al. (1997) reported on the tibial periosteal edema and bone marrow edema in 19 symptomatic individuals (mean symptom duration 23,8 months). They found that periosteal edema was present in 36,8 % (n = 7) of athletes, bone marrow edema/hemorrhage was present in 26,3 % (n = 5), and 10,5 % (n = 2) had both. The periosteal edema was located along the anteromedial surface of the tibia in 6/7, and along the posterior surface of the tibia in 1/7. Abnormal marrow signal intensity was identified in five patients, involving the middle third of the tibia in 4, and proximal tibia in 1, of which two had overlying periosteal fluid along the anteromedial surface. They also found that 10,5 % (n = 2) had a stress fracture extending longitudinally through the anterior tibial cortex in the middle and middle to distal tibia, despite having a clinical diagnosis of MTSS, including diffuse tenderness spanning > 5 cm along the posteromedial tibial border. They found a strong correlation between increased symptom duration and a normal MR image ($p = 0.002$). Those with abnormal MRI findings had a mean symptom duration of 10 months, and those with normal MRI findings had a mean symptom duration of 46 months.

The prevalence of periosteal and bone marrow edema found in symptomatic and asymptomatic legs across studies, are summarized in table IV.

Table IV. Magnetic resonance imaging (MRI). Imaging findings in symptomatic and asymptomatic lower legs of individuals with medial tibial stress syndrome. Between group comparisons in Moen et al. were not statistically significant for any outcome.

		MRI findings in symptomatic legs				MRI findings in asymptomatic legs			
Study	Systematic legs	Yes (N)	%	No (N)	%	Yes (N)	%	No (N)	%
Anderson et al. (1997)	Periosteal edema	7/19	36,8	12/19	63,2	-	-	-	-
Aoki et al. (2004)	Periosteal edema	12/14	85,7	2/14	14,3	-	-	-	-
Mattila et al. (1999)	Periosteal edema	27/28	96,4	1/28	3,6	-	-	-	-
Moen et al. (2014)	Periosteal edema	19/92[a]	20,7[a]	73/92[a]	79,3[a]	4/12	33,3[a]	8/12	66,7
Anderson et al. (1997)	Bone marrow edema	5/19	26,3	14/19	73,7	-	-	-	-
Aoki et al. (2004)	Bone marrow edema	7/14	50,0	7/14	50,0	-	-	-	-
Mattila et al. (1999)	Bone marrow edema	4/14	28,6	10/14	71,4	-	-	-	-
Moen et al. (2014)	Bone marrow edema	38/92[a]	41,3[a]	54/92[a]	58,7	5/12	41,7[a]	7/12	58,3
Anderson et al. (1997)	Periosteal and bone marrow edema	2/19	10,5	17/19	89,5	-	-	-	-
Aoki et al. (2004)	Periosteal and bone marrow edema	5/14	35,7	9/14	64,3	-	-	-	-
Mattila et al. (1999)	Periosteal and bone marrow edema	4/14	28,6	10/14	71,4	-	-	-	-
Moen et al. (2014)	Periosteal and bone marrow edema	-	-	-	-	2/12	16,7	10/12	83,3
Anderson et al. (1997)	Periosteal and/or bone marrow edema	10/19[a]	52,6[a]	9/19[a]	47,4[a]	-	-	-	-
Aoki et al. (2004)	Periosteal and/or bone marrow edema	14/14[a]	100[a]	0/14[a]	0,0[a]	-	-	-	-
Mattila et al. (1999)	Periosteal and/or bone marrow edema	13/14[a]	92,9[a]	1/14[a]	7,1[a]	-	-	-	-
Moen et al. (2014)	Periosteal and/or bone marrow edema	40/92	43,5	52/92	56,5	7/12	48,3	5/12	41,7

N, number of legs; [a]calculated from the available data.

3.4.2. Three-Phase Bone Scan

The literature search identified 5 studies reporting on Three-Phase Bone Scan (TPBS) findings in symptomatic lower legs of individuals with MTSS (Allen et al., 1995; Aoki et al., 2004; Bhatt et al., 2000; Holder & Michael, 1984; Wallensten & Karlsson, 1984). One study presented data on asymptomatic legs of individuals with unilateral symptoms (Holder & Michael, 1984). The quality of the trials was «poor» in three, and «good» in one.

Allen et al. (1995) reported on the scintigraphic uptake pattern in the tibia of 32 athletes (symptom duration not stated). The perfusion and immediate blood-pool phases were normal in all cases. On the delayed images, they found abnormal scintigraphic uptake in 87,5 % (n = 28). 75 % (n = 24) had a distinctive tubular uptake pattern, that were longitudinally oriented, and involved the anterior and posterior cortices in most of the diaphyseal tibial cortex. 12,5 % (n = 4) had a focal uptake, which the authors were certain did not indicate stress fractures, as subsequent plain radiographs were normal. 12,5 % had a normal scan.

Aoki et al. (2004) reported on the scintigraphic uptake pattern in the tibia of 9 athletes (symptom duration ≤ 6 weeks). They found abnormal scintigraphic uptake in 55,6 % (n = 5), all of which were longitudinally oriented (see example in Figure 6). Four extended linearly along the medial posterior surface of the tibia, and one was spindle shaped. All athletes that had abnormal scintigraphic uptake also had a linear abnormally high signal along the medial aspect of the bone marrow on MRI. Of the 4 athletes with a normal scan, 3 had periosteal edema on MRI.

Bhatt et al. (2000) reported on the scintigraphic uptake pattern in the tibia of 32 symptomatic lower legs of 20 individuals (symptom duration 15-22 months) undergoing surgery for this condition. The perfusion and immediate blood-pool phases were normal in all cases. On the delayed images, they found abnormal scintigraphic uptake in 65,6 % (n = 21; see example in Figure 6).). 50 % (n = 16) had a diffuse tubular uptake, 15,6 % (n = 5) had a focal uptake. 34,4 % (n = 11) had a normal scan.

Holder and Michael (1984) reported on the scintigraphic uptake pattern in the tibia and fibula of 14 symptomatic legs of 10 individuals (symptom duration 2-36 months) and their 6 asymptomatic lower legs. The perfusion and immediate blood-pool phases were normal in all cases. On the delayed images, they found abnormal scintigraphic uptake in the tibia in 92,9 % (n = 13) of the symptomatic legs, and in 33,3 % (n = 2) of the asymptomatic legs. All tibial lesions involved the posterior tibial cortex, were longitudinally oriented, and were relatively long, often involving a third of the length of the bone, with varying intensity of tracer activity along its length. 64,3 % (n = 9) of the lesions were located at the junction between the distal and middle third of the tibial cortex, 21,4 % (n = 3) were in the middle third, 14,3 % (n = 2) were located in the junction between the proximal and middle third, and 7,1 % (n = 1) in the proximal third. They did not present any statistical analysis of the differences between the findings in symptomatic and asymptomatic legs.

Wallensten and Karlsson (1984) included 8 individuals with 14 symptomatic legs (mean symptom duration 20 ± 12 months) and reported that 2 individuals had a mild diffuse uptake in the tibia. However, they failed to specify the total number of individuals and legs that were scanned, and the main author did not respond to the request for a information.

The prevalence of abnormal scintigraphic uptake found in symptomatic and asymptomatic legs across studies is summarized in table V.

3.4.3. Ultrasound

The literature search identified 2 studies reporting on ultrasound findings in symptomatic lower legs of individuals with MTSS (Winters et al., 2017b; Zhang et al., 2022). Both studies compared their findings to an asymptomatic control group. The quality of the trials was «poor» in one, and «good» in one.

Table V. Scintigraphic uptake on three-phase bone scan (TPBS) in symptomatic legs in individuals with medial tibial stress syndrome.

		Symptomatic		Asymptomatic	
Study	**Uptake pattern**	**N**	**%**	**N**	**%**
Allen et al. (1995)	Longitudinal	24/32	75,0	-	-
Aoki et al. (2004)	Longitudinal	4/9	44,4	-	-
Bhatt et al. (2000)	Longitudinal	16/32	50,0	-	-
Holder and Michael (1984)	Longitudinal	13/14	92,9	1/6	16,7
Allen et al. (1995)	Focal	4/32	12,5	-	-
Aoki et al. (2004)	Focal	1/9	11,1	-	-
Bhatt et al. (2000)	Focal	5/32	15,6	-	-
Holder and Michael (1984)	Focal	0/14	0,0	1/6	16,7
Allen et al. (1995)	Focal or longitudinal	28/32	87,5	-	-
Aoki et al. (2004)	Focal or longitudinal	5/9	55,6	-	-
Bhatt et al. (2000)	Focal or longitudinal	21/32	65,6	-	-
Holder and Michael (1984)	Focal or longitudinal	13/14	92,9	0/6	0
Allen et al. (1995)	Normal scan	4/32	12,5	-	-
Aoki et al. (2004)	Normal scan	4/9	44,4	-	-
Bhatt et al. (2000)	Normal scan	11/32	34,4	-	-
Holder and Michael (1984)	Normal scan	1/14	7,1	4/6	66,7

N, number of legs.

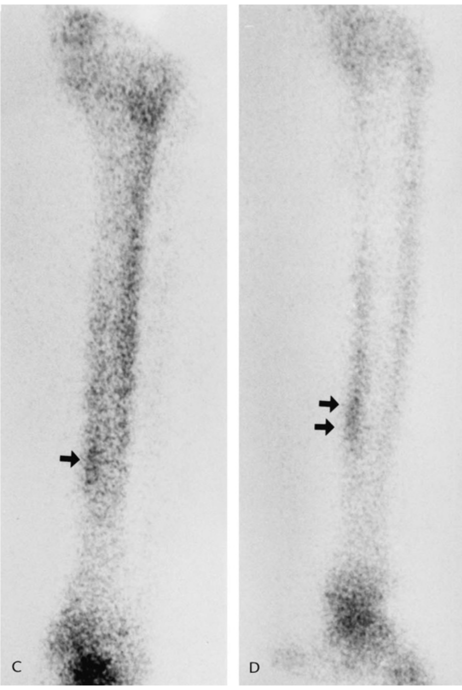


Figure 6. Longitudinal scintigraphic uptake in the anteroposterior (C) and lateral views (D) of an individual with medial tibial stress syndrome. This patient is exhibiting the «double stripe sign» in the anteroposterior view, which is a characteristic imaging feature of medial tibial stress syndrome. Reused from Aoki et al. (2004), with permission.

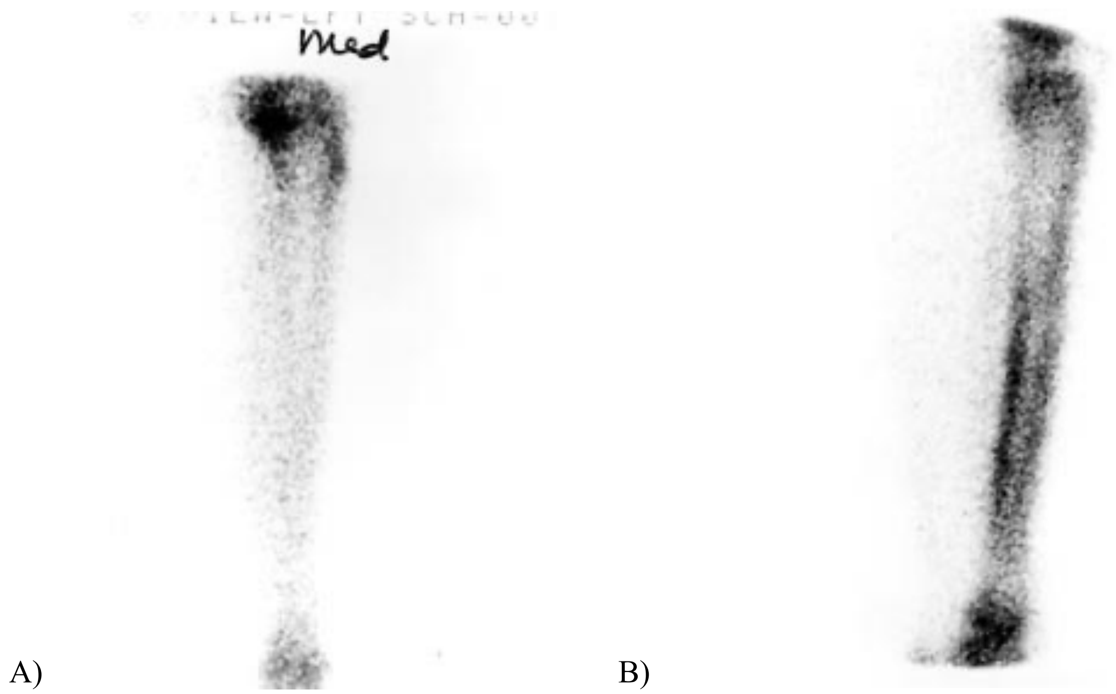


Figure 7. A) «Medial view of the tibia on isotope bone scintigraphy: normal appearance»; B) «Medial view of the tibia on isotope bone scintigraphy: tubular pattern characteristic of medial tibial syndrome». Reused from Bhatt et al. (2000), with permission.

Winters et al. (2017b) compared ultrasound findings in the most symptomatic lower leg of 15 legs of 15 college dance athletes (mean symptom duration 5 months), to 27 asymptomatic legs of 27 dance athletes from the same population. They found periosteal edema in 53,3 % (n = 8) of the symptomatic legs, measured at the two most painful spots along the distal 2/3 of the medial tibial border, compared to 37,0 % (n = 10) of the asymptomatic legs, measured at two randomly generated spots along the distal 2/3 of the medial tibial border. The difference was not statistically significant (p = 0.35). They found no cases of increased periosteal thickness in the specific spots, but reported that two athletes with MTSS and one control athlete had increased periosteal thickness along the posteromedial border, outside of these spots.

They found 1 case (3,7 %) of irregular bone surface, and 1 case (3,7 %) of cortical edema along the medial tibial border. Both were found in asymptomatic legs. They found no such changes in the symptomatic legs. They found no signs of increased vascularization in the periosteum of any athlete. Tendinous abnormalities were found in 46,7 % (n = 7) symptomatic legs, compared to 48,1 % (n = 13) in asymptomatic legs. Tendinous edema in the tibialis posterior muscle was the most prevalent finding. There were no statistically significant differences between groups on any tendon abnormalities found.

Zhang et al. (2022) compared ultrasound findings in 42 symptomatic lower legs from 23 non-athletic individuals that had developed MTSS during participation in a 1-month long distance running program (MTSS group), to 40 asymptomatic legs of 20 non-injured individuals from the same cohort (symptomless group), and 40 asymptomatic legs of 20 non-injured individuals that did not participate in the running program (control group). Periosteal thickness was significantly higher in the symptomatic legs than asymptomatic legs in both the symptomless group (1,44 mm vs. 1,27 mm, $p<0.001$) and the control group (1,44 mm vs. 0,83 mm, $p<0.001$).

3.4.4. Dual X-ray Absorptiometry (DXA)

The literature search identified 1 study reporting on Dual X-ray Absorptiometry (DXA) findings in symptomatic lower legs of individuals with MTSS (Özgürbüz et al., 2011). The quality of the trial was «fair». They compared tibial bone mineral density (BMD) measured at three locations along the length of the tibia, between 22 symptomatic lower legs in 11 athletes (mean symptom duration 5 weeks) and 22 legs of 11 asymptomatic athletes. They found no statistically significant differences in bone density at any of the three locations.

3.4.5. Plain Radiographs

The literature search identified 5 studies reporting on X-ray findings in symptomatic lower legs in individuals with MTSS (Anderson et al., 1997; Aoki et al., 2004; Bhatt et al., 2000; Holder & Michael, 1984; Wallensten & Karlsson, 1984). The quality of the trials was «poor» in three, and «good» in two.

Anderson et al. (1997) reported on plain radiographic findings in 4 individuals with a clinical diagnosis of MTSS. All had normal radiographs. One individual was diagnosed with a stress fracture on MRI, despite having diffuse tenderness spanning > 5 cm.

Aoki et al. (2004) reported on plain radiographic findings in symptomatic lower legs of 14. Athletes with periosteal reaction, callus formation, or a fracture line at the initial examination or at a subsequent follow-up scan at 2, 4, 8, or 12 weeks, were allocated to the «stress fracture» group. Individuals with no abnormalities on any follow-up scan were allocated to the MTSS-group. This division was compared with MRI-findings, which showed clear evidence of stress fractures on the MRI scans (an abnormally wide high signal in the localized bone marrow) in all patients allocated to the stress fracture group, and no such changes in the MTSS-group. Therefore, changes seen on plain radiographs was in all cases associated with stress fractures, and not MTSS.

Bhatt et al. (2000) reported on plain radiographic findings in 32 lower legs of 20 individuals with «medial tibial syndrome», undergoing surgery for this condition (symptom duration 15-22 months). Three-phase radionuclide bone scan excluded stress fractures. All participants had normal radiographs.

Holder and Michael (1984) reported on plain radiographic findings in 8 legs of 4 athletes with «shin splints», involved in various sports (5 male, 5 female; mean age 25,1 years; symptom duration 2-36 months). Three-phase radionuclide bone scan excluded stress fractures. All participants had normal radiographs.

Wallensten and Karlsson (1984) reported on plain radiographic findings in 14 legs of 8 male individuals with «medial tibial syndrome» (mean age 24; mean symptom duration 20 months). Three-phase radionuclide bone scan excluded stress fractures. All patients had normal recent radiographs of the lower legs.

In summary, there were no plain radiographic findings in symptomatic legs of individuals with MTSS.

3.4.6. Biopsies

The literature search identified 2 studies reporting on biopsy findings in symptomatic lower legs of individuals with MTSS (Bhatt et al., 2000; Winters et al., 2019). Neither study compared their findings to an asymptomatic control group. The quality of the trials were «poor».

Bhatt et al. (2000) reported on the biopsy findings from 32 lower legs in 20 individuals undergoing surgery for «medial tibial syndrome» (symptom duration 15-22 months). They harvested 32 periosteal samples and 26 bone samples. They found abnormal periosteum in 65,6 % (n = 21), including increased periosteal thickness (>1 mm) in 53,1 % (n = 17), fibrosis in 59,4 % (n = 19), increased vascularity in 56,3 % (n = 18), acid mucopolysaccharide (mucin) deposition in 12,5 % (n = 4), and hemosiderin (iron) deposition indicating previous trauma in 3,1 % (n = 1). Chronic inflammatory cell infiltration was only rarely found. They found loss of osteocytes in 65,4 % (n = 17), lamellar structure damage (enlargement of lacunae and disruption of the lamellar structure) in 57,7 % (n = 15), and chronic inflammation changes in 11,5 % (n = 3) of the samples. 61,5 % (n = 16) biopsies were classified as having significant changes. They found no correlation between the overall biopsy findings and bone scintigraphy. They did, however, find that cases that had periosteal thickness > 1 mm had mostly normal scan appearance (p = 0.002), and those with low levels of osteocyte loss had mostly abnormal bone scintigraphy (p = 0.0946).

Winters et al. (2019) reported on biopsy findings from 18 specimens taken from 6 athletes undergoing surgery for MTSS (5 male, 1 female; mean age 22,7 years; symptom duration 1,5-multiple years). The specimens were harvested from the medial tibial border. 2 specimens had damages that were attributed to the biopsy harvest. 44,4 % (n = 8) of the specimens had linear shear, longitudinal or transverse microcracks, of which 3 may also be artefacts from the biopsy harvest, however with less certainty than the other damaged specimens. Only 1 specimen showed putative signs of remodeling activity near the microcrack, with a cutting front coming from the periosteal surface. They found no diffuse microdamage in any of the biopsies harvested.

4. DISCUSSION

4.1. Periosteal changes

Bhatt et al. (2000) frequently found abnormalities on biopsies of the medial tibial border periosteum, including increased periosteal thickness, fibrosis and increased vascularity. However, there were rarely any signs of chronic inflammation. This is in agreement with Johnell, Rausing, Wendeberg, and Westlin (1982), who hardly found any inflammatory changes in a population of 37 athletes with “shin splints”, which included 4 individuals with radiographic signs of a stress fracture. Of 33 soft tissue biopsies, they found only one individual with an inflammatory cell infiltration in the periosteum. This suggests that the frequently used term *periostitis* is inaccurate and should not be used to describe this condition.

4.2. Bone changes

Bhatt et al. (2000) note a high prevalence of bone changes, including loss of osteocytes and damage to the lamellar structure, in the majority of symptomatic limbs, and Winters et al. (2019) remarked on a notable absence of a repair reaction to the presence of microcracks in the cortical bone. These findings suggests that the osteocyte response to bone microdamage may be impaired in individuals with MTSS. However, neither study compared their findings to asymptomatic limbs, and its relationship to MTSS is therefore unclear.

4.3. Alterations to bone metabolism

According to the mechanostat theory, bone is a dynamic tissue that responds to the physical stresses it experiences in a dose-response relationship (Hart et al., 2017). If the strain magnitude exceeds the level of strain necessary to elicit a response, known as the minimum effective strain. The response may be resorptive, regenerative, or formative, depending on various aspects of strain (Hart et al., 2017).

Scintigraphic uptake in bone is dependent on metabolic activity of osteoblasts. The high number of positive scans in individuals with MTSS indeed shows that increased osteoblastic activity along the medial tibia is common in individuals with MTSS. This can be a sign of a regenerative process or a formative process.

Alterations to bone density may be observed when there is a mismatch between osteoblast and osteoclast activity. Özgürbüz et al. (2011) found no differences in bone density between symptomatic and asymptomatic limbs in individuals with short duration of symptoms. A study of Magnusson et al. (2001) assessed tibial bone density in individuals with long-duration activity related medial tibial pain and diffuse scintigraphic uptake along the medial tibial border, and found reduced bone mineral density in the junction between the lower two thirds of the tibia. The study was excluded from this review due to failure to report medial tibial tenderness, and it is therefore unknown if the subjects accurately represent individuals with MTSS.

4.4. The role of imaging studies in diagnosing MTSS

Medial tibial stress syndrome is a clinical diagnosis with specific diagnostic criteria. This means that medical imaging is not necessary to confirm the diagnosis. However, are there certain imaging features associated with this condition, or not?

MRI - The studies included in this systematic review show that periosteal edema along the anteromedial and posteromedial tibial cortex and bone marrow edema are common findings in symptomatic lower legs. However, Moen et al. (2014) found that periosteal edema or bone marrow edema on MRI in 33,3 % and 41,7 % of asymptomatic lower legs in individuals with unilateral MTSS, and they did not find any statistically significant differences in the occurrence or appearance of MRI abnormalities between symptomatic and asymptomatic lower legs. In a MRI-study on asymptomatic long-distance runners, Bergman, Fredericson, Ho, and Matheson (2004) found abnormalities consistent with grade 1-3 tibial stress reactions in 33,3 % of lower legs (Grade 1: 9,5 %, Grade 2: 19 %; Grade 3: 4,8 %), showing that the occurrence of periosteal and bone marrow edema is high in asymptomatic legs of active individuals. 6 of the subjects with abnormal findings were followed for 48 months, and none developed symptoms of a tibial stress injury.

What this suggests is that periosteal and bone marrow edema are not strongly correlated with symptoms but might to a greater extent be explained by some other unknown parameter. Also, Moen et al. (2014) found no correlation between MRI findings and length of palpation pain along the medial tibial border or symptom severity.

A shared trait between groups is that participants are physically active individuals, and my suspicion is that these findings might better relate to activity status and history, than MTSS. This includes training load, which is dependent on type of activity (weight-bearing or non-weight-bearing, high or low impact, degree of repetitiveness), duration, and intensity of the training, and if there have been any recent changes to these parameters. This notion was also presented by Bergman et al. (2004) and Winters et al. (2017b), who both discuss their findings in relation to a possible physiological accelerated bone remodeling process in the tibia.

Also, up to 79,3 % of symptomatic lower legs have no sign of periosteal edema, and up to 73,7 % have no sign of bone marrow edema on MRI. These high rates of false negative MRI scans (negative scan despite having MTSS) show that even if periosteal edema and bone marrow edema could be attributed to the MTSS-diagnosis, the sensitivity of MRI to detect MTSS would be considered low, making its predictive value in a clinical setting highly questionable. However, its high sensitivity and specificity in detecting stress fractures makes it a useful instrument for ruling it out.

TPBS - Increased scintigraphic uptake was frequently found in individuals with MTSS, with a longitudinal uptake in 44,4 % to 92,9 % of symptomatic limbs. Allen et al. (1995) and Bhatt et al. (2000) noted that most lesions found on three-phase bone scan had a tubular appearance, commonly known as exhibiting the “double stripe sign” (Lieberman & Hemingway, 1980) (see Figure 6 and 7), and both stated that it is a characteristic finding in individuals with MTSS. There was, however, a notable absence of studies comparing symptomatic and asymptomatic lower legs. The specificity of the scintigraphic uptake to the MTSS-diagnosis and not some other factor pertinent to this group of individuals such as activity status or history, is therefore unclear. Also, according to the included studies in this review, up to 55,6 % of symptomatic legs may not display an abnormal scintigraphic uptake. A high rate of false negative scans makes the positive predictive value for TPBS low. Also, skeletal TPBS is an invasive imaging technique which exposes the patient to a substantial radiation, and has less specificity than MRI.

Ultrasound – Ultrasound does not seem to provide any value in diagnosing MTSS, as there were no significant differences in soft tissue abnormalities between symptomatic and asymptomatic limb. However, it may be used to rule out soft tissue pathology, e.g., muscle tears, as a source of medial tibial pain.

Radiographs – All available radiographs were normal in all symptomatic limbs included in this review, and radiographs are therefore not helpful in diagnosing MTSS. A stress fracture should be suspected if there are signs of periosteal elevation or uneven bone surface, while a definite diagnosis is made if a fracture line is observed.

DXA – DXA scans are used to assess bone density, and is not helpful in diagnosing MTSS.

4.6. Correlations between clinical parameters and imaging findings

Symptom duration - Several studies assessed a possible correlation between symptom duration and MRI-findings. Aoki et al. (2004) found no correlation between symptom duration and MRI-findings in individuals with short duration pain (average 19 days (range 7-42)). Neither did Moen et al. (2014), in patients with long duration pain (449.2 ± 62.2 (SE) days). Anderson et al. (1997), however, found a strong correlation between the presence of an abnormal MRI and short duration of symptoms (10 months) and a normal MRI and long duration of symptoms (46 months). They also noted that there was a tendency for increasingly severe MRI findings with shorter symptom duration. Although the short range in symptom duration of the participants in Aoki et al. (2004) might explain the why they did not find the same correlation as Anderson et al. (1997), the disagreement between Moen et al. (2014) and Anderson et al. (1997), who both included patients with longer duration pain and a greater range, is less clear.

A noteworthy observation is that Aoki et al. (2004) and Mattila et al. (1999), which both exclusively included participants with short duration symptoms (<12 weeks, mean 19 days and 34 days, respectively), found a very high prevalence of periosteal edema of 85,7 % and 96,4 % in symptomatic lower legs. This contrasts the substantially lower prevalence found in in Moen et al. (2014) and Anderson et al. (1997) of 20,7 % and 36,8 %, respectively, in which the mean symptom duration was long (15,0 and 23,8 months, respectively). A similar observation was not made for bone marrow edema, which was found in 50,0 % and 28,6 % of symptomatic lower legs in Aoki et al. (2004) and Mattila et al. (1999), respectively, and 41,3 % and 26,3 % in Moen et al. (2014) and Anderson et al. (1997), respectively. A possible confounding variable here is the MRI sequences used in the studies. Anderson et al. (1997) only used T1-weighted MRI sequence in their analyses, while the other authors included sequences that better depict water content (T2-weighted, proton-density weighted and fat-suppressed sequences). Mattila et al. (1999) noted in their study that T1-weighted sequences was insensitive to periosteal edema, compared to STIR-images and T2-weighted or proton density images, which may account for the less frequent scoring of periosteal and bone marrow edema in Anderson et al. (1997). On the other hand, the high number of positive findings in Mattila et al. (1999) could relate to the fact that they had the most extensive MRI examination of all the studies, including dynamic contrast-enhanced images which managed to depict four cases of periosteal edema that was not found on conventional T2-images, and one case that was not found on the STIR-sequence.

None of the studies included in this review assessed a possible correlation between symptom duration and findings on any other medical imaging study or biopsy study.

4.7. Implications for clinical practice

A comprehensive clinical examination and patient history is crucial in assessing any overuse injury. This is highlighted by the seemingly low sensitivity and specificity of the various diagnostic imaging modalities in diagnosing this condition. Of all the modalities included in this trial, TPBS seems to be the most sensitive in detecting abnormalities in symptomatic legs, however, the scintigraphic uptake pattern of asymptomatic controls from the same population has not been adequately assessed, which questions the specificity of these findings.

When the clinical picture suggests MTSS, the main differential diagnoses to consider is medial tibial stress fracture, which has a clinical picture that resembles MTSS. The clinical features that set it apart from MTSS include focal pain and focal tenderness (< 5 cm). Also, indirect percussion (pain elicited with percussion at a distance from the painful area), although being a less sensitive finding, has been found to be very specific to higher grades of stress injury (grade 3 and 4) (Fredericson et al., 1995). If there is a need for clarification, both

MRI and TPBS has high sensitivity in detecting stress fractures, with MRI having the highest specificity. A plain radiograph may reveal cortical changes if some time has passed since the onset of pain.

4.8. Strengths and limitations

Strengths of this review includes the broad literature search and the use of diagnostic criteria that is in accordance with the generally recommended approach towards identifying patients with MTSS in a clinical setting (Winters et al., 2018). A downside to this is that relevant studies might have been excluded due to insufficient reporting, including studies that have been highly influential to our current understanding of MTSS. Indeed, the most common reason for exclusion from this study was that studies did not declare medial tibial tenderness spanning ≥ 5 cm along the posteromedial border.

Limitations of this study includes the lack of a duplicated literature search and duplicated risk of bias assessment of the included trials. To minimize bias, these processes should have been performed independently by two researchers, in which case disagreements should be settled by an independent third party. Other limitations include the small number of studies for each outcome, the overall lack of asymptomatic controls.

4.9. Recommendations for future research

Future biopsy and imaging studies on individuals with MTSS should consider including asymptomatic controls from the same cohort, and to control for clinical parameters that might influence the results, e.g., activity status and history, and symptom duration.

Also, the main reasons for exclusions in this review were that studies included individuals with various stress injuries and did not precent data for subgroups of stress injuries.(e.g., injuries in the anterior and medial tibial cortices, or MTSS and tibial stress fractures), and secondly, several studies were excluded because the articles did not report on tenderness or the span of such tenderness, even though this is a highly relevant clinical future for all stress injuries. Improving on the reporting of the articles would be beneficial for future systematic reviews on the topic of MTSS.

5. CONCLUSION

Abnormalities in the lower leg are frequently reported in individuals with MTSS, including periosteal edema along the anteromedial and posteromedial tibial cortex, tibial bone marrow edema, and abnormal scintigraphic uptake along the medial tibial border. Few studies have compared findings in symptomatic and asymptomatic legs, which make it difficult to assess whether these abnormalities relate to the pathology of MTSS or to some other unknown parameter, such as activity status and history. The limited body of evidence suggests that several of these abnormalities may represent normal adaptation to physical stresses, rather than MTSS. Imaging studies can be helpful in diagnosing concomitant pathology such as a tibial stress fracture or soft tissue pathology in the lower leg but is not necessary or appropriate in diagnosing MTSS. Future studies should

6. FUNDING

I received no funding for undertaking this review. I declare no conflict of interest related to this study.

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SUPPLEMENTARY MATERIAL

APPENDIX A: List of excluded studies

List of excluded studies	Main reason for exclusion
Abreu et al. (2007)	MTSS criteria not fulfilled ("*generally* reported diffuse tenderness"; not specifying length >5 cm; scintigraphy showed focal uptake in multiple patients)
Akiyama et al. (2016)	No relevant data for extraction.
Allen and Barnes (1986)	No relevant data for extraction.
Allen and Barnes (1986)	MTSS criteria not fulfilled (Not specified tenderness > 5 cm, not excluded stress fractures)
Batt et al. (1998)	Discrepancies in their data: multiple numbers was presented for the same outcome; no isolated results from symptomatic and asymptomatic limbs. The discrepancies are presented in Appendix B.
Beck et al. (2012)	Includes multiple tibial stress injuries
Beck, Rudolph, Matheson, Bergman, and Norling (2015)	Includes multiple tibial stress injuries
Dumont, Lamoureux, Danais, and Lamoureux (1982)	MTSS criteria not fulfilled (No mention of tenderness along the medial tibial border)
Franklyn, Oakes, Field, Wells, and Morgan (2008)	MTSS criteria not fulfilled (Inclusion criteria states "anteromedial OR posteromedial pain")
Fredericson et al. (1995)	Includes multiple tibial stress injuries
Gaeta et al. (2005)	Includes multiple tibial stress injuries
Gaeta et al. (2006)	MTSS criteria not fulfilled (Palpation did not produce discomfort in all patients.)
Gmachowska et al. (2018)	Includes multiple tibial stress injuries
Hadid et al. (2014)	Includes multiple tibial stress injuries
Johnell et al. (1982)	MTSS criteria not fulfilled (No mention of tenderness along the medial tibial border)
Jose, Fichter, and Clifford (2011)	Includes multiple tibial stress injuries
Lieberman and Hemingway (1980)	Case-report
Magnusson et al. (2001)	MTSS criteria not fulfilled (No mention of tenderness along the medial tibial border)
Magnusson, Ahlborg, Karlsson, Nyquist, and Karlsson (2003)	MTSS criteria not fulfilled (No mention of tenderness along the medial tibial border)
Malliaropoulos et al. (2022)	Includes multiple tibial stress injuries
Mammoto et al. (2012)	Includes multiple tibial stress injuries
Mann et al. (2020)	Not MTSS
Mattock, Steele, and Mickle (2019)	MTSS criteria not fulfilled (Unsatisfactory description of inclusion/exclusion criteria)
Mattock, Steele, and Mickle (2021)	No relevant data for extraction.

Michael and Holder (1985)	MTSS criteria not fulfilled (MTSS not clearly defined)
Milgrom et al. (1986)	Includes multiple tibial stress injuries Palpation did not produce discomfort in all patients. Not all cases were symptomatic to exertion
Moen et al. (2012)	No relevant data for extraction
Newsham-West, Lyons, and Milburn (2014)	Includes multiple tibial stress injuries
Nielsen, Hansen, Hølmer, and Dyrbye (1991)	Includes multiple tibial stress injuries
Nussbaum et al. (2019)	Includes multiple tibial stress injuries
Ohnishi (2015)	MTSS criteria not fulfilled (No mention of tenderness along the medial tibial border)
Reinking (2006)	No relevant data for extraction.
Palmer, Clasey, Hosey, and Mattacola (2013)	MTSS criteria not fulfilled (Includes patients with point tenderness, without MRI or scintigraphy to exclude stress fractures). Only 4/36 was physically assessed.
Stürznickel et al. (2021)	MTSS criteria not fulfilled (No mention of tenderness along the medial tibial border; not describing activity induced pain)
Swischuk and Jadhav (2014)	Includes multiple tibial stress injuries
Yates and White (2004)	No relevant data for extraction
Åkermark, Ljungdahl, and Johansson (1991)	No relevant data for extraction

APPENDIX B: Exclusion of Batt et al. (1998)

Batt et al. (1998) was excluded due to discrepancies in their data for MRI and TPBS-outcomes, and symptomatic and the number of symptomatic and asymptomatic lower legs.

There following discrepancies on the data for TPBS-findings were noted:

- (Section: Abstract) "In the 5/46 asymptomatic legs, 3/5 demonstrated uptake on bone scan …"
- (Section: Results) "Of the five asymptomatic legs, four had abnormal findings on both TPBS (grades 1a x 2, 1b and 2) … "
- (Section: Discussion) "The remaining four had abnormal findings on both MRI (grade 2) and TPBS (grades 1 x 4)."
- (Section: Results) In Table 2, only 3 individuals were graded as asymptomatic (clinical -ve), of which 2 had findings on TPBS, and 1 had no findings (TPBS -ve).
- In the description for Table 3, it says that the percentages were related to the symptomatic legs, which is 41 legs. However, the same percentages were presented in-text as a percentage of 46 legs, which is the total legs for symptomatic + asymptomatic legs.

Discrepancies in the data on MRI-findings

- (Section: Results) "Based on the classification of Fredericson et al., 8 normal scan were reported in 46 legs".
- (Section: Results) "Forty-six abnormal MRI foci were seen in 35 legs, with a distribution given in Table 3".
- (Section: Results) In Table 2, only 3/46 individuals were graded as asymptomatic (clinical -ve), of which 2 had findings on MRI, and 1/46 had no findings (TPBS -ve).
- In the description for Table 3, it says that the percentages were related to the symptomatic legs, which is 41 legs. However, the same percentages were presented in-text as a percentage of 46 legs, which is the total legs for symptomatic + asymptomatic legs.

APPENDIX C: Coding Manual for the Newcastle-Ottawa Quality Assessment Form for Case-Control Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection (maximum of 4 stars)

1. Is the Case Definition Adequate?
   Description: Case definition: Exercise induced medial tibial pain, with tenderness along the posteromedial border > 5 cm. If the study did not state that the span of tenderness was >5 cm, stress fractures were excluded by means of MRI or TPBS.
   a) Yes, with independent validation (★)
   b) Yes, e.g., record linkage or based on self-reports
   MTSS determined by another source, e.g., record linkage or self-reports.
   c) No description

2. Representativeness of the Cases
   Description: Representativeness to the general population of MTSS patients.
   a) Consecutive or obviously representative series of cases (★)
   Description: E.g., all consecutive cases with MTSS over a defined period, across all athletic fields in a high school, in a defined hospital or group of hospitals, from respondent driven sampling, mixed-methods, time-location-sampling, or an appropriate sample of those cases (e.g., random sample).
   b) Potential for selection biases or not stated
   Not consecutive or obviously representative series of cases, or not stated. Non-representative series of cases include sub-populations of MTSS-patients, such as limiting inclusion to patients with a specific foot type, athletes with a specific amount of running experience, or requiring a certain degree of symptom duration or severity.

3. Selection of Controls
   Description: This item assesses whether the control series used in the study is derived

from the same population as the cases and essentially would have been cases had the outcome been present.

a) Community controls (★)

b) Hospital controls

c) No description

4. Definition of Controls

   a) No history of disease (endpoint) (★)

   Description: If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded. For this review, a point is awarded if controls have no history of activity related leg pain / MTSS in the last 6 months.

   b) No description of source

Comparability (maximum of 2 stars)

1. Comparability of cases and controls on the basis of the design or analysis

   Description: A maximum of 2 stars can be allotted in this category. Either cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment. There may be multiple ratings for this item for different categories of exposure (e.g., ver vs. never, current vs. previous or never).

   a. Study controls for hours of weight-bearing exercise per day/week/month. (★)

   Description: This factor was chosen as the main factor due to it being a likely confounder for the outcomes of interest, e.g., periosteal edema, bone marrow edema, and osteocyte activity.

   b. Study controls for any additional factor (★)

   Description: Additional factors of interest: Age, gender, previous history of MTSS.

Exposure (maximum of 3 stars)

Description: For this systematic review, exposure equals having the outcomes of interest, e.g., tibial periosteal edema, tibial bone marrow edema, or microdamage in the cortical tibial bone.

1. Ascertainment of Exposure
    a) Secure record (e.g., surgical records) (★)
    b) Structured interview were blind to case/control status (★)
    c) Interview not blinded to case/control status
    d) Written self-report or medical record only
    e) No description

2. Same method of ascertainment for cases and controls?
    a) Yes (★)
    b) No

3. Non-response rate

   Description: Withdrawal from the study or errors during sampling.
    a) Same rate for both groups (★)
    b) Non-respondens described
    c) Rate different and no designation

APPENDIX D: Coding Manual for the Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection (maximum of 4 stars)

1. Representativeness of the exposed cohort
   Description: Representativeness of the cohort to the general population of MTSS patients.
   a) Truly representative (★)
      Description: E.g., all consecutive cases with MTSS over a defined period, across all athletic fields, in a defined hospital or group of hospitals, from respondent driven sampling, mixed-methods, time-location-sampling, or an appropriate sample of those cases (e.g., random sample).
   b) Somewhat representative (★)
      E.g., clinic-based sample, or from a specific high-school
   c) Selected group of users, e.g., nurses, volunteers
      Description: Other examples might include one sports team or one type of sport.
   d) No description of the derivation of the cohort

2. Selection of the non-exposed cohort
   a) Drawn from the same community as the exposed cohort (★)
   b) Drawn from a different source
   c) No description of the derivation of the non-exposed cohort

3. Ascertainment of exposure
   Description: Exposure = having the outcomes of interest. E.g., periosteal edema, bone marrow edema, or microdamage in bone. Is bone marrow edema (exposure) a reason for having medial tibial pain (becoming a case)? Or do you find bone marrow edema in asymptomatic individuals, so that it is not associated with MTSS?
   a) Secure record (e.g., surgical record) (★)

b) Structured interview (★)

Description: Including physical examination.

c) Written self-report

d) No description

4. <u>Demonstration that outcome of interest was not present at start of study</u>

Description: The same biopsy or medical imaging study was taken upon inclusion in the study, and results are available or compared with follow-up results.

a) Yes (★)

b) No

Comparability (maximum of 2 stars)

1. <u>Comparability of cohorts on the basis of the design or analysis controlled for confounders</u>

Description: A maximum of 2 stars can be allotted in this category. Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment. There may be multiple ratings for this item for different categories of exposure (e.g., ever vs. never, current vs. previous or never).

a) Study controls for previous MTSS (★)

Description: Hours of weight-bearing exercise (e.g. walking, running, skiing, dancing, gymnastics) per day/week/month. This factor was chosen as the main factor due to it being a likely confounder for the outcomes of interest, e.g., periosteal edema, bone marrow edema, and osteocyte activity.

b) Study controls for any additional factor (★

Description: Age, gender, previous history of MTSS.

Outcome (maximum of 3 stars)

1. Assessment of outcome

   Description: For some outcomes (e.g., fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to x-rays would be required. Outcomes for this study includes, but is not limited to, tibial periosteal edema, tibial bone marrow edema, and tendinous abnormalities in the lower leg.

   a) Independent blind assessment (★)

      Description: Stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.).

   b) Record linkage (★)

      Description: MTSS determined by another source, e.g., record linkage (connecting data across different data sources).

   c) Self-report

   d) No description

      Description: Or independent non-blinded assessment.

2. Was follow-up long enough for outcomes to occur?

   Description: Most cases of MTSS occur within the first 6 weeks of increased physical activity, and therefore the same time will be used for this criterion (≥ 6 weeks).

   a) Yes (★)

   b) No

3. Adequacy of follow-up of cohorts

   Description: This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.

   a) Complete follow up - all subject accounted for (★)

   b) Subjects lost to follow up unlikely to introduce bias - small number lost - ≥ 85 % follow-up, or description provided of those lost) (★)

   c) Follow up rate < 85 % and no description of those lost

   d) No statement

APPENDIX E: Coding Manual for the Newcastle-Ottawa Quality Assessment Form Adapted for Cross-Sectional Studies

Selection (maximum of 4 stars)

1. Representativeness of the sample

   Description: Representativeness to the general population of MTSS patients

   a) Truly representative of the average in the target population (★) (all subjects or random sampling). Target population are all individuals with exercise-induced pain

      Description: E.g., all consecutive cases with MTSS over a defined period, across all athletic fields, in a defined hospital or group of hospitals, from respondent driven sampling, mixed-methods, time-location-sampling, or an appropriate sample of those cases (e.g., random sample).

   b) Somewhat representative (★)

      E.g., clinic-based sample, or from a specific high-school.

   c) Selected group of users, e.g., nurses, volunteers

      Description: Other examples might include one sports team or one type of sport.

   a) No description of the sampling strategy

2. Sample size

   a) Justified and satisfactory (★)

      Description: Sample size has been pre-determined based on objective criteria.

   b) Not justified

3. Non-respondents

   a) Comparability between respondents and non-respondent's characteristics is established, and the response rate is satisfactory (★)

   a) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory

   b) No description of the response rate or the characteristics of the responders and the non-responders

4. Ascertainment of the exposure (risk factor):
   Description: Exposure = Having MTSS, as a risk factor for getting the outcome (periosteal edema, bone marrow edema, etc.).
   a) Validated measurement tool (★). Clinical examination by criteria by (Yates & White, 2004) is frequently being used as the very definition of this syndrome. Clinical examination confirming exercise-induced pain on the inside of the lower leg that is exacerbated by activity, and pain on palpation of the medial border of the tibia. If pain on palpation does not span ≥ 5 consecutive centimeters or is not reported, stress fractures must have been ruled out using MRI or DXA.
   b) Non-validated measurement tool, but the tool is available or described (★)
   a) No description of the measurement tool

Comparability (maximum of 2 stars)

1. The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled
   a) The study controls for the most important factor (★)
      Description: Symptom duration.
   b) The study control for any additional factor (★)
      Desctiption: Hours of weight-bearing exercise, age, gender, previous history of MTSS.

Outcome (maximum of 2 stars)

1. Assessment of the outcome
   Description: E.g., tibial periosteal edema, tibial bone marrow edema, or tendinous abnormalities in the lower leg.
   a) Independent blind assessment (★).
      Description: Confirmation of the outcome by reference to secure records (MRI, laboratory tests, medical/hospital records).
   b) Independent non-blinded assessment using validated measurement tools, or record linkage (★)
      Description: Record linkage = Connecting data across different data sources. In

this modified version of the NOS, blind assessment no longer is needed to earn a star. The reason for this, is an assumption that the knowledge about the patient's status (MTSS) does not have the same potential to introduce bias to the assessment, as it would have it the population consisted of symptomatic and asymptomatic individuals. A bias then, would be linked to certain characteristics of the individuals with MTSS, such as symptom duration, activity level, and so forth. Reference to an MRI assessment report.is considered to have a substantially higher value than self-report, and a star is therefore awarded.

c) Self -report. Some modified versions give one star for self-reports. As the outcomes of interest are findings on imaging studies or biopsies, this item will not be awarded with a star.

d) No description

2. Statistical test

   a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p-value) (★)

   b) The statistical test is not appropriate, not described, or incomplete