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ORIGINAL ARTICLE

Microcrack-associated bone remodeling is rarely observed in biopsies from athletes with medial tibial stress syndrome

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Abstract

The pathology of medial tibial stress syndrome (MTSS) is unknown. Studies suggest that MTSS is a bony overload injury, but histological evidence is sparse. The presence of microdamage, and its potential association with targeted remodeling, could provide evidence for the pathogenesis of MTSS. Understanding the pathology underlying MTSS could contribute to effective preventative and therapeutic interventions for MTSS. Our aim was to retrospectively evaluate biopsies, previously taken from the painful area in athletes with MTSS, for the presence of linear microcracks, diffuse microdamage and remodeling. Biopsies, previously taken from athletes with MTSS, were evaluated at the Department of Anatomy and Cell Biology at the Indiana University. After preparing the specimens by en bloc staining, one investigator evaluated the presence of linear microcracks, diffuse microdamage and remodeling in the specimens. A total of six biopsies were evaluated for the presence of microdamage and remodeling. Linear microcracks were found in 4 out of 6 biopsies. Cracking in one of these specimens was artefactual due to the biopsy procedure. No diffuse microdamage was seen in any of the specimens, and only one potential remodeling front in association with the microcracks. We found only linear microcracks in vivo in biopsies taken from the painful area in 50% of the athletes with MTSS, consistent with the relationship between linear cracks and fatigue-associated overloading of bone. The nearly universal absence of a repair reaction was notable. This suggests that unrepaired microdamage accumulation may underlie the pathophysiological basis for MTSS in athletes.

Keywords Medial tibial stress syndrome · Shin splints · Pathology · Bone · Microdamage

Introduction

Medial tibial stress syndrome (MTSS) is a frequent sports overuse injury found in running and jumping athletes [1, 2]. MTSS is defined as exercise-induced pain along the distal 2/3 the posteromedial tibial border with pain present to palpation over ≥ 5 cm. [3] Historically, the term 'shin splints' was used for exercise-induced pain on the inside of the lower leg. However, MTSS, tibial stress fractures and compartment syndromes are now fully acknowledged as clinically identifiable entities. A recent study showed that MTSS can be diagnosed reliably based on history and physical examination [4].

Strong evidence for any intervention in the treatment of MTSS is lacking, however, the available studies suggest that it takes a long time for athletes to recover from MTSS [5, 6]. The current thinking regarding the pathology of MTSS is that it is either a crural fasciopathy, a tibial bone overload injury or a combination of these two [7, 8]. The limited

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understanding of the pathology of MTSS may be one of the causes for poor treatment outcomes. A better understanding about which structures are affected in MTSS could improve targeting new prevention and treatment interventions for athletes with MTSS.

The bone overload theory, a pathogenic process similar to stress fractures, has been frequently cited in the past years. Moen linked insights from Frost's Utah paradigm to MTSS [9–11]. In this paradigm, bone strains that exceed the modeling threshold cause microdamage. Under most physiological circumstances, microdamage stimulates remodeling and strengthens the bone. However, repetitive or large strains may induce microdamage accumulation that increases skeletal fragility and the susceptibility to injury, in particular in the absence of a remodeling response [12].

Studies in mice found that repeated bending leads to adaptation of the tibial bone, predominantly at sites where strains are highest: the junction of the mid- and distal 1/3 of the tibia, where MTSS commonly occurs [13, 14]. Moreover, studies in rabbits show that in this region high shear stresses occur, which predisposes this region to injury [15, 16]. The presence of microdamage in tibial biopsies taken from the painful area in athletes with MTSS would support the theory that bone microdamage is a component of the pathophysiology of MTSS. Therefore, our aim was to retrospectively evaluate bone biopsies taken from the painful area in athletes with MTSS and investigate these for the presence of microdamage.

Materials and methods

Design

Retrospective case series.

Procedure

Between 2011 and 2013 tibial bone biopsies were taken from 4 athletes in Berman Clinics, The Netherlands, and from 2 athletes at the University Hospital Leuven, Belgium. The athletes had persistent MTSS that was not resolved with multiple conservative treatment interventions. For this group of patients, fasciotomy and periosteal stripping is usually offered, and was performed in all athletes in our sample. Tibial bone biopsies were taken during surgery as part of usual care; these are taken for evaluation of bone quality by a pathologist. Patients provided written informed consent for the procedure and were informed about the risks associated with surgery.

Instead of the usual analysis at the department, bone biopsies were shipped to the Department of Anatomy and Cell Biology at the Indiana University School of Medicine, USA. There they were prepared, imaged and evaluated for the presence of microcracks and diffuse microdamage and remodeling. All athletes received post-surgery rehabilitation consisting of rest and gradual loading under supervision of a physiotherapist. No approval for this retrospective analysis was sought from a medical ethical committee; retrospective studies handling data anonymously do not fall within the Medical Research Involving Human Subjects Act in The Netherlands and Belgium [17–19].

Athletes with MTSS

In each centre an experienced physician (MM, HVDH and JB) made the diagnosis of MTSS, following a standardized history and physical examination [4]. In short, MTSS was diagnosed if exercise-induced pain was present along the medial border and the pain could be provoked upon palpation over at least 5 cm. This approach accounts for differentiating between the various lower leg injuries, including the most common, MTSS, tibial stress fractures and chronic exertional compartment syndrome. Athletes' demographic data were obtained retrospectively from medical records (gender, age, duration of symptoms prior to operation, side of pain, and side of surgery/biopsy).

Harvesting tibial bone biopsies

Biopsies were harvested from the medial tibial border during fasciotomy/periosteal stripping. Longitudinal fasciotomy and periosteal stripping were performed under general anaesthesia in all athletes, following the procedures described by Yates et al. [20].

A 5 mm osteotome was used to harvest a 2–3 mm square bone biopsy from the middle point of the painful area along the medial aspects of the tibia. After taking the biopsies, they were packaged in sterile conditions on dry swab and shipped to the Department of Anatomy and Cell Biology at the Indiana University School of Medicine, USA.

Preparing specimens

Biopsies were evaluated at the Department of Anatomy and Cell Biology at the Indiana University School of Medicine, USA. Researchers of this department (DB and KCW) are experts in the field of bone microdamage and previously performed a large number of studies in this field. One investigator (KCW) prepared the samples for microdamage analysis. The specimens were stained en bloc with basic fuchsin following the approach of Burr and Hooser [21]. The specimens were dehydrated through a graded series of ethanols (80, 95, 100%, two changes each) containing 1% basic fuchsin. Each dehydration/staining step was done under vacuum for 1 h. The specimens were then infiltrated

with unpolymerized methyl methacrylate (MMA) for 24 h under vacuum and then infiltrated with a mixture of unpolymerized MMA plus a softener (dibutyl phthalate; 4%) for an additional week, also under vacuum. Since basic fuchsin is not miscible with MMA, the dye is trapped in any void within the bone tissue (e.g., vascular channels, lacunae, canaliculi, as well as microcracks) and thus rendered visible by both brightfield and ultraviolet fluorescence microscopy. Following infiltration, a catalyst was added to the infiltration media and the MMA was permitted to polymerize at room temperature.

Following polymerization the blocks were shaped for sectioning on a diamond wire saw, and 100 µm thick sections (i.e., 3 sections for each biopsy) were made from the middle of the cores. The sections were washed, dried and mounted onto glass slides using a UV safe resin-based mounting medium (Eukitt) [21].

Imaging biopsies and microdamage evaluation

Photomicrographs were collected on a Leica DM 3000 microscope using Leica Application Suite (version 4.1.0) software. Microdamage can be differentiated into microcracks, diffuse microdamage and trabecular microfractures. Linear microcracks are discrete cracks in the bone matrix, with linear lengths in cross-section of 40–100 µm. The crack itself is easily visible with brightfield microscopy, and is repaired via normal remodeling processes. Diffuse damage represents regions of very small cracks (1–3 µm in cross-section). They are often only observable as regions of more intense staining on specimens stained en bloc with basic fuchsin. They can either be repaired by remodeling or in some cases by direct physico-chemical mineral deposition [22]. Microfractures, on the other hand, are complete fractures of trabecular struts that heal via normal fracture healing processes (i.e., endochondral ossification). More complete descriptions of these different types of microdamage can be found in Burr [23]. Images were reviewed for the presence of microcracks, diffuse microdamage and associated remodeling by one investigator (DBB). Diffuse microdamage appears as a focal, but diffuse area of increased staining. In contrast, linear microcracks appear as sharply defined lines with edges that are more deeply stained [12]. Remodeling was identified by the presence of a resorption space cutting front, with the presence of Howship's lacunae. If this front were within 250 µm of an area of damage, it would be considered associated with the damage, in accordance with our previous convention [24–26]. For each section, we labelled diffuse microdamage, microcracks and remodeling as present or absent.

Results

We provide demographic information for all six operated athletes in Table 1. Tibial bone biopsies were taken from 5 females and 1 male athlete. Their age ranged from 16 to 29 on the day of harvesting the biopsy.

Diffuse microdamage, linear microcracks and remodeling

We evaluated 3 sections of each specimen (total $N = 18$) for the presence of diffuse microdamage, microcracks and remodeling. Table 2 provides an overview. None of the specimens showed diffuse microdamage whereas linear microcracks were seen in several specimens.

We found a small longitudinal/shear crack running at 45° in the first of 3 sections of specimen 1. No cracks were seen in the other two sections. We did not see any cracks in the sections of specimen 2. We observed a shear crack in the second section of specimen 3 (Fig. 1). The other two sections of specimen 3 could not be evaluated due to much splitting and cracking likely due to the biopsy harvest.

Table 1 Demographic information for each athlete

Variable	Athlete 1	Athlete 2	Athlete 3	Athlete 4	Athlete 5	Athlete 6
Sex	Female	Female	Female	Female	Male	Female
Age in years	26	29	19	18	28	16
Sport	Hockey	Dance	Athletics	Dance	Tennis	Athletics
Duration of symptoms in years	2.5	Multiple years	3	1	1.5	3
Affected leg(s)	R > L	R + L	R + L	R > L	R	R + L
Leg biopsy analysed	R	R	R	R	R	R
Status at follow-up 1 year	Unknown Note: pain free after 3 months	Returned to sport	Pain in ADL	Pain in ADL	Returned to sport	Pain in ADL
Adverse effects due to surgery or biopsy taking	None	None	None	None	None	None

R right, *L* left, *ADL* activities of daily living

Table 2 Microdamage and remodeling in athletes' tibial bone biopsies

Athlete	Biopsy section	Diffuse Mxd	Linear microcracks	Crack type	Remodeling adjacent to crack
1	1	No	Yes	Longitudinal/shear	Absent
	2	No	No		
	3	No	No		
2	1–3	No	No		NA
3	1	No	Yes/artefact		Absent
	2	No	Yes	Shear	May be present
	3	No	Yes/artefact		Absent
4	1	No	Yes	Transverse	Absent
	2	No	Yes	Transverse	Absent
	3	No	Yes	Longitudinal	Absent
5	1	No	Yes/may be artefact	Longitudinal	Absent
	2	No	Yes/may be artefact	Longitudinal	Absent
	3	No	Yes/may be artefact	Longitudinal	Absent
6	1–3	No	No		NA

Mxd microdamage, *NA* not applicable

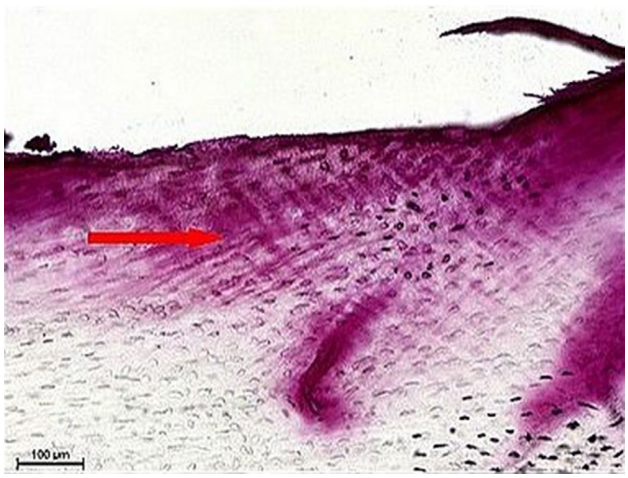

Fig. 1 Cross-hatched microdamage, indicative of multiple shear microcracks caused by compression, in a biopsy taken from the medial tibial border, the painful MTSS area (biopsy section 2 of specimen 3) [36]

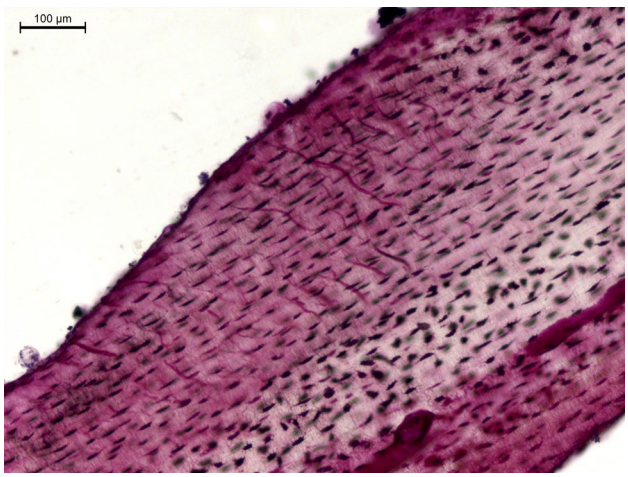

Fig. 2 Transverse cracks in a biopsy taken from the medial tibial border, the painful MTSS area (biopsy section 2 of specimen 4)

Microcracks were seen commonly in specimen 4. Large transverse microcracks were found in biopsy section 1 and biopsy section 2 from this specimen (Fig. 2). Two large longitudinal cracks were observed in specimen 3 (Fig. 3). Specimen 5 had multiple pieces and a lot of damage (longitudinal splits), most likely due to the biopsy harvest. None of the sections in specimen 6 showed microcracks.

Remodeling fronts were not observed near microcracks in those specimens where microcracks were present, except for one putative cutting front coming from the periosteal surface in specimen 3.

Discussion

This is, to the best of our knowledge, the first study to evaluate MTSS athletes' tibial bone for the presence of diffuse microdamage, microcracks and remodeling. We retrospectively analysed 6 bone biopsies taken upon surgery from the painful MTSS area and evaluated these specimens for the presence of diffuse microdamage, microcracks and remodeling. The photomicrographs showed the presence of microcracks in 4 out of 6 biopsies (67%). The damage in specimen 5 may be artefact; due to harvesting the specimens. Besides the presence of linear microcracks

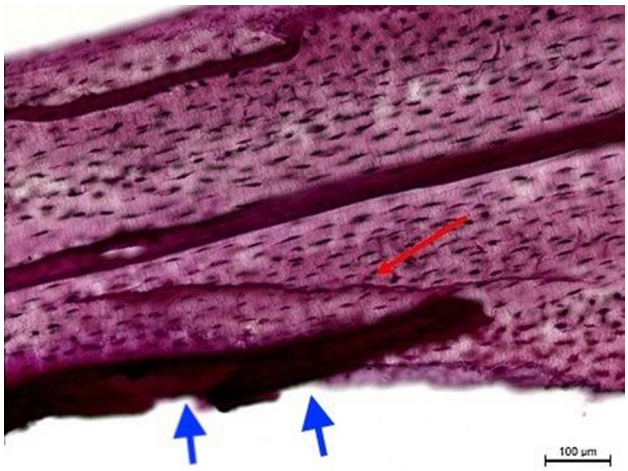

Fig. 3 Red arrow points at a large longitudinal crack in a biopsy taken from the medial tibial border, the painful MTSS area (biopsy section 3 of specimen 4). There appears to be a remodeling front entering from the periosteal surface in association with a large linear microcrack (blue arrows)

in athletes with MTSS, the most notable observations were the absence of any diffuse microdamage in these biopsies, and the mostly absent remodeling reaction to the presence of damage. There may be one case in which there was a remodeling reaction from the periosteal surface adjacent to a large linear microcrack. Our study provides preliminary histological evidence for the presence of linear microcracks in athletes with MTSS, usually without an observable repair reaction.

Microdamage: physiological or pathological?

Microdamage contributes to two related but contradictory processes: it can induce remodeling to strengthen bone (i.e., physiology), but if microdamage accumulates without repair, it also can induce injury (i.e., pathology) [12]. Mori et al. [12] described the mechanisms through which accumulation of microdamage could occur. They stipulated that accumulation of microdamage may occur through an increased microdamage production or through an impaired microdamage repair pathway [12]. Speculatively, increased microdamage production in athletes with MTSS would suggest a lowered level of resistance to loading, higher strains or altered strain distribution in the tibia, an impaired repair mechanism, or a combination of these factors in athletes with MTSS.

In this regard, the rarity of remodeling fronts associated with the linear microcracks from these biopsies may provide clues to the pathogenesis of MTSS. It is now reasonably well accepted that the introduction of microcracks to bone tissue will stimulate a targeted repair reaction [24, 25, 27–31]. It is also known now that this repair reaction is consequent to osteocyte apoptosis [32, 33], and signals to adjacent osteocytes to increase secretion of receptor activator of nuclear factor-kappa B ligand (RANKL), a protein that regulates bone remodeling [34, 35]. Thus, the infrequency of a repair reaction in athletes who sustain MTSS may suggest an inhibition or dysfunction of the cell-signaling/detection system that prevents the bone from mounting a remodeling response.

Previous research suggests that an artificial suppression of remodeling in a physically active population may be associated with slightly higher risk of stress injury. When treated with a bisphosphonate during a 15 week basic training program, the incidence of tibial stress fractures in military recruits increased by 63% [36]. This suggests that the failure to repair microdamage could ultimately lead to MTSS.

Frost's Mechanostat theory posits that increased strain, at least up to the load levels that will generate significant amounts of microdamage, suppresses intracortical bone remodeling [37, 38]. Given this, we could hypothesize that the pathogenic basis of stress-related injuries in active athletes involves both an overload of the bone that creates an additional microdamage burden, but a suppression of the repair process caused by the higher levels of strain associated with activity. In the sample population reported in this study, both of these conditions occur: microdamage is present, but there is no evidence for repair.

Microcracks and types of stress in athletes with MTSS

Wolfram et al. [39] studied tension, compression and torsion loading and their effect on microcrack characteristics. They found that tension forces led to transverse cracks, perpendicular to the loading axis; compression yielded shear cracks; and, torsion led to longitudinal cracks [39]. In our study we found all these crack types suggesting that tension, torsion and compression forces play a role in the onset of microcracks in athletes with MTSS. However, others have found that diffuse damage is more common on tensile cortices than on compressive ones [40–42]. The failure to find any diffuse damage in these biopsy specimens suggests that shear stresses, which are produced by both compression and torsional loading, may play a more dominant role in the onset of MTSS.

The absence of diffuse damage in our young population is particularly remarkable because bone from younger individuals is more likely to accumulate diffuse damage than linear microcracks [43]. The importance of this is underscored by the relationship between linear microcracks and fatigue life. It has been shown that linear microcracks dissipate less energy than diffuse damage, and therefore are associated with a greater risk of earlier failure from fatigue processes [44, 45]. The presence of only linear miocrocracks in this sample with MTSS is consistent with this relationship

between linear microcracks and fatigue-associated bone overloading injuries.

We are aware of only one report that described microcracks in a similar population, in a patient with a tibial stress fracture [12]. This case showed diffuse microdamage with histological observations of bone repair [12]. It seems evident that a larger population is needed to elucidate the type of cracks in athletes with MTSS. Such information could also improve the understanding of how MTSS and tibial stress fractures may differ in terms of bone stress and damage.

Clinical implications

A graded loading program is the cornerstone of rehabilitation in athletes with MTSS [5, 46–50]. Our findings suggest that loading the tibial bone to induce remodeling is unlikely to be beneficial for at least a subset of athletes with MTSS; those that have a long duration of pain and for whom conservative interventions have failed. Although we know from the studies of Milgrom et al. [36] that suppression of remodeling is not likely to be beneficial in preventing stress-related injuries [36], it is possible that interventions that stimulate tibial bone remodeling, such as parathyroid hormone, i.e., teriparatide, or parathyroid hormone-related protein, i.e., abaloparatide, could be effective in the prevention and treatment of MTSS.

Study limitations

This study provides some preliminary evidence that MTSS is a bony overload injury. However, this study also has some limitations. First, this is not a consecutive case series and the sample is small. Transferring and evaluating bone biopsies is expensive and only limited resources (our own money, time and efforts) were available. Therefore, we could not evaluate a larger number of specimens.

Some of the sections/specimens (specimens no. 3 and 5) exhibited too much damage due to harvesting the biopsies. Therefore, not all available specimens could be evaluated. Finally, there was no control group with active athletes. This limits the ability to compare our findings with non-injured athletes and make a more robust association between microcracks, the absence of remodeling and MTSS. Future studies, taking control tibial bone biopsies from active, non-injured athletes, could elucidate the relation between microcracks, remodeling and MTSS.

Conclusions

Microcracks are present in biopsies taken from the painful area in athletes with MTSS, suggesting that MTSS stems from overloading the bone. However, this effect could be exacerbated by the failure of a repair response in those individuals that eventually present with MTSS; remodeling around microcracks was almost never observed in this sample. The morphology of the cracks, and the prevalence of linear microcracks over diffuse damage even in this younger population, suggest that the incidence of MTSS may be associated with activities that create greater shear stress in bone. Our findings suggest that loading activities are unlikely to be beneficial for athletes with a prolonged duration of MTSS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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