Review Article

Stress Fracture: A Review of the Pathophysiology, Epidemiology and Management Options

Jagannath Sharma[1-3]* and R Heagerty[1]

[1]Medical Centre Defence Primary Healthcare, Infantry Training Centre Catterick Garrison, UK
[2]School of Health and Social Care, Teesside University, UK
[3]251 Medical Squadron 3 Medical Regiment Sunderland, UK

*Corresponding author

Dr Jagannath Sharma, PhD MCSP RAMC, Superintendent Physiotherapist, Medical Centre Defence Primary Healthcare, Infantry Training Centre Catterick Garrison, DL9 3PS, North Yorkshire, UK, Tel: 44-1748-872-916; Email: Jagannath.sharma706@mod.uk; Jagannath.sharma13@gmail.com

Abstract

Stress fractures of the lower limbs are commonly observed in both military and physically active civilian populations. They represent a breach in the bones capacity to tolerate repetitively applied mechanical loading such that repair is exceeded by structural damage resulting in localized tenderness and pain. Prevention of stress fracture should remain the priority however once diagnosed, effective management, born from a thorough understanding of the pathophysiological inter-actions, is required in order to expedite healing and increase the likelihood of a return to pre injury status. Multi-factorial in causation, they are considered as the physiological consequence of a dynamic interplay between both extrinsic and intrinsic factors. Although stress fractures usually heal without complication, restoration of bone integrity is only part of the rehabilitation process. Comprehensive management should include assessment and consideration of the entire kinetic chain in order to return the injured individual to pre-morbid functional status. However, irrespective, high risk stress fractures are more likely to result in delayed union and as such require extended periods of reduced weight bearing followed by prolonged therapeutic rehabilitation. Description of pathophysiology, epidemiology as well as an overview of management perspectives will be considered in this paper.

INTRODUCTION

Stress fractures are a commonly observed sub-classification of overuse musculoskeletal injury (MSKI) and as such have drawn specific attention within athletes, ballet dancers and the military [1-9]. Although, reported in the pelvis, spine and less frequently in the upper limb, [7,9,10] as much as 80-90% of all stress fractures are observed in the lower limb with incidence rates reported to range from 0.7 to 20% across active populations [7,9-12].

It is well recognized that the pathogenesis of stress fracture is multifactorial in nature[13-19] however the precise mechanisms are yet to be confirmed and so remain theoretically proposed. However, the incremental rate of progression in both volume and intensity of high impact physical activity is a major determinant of these injuries [2,6]. Ultimately, these injuries represent a breach in the bones capacity to tolerate repetitively applied mechanical loading such that repair is exceeded by damage [1-6].

Recovery times vary from between 4 weeks to a year, with the anatomical site of injury considered to influence bone union [6,7,10]. High risk of non-union is associated with anatomical sites where blood supply is relatively less than those well perfused areas where local blood flow to the fracture site is abundant (Table 1) [6,7,20,21].

Stress fractures are considered to require some of the longest recovery times of all MSKI [9,22]. The management pathway to return performance orientated professionals such as athletes or military personnel to pre-injury levels is reported to range from three weeks to several months [2,7,9-10,22]. Requiring lengthy and careful management, these injuries have significant impact

Table 1: Average return to full weight bearing status both low risk and high risk of stress fracture.

Stress Fracture	Average return time to full weight bearing status (week)
Foot low risk Cuneiform fractures Cuboid fractures Calcaneal fractures Distal second to fifth metatarsals	4-6
Foot High risk Sesamoids The talus Navicular Fifth metatarsal	4-6
Lower leg Low risk Fractures of the fibula Tibial shaft- posteromedial cortex	2-4 6-8
Lower leg High risk Tibial shaft anterior cortex the medial malleolus	6-8
Femur Low risk Femoral neck medial cortex Femur shaft	4-8
Femur High risk Femoral neck superior cortex	4-6
Pubic low risk Ramus sacrum	7-12

on the individual, employer, coach and team and therefore have drawn considerable attention in the academic and clinical press.

Specifically within military populations these injuries are associated with significant morbidity, attrition, failure to complete training, failure to return to pre-injury level activity as well as increased likelihood of re-injury [2,9]. Days lost to work due to reduced duties impacts upon the numbers of deployable assets available to Commanders whilst the burdens on the medical chain along with associated financial implications are well recognised. Consequently, the impact on organizational effectiveness is far reaching both for military training establishments as well as for the wider military community. As potentially career and therefore life changing injuries they represent psychological and socio-economic challenges which are considered to have a negative impact on public health and to represent a strain on organizational efficiency [91,22].

The Professional, legal and moral responsibility to investigate causation, management and mitigation of these costly injuries is the property of both organisation and individual clinician. The purpose of this review is to present an overview of the pathogenesis, epidemiology and provide a brief overview of management perspectives.

Pathophysiology

The precise pathophysiological mechanisms involved with the development of stress fractures are not fully understood. Consequently, theoretical descriptions are proposed in the literature. Although schools of thought may differ when discussing the detailed physiological actions, the pragmatic application of science describes a breach of tissue homeostasis where structural capacity to withstand load is exceeded, where rate of repair is overcome by damage and where pain limits function.

Repetitive loading is considered to result in bone deformation the degree of which is described as bone strain. A conceptual and therefore unit less value it has been described in terms of micro-strain with arbitrary values offered to describe theoretical threshold values [1,6,11,22]. Ultimately, increase load is associated with increase strain which increasingly challenges the musculoskeletal system to disseminate the repetitive ground reaction forces through the kinetic chain. The ability for the musculoskeletal system to cope with the applied load is dependent upon the complex interplay of numerous internal and external factors all of which vary between individuals.

A basic understanding of the architecture, physiology and metabolism of bone is fundamental to an appreciation of the patho-physiology of stress fractures [23,24]. The mis-match between tissue tolerance and a externally applied load result from an imbalance in the interaction between bone remodeling (osteoblastogenesis and osteoclastogenesis activity) [22,25] and identifiable risk factors [27,28]. Basic illustrative microscopic structure of the bone is presented in Figure 1. At the microscopic level bone is described in two forms, woven and lamellar bone. Woven bone is immature, characterised by a randomly orientated matrix of collagen. Conversely, lamellar bone is mature in that it presents with an organized stress-oriented collagen profile, the mechanical properties of which are subject to change depending

on the direction, magnitude, frequency of the applied force [23,25].

Lamellar bone is subdivided into cortical and cancellous or trabecular bone. The former is described as a densely composed network of bone cells or osteons collectively referred to as the Haversian system. It is within the embedded Haversian canals, illustrated in Figure 1, that the neurovascular support network is contained and distributed to the bone. Unlike the slowly regenerating cortical bone, cancellous bone, is less dense (30 to 90 % porous) and as such has a fast turnover rate and is commonly found in the metaphysis while the slower regenerating cortical bone is found in the diaphysis of long bones [23,25].

Bone is constantly metabolising or replacing as a result of a balanced sequence of bone osteoclastogenesis and osteoblastogenesis [25]. Osteoclasts are the cells primarily responsible for osteoclastogenesis, and osteoblasts for osteoblastogenesis. Bone synthesis is regulated through the complex hormonal interactions [29] primarily between; Parathyroid hormone (PTH), calcitonin, growth hormone, thyroid hormone, oestrogen, and testosterone [30,25]. Others hormones which regulate both calcium and bone metabolism are endogenous and exogenous steroids, including vitamin D and glucocorticoids [30]. Bone structural formation is the consequences of osteoblastogenesis (e.g., PTH, vitamin D) promotion and osteoclastogenesis (e.g., calcitonin, oestrogen) inhibition. The inverse relationship is such that bone break-down typically suppresses osteoblastogenesis [25] whilst the resultant structural damage serves as a natural phenomenon to dissipate energy thereby preventing fracture and serving as a target for remodeling [1,2,5,21].

According to Wolff's law, bone remodeling is a positive structural adaptation in response to applied mechanical loading where the magnitude, rate and total volume of loading maintains balanced osteoblastic and osteoclastic activity or bone metabolism. The amount of newly laid bone is proportionate to the amount of applied stress [6].

The preservation of "skeletal mechanical competence" requires a balance between local micro-damage formation and efficient remodeling through osteoclastic removal of damaged
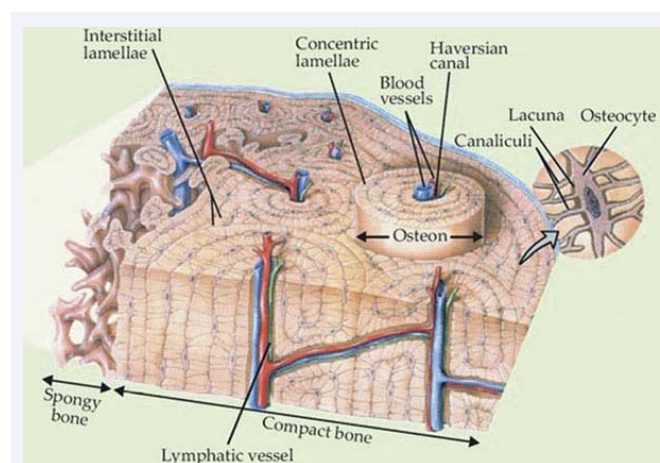

Figure 1 Basic structure of bone and Haversian system [25].

tissue [5]. Tissue homeostasis is maintained where remodeling occurs as quickly as damage occurs-otherwise known as positive adaptation. Positive bone adaptation will result in an increased capacity of the bone to tolerate greater subsequent strain and load such that the threshold for future micro-damage is raised. An appreciation of this is fundamental to progressive axial loading and the design of both rehabilitative and performance orientated exercise programs.

The exact mechanism is unknown, however two main theories are proposed across the literature. These are the piezoelectric charge theory and the Hueter-Volkmann law. The Piezoelectric theory suggests that tensile-sided strain produces electropositive forces that stimulate local osteoclastogenesis while compressive forces stimulate electronegative forces and osteoblastogeneis [5,22,30]. As a response to repeated mechanical stress the remodeling of bone results in an increase in volume on the compressed aspect [23]. However, the decreased bone mass on the tensile strained aspect may be as a result of a slower rate of remodeling and therefore perhaps renders the bone more susceptible to delayed union, non-union or re-fracture which may be of clinical consequence in terms of stress fracture classification, management and prevention [22]. The Hueter–Volkmann law describes a process of osteocalstic tunneling in which bone remodeling occurs in small packets of cells, where reabsorption is followed by neuro-vascularisation and the subsequent laying down of new osteoids [30].

The term "Stress fracture" is a descriptive reference for a range of overuse bone injuries which includes bone strain, stress reaction, and stress fracture (Figure 2) [2,13,22,31]. These injuries are considered to fall along a continuum ranging from bone strain to complete fracture. Stress responses are associated with increased bone turnover as observed with periosteal and marrow oedema whereas stress fractures result in structural fault lines observable on imaging [1]. The underlying cause of stress fracture is the inability of the remodeling process to sustain the physiological stress applied through repetitive mechanical loading [22,25] and is often associated with a relatively sudden increase in either or both intensity and duration of external loading [6]. Equally, if there is insufficient time between loading cycles for the newly replaced bone to adapt to a mechanical stimulus then further micro-damage may result [1,5].

The stress fracture represents a point in the continuum where a stress response to applied load starts as "silent micro-damage" (Figure 2). Insufficient healing of the micro-trauma develops into fatigue failure at a specific point which if not suitably managed progresses to create structural "cracking" in the bone [22,24]. Ground reaction forces (GRF) through the axial skeleton increase with both speed and load and are greatest through the peripheral joints of the lower limb.

Unsurprisingly, stress fractures occur most commonly in the lower limb, a consequence of repetitive high impact activities such as jogging, running or hopping [6-11]. Notably, 2-3 times bodyweight is accepted at the ankle/foot during walking, increasing to 4-6 times during jogging and as much as 8-12 times depending upon the speed and gait during running [2,32-34].

During these activities the musculoskeletal system is

Figure 2 Modified simple model for the continuum propagation of stress fracture [6,13,22].
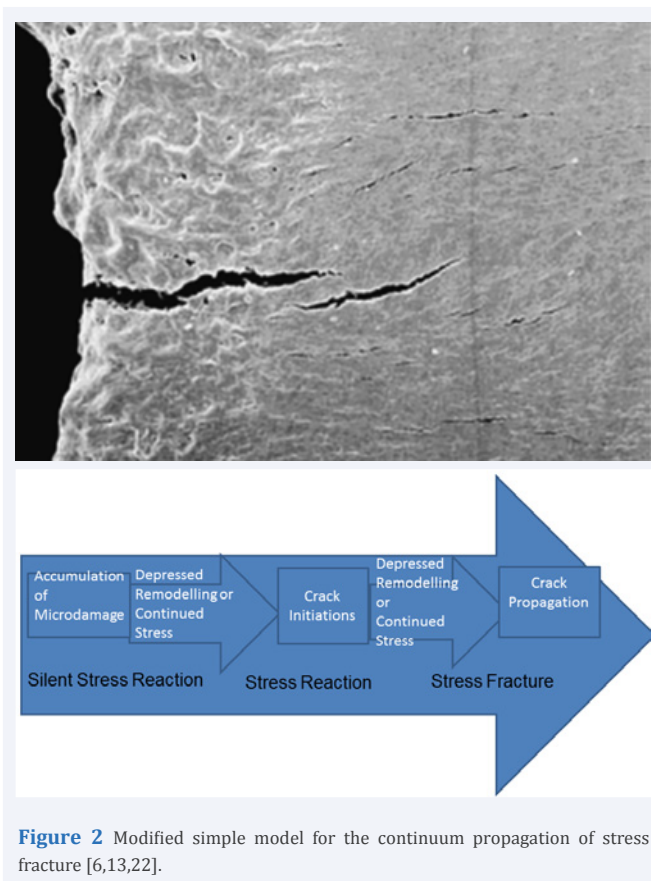
presented with the challenge of efficiently disseminating the GRF in such a way that osteoblastic activity is neither suppressed nor exceeded by osteoclastic activity. Whilst it is recognised that the neuro-muscular system has a critical role in the dissemination of GRF a sudden increase in repetitive high impact loading with or without insufficient rest between loading cycles will overcome the structural tolerance of the bone and create an environment conducive to the development of an adverse stress response. Under these circumstances the physiological trigger is pulled on the pathological continuum. Large volumes of high impact physical activity is a characteristic of both Military and sporting populations which in turn is reflected in the incidence rates within these groups [7,9].

As mentioned above, the neuro-muscular system also considered to play a key role in the pathophysiology of stress fractures [22,23,25]. It has been suggested that co-ordinated sequential muscle action may protect bone through recruitment and relaxation producing compression and lengthening activity that in turn may counteract the joint reaction forces resulting in reduced net shear stresses at the bone. It has been postulated that reduced absolute lower leg muscle strength and/or strength imbalances may increase the risk of stress fracture [23,35,24]. The potential protective contribution of the neuro-muscular system is likely to diminish with fatigue as well as during the execution of new exercises when muscle recruitment and firing may be less than optimal. Compromised neuro-muscular contribution is therefore associated with rapid increases in the volume of training, insufficient recovery between activity and

the undertaking of new physical tasks where the individual is yet to adapt to the physical requirements. These challenges to the neuro-muscular system have been identified in military training environments as well as during arduous selection tests or during competitive athletic training [18]. This may in part explain the vulnerability to bony stress injury in military recruits or similarly in athletes found over training or in those learning a new sport or skill. Progressive introduction of exercise intensity, volume, frequency and type as well as gait education is therefore fundamental to avoiding such injuries [2,9,34]. Although, not specifically addressed in this paper, the maturing adolescent musculoskeletal system in is particularly vulnerable to overload or over use training injuries of this nature.

Development of Stress fracture has also been attributed to oxidation deprivation, a bi-product of repeated mechanical compressive load [36] which leads to transient ischemia [37] in the weight-bearing bones. Ischemia, as a secondary effect of compressive axial loading is thought to stimulate the bone remodeling process, specifically by increasing osteoclastogenesis [21]. However, excessive compressive loading is thought to enhance osteoclastogenesis such that the bone is weakened and susceptible to stress response and ultimate fracture. This theory may in part explain the observation that a rapid and sustained increase in prolonged high impact lower limb activity renders individuals susceptible to increased risk of stress fracture [3,8,22]. In addition to the conditioning of the neuro-muscular system further factors identified in the literature considered to influence bone's response to load include the direction of the applied force, bone geometry, bone micro architecture as well as bone density [3,22].

Epidemiology

Although, the methods of calculating incidence varies between countries it is clear from the widely reported evidence that there is a higher incidence of stress fracture in females than in males [25]. In a mixed American cadets population 19.1 % of females presented with stress fractures compared to 5.7 % of males from the same cohort [26]. Knapik et al. [38], observed increased stress fracture incidence in female US military recruits (79.9/1,000) compared to males (19.3/1,000) whilst stress fracture incidence observed in the Israeli military highlighted a higher rate in females (23.9 %) compared to that in males (11.2 %). The total incidence rate of stress fractures in Finnish conscripts was described as 311/100,000 person- years (95 % CI: 277-345) with a female to male bone stress injury ratio of 9:2 [4]. A Review paper by John et al. [39], reported cumulative incidence during initial military training ranging from 0.85 to 6.9% for males and 3.4% to 21.0% for female recruits. Another study by Gam [40] found a female: male stress fracture relative ratio of 2.13 with an 11.2% incidence in males and 23.91% in females of the Israeli Defence Forces.

A prevalence of stress fractures in females has also been documented within the athletic population, most notably within long distance runners [42]. Notably, a prospective study in competitive cross-country and track runners found a higher incidence of these injuries in females (5.4%) as compared to their male counter parts (4.0%) [43].

Fracture location

Lower limb stress fractures are prevalent in physically active populations, accounting for up to 90% of all stress fractures and represents up to 20% of all sports related injury [41].

Most commonly presenting within the lower limb, a prevalence of these injuries has been reported in the tibia 23.6% [10], 25% [44], 71% [45] and 1.3% [2,9], the metatarsals (10-20%), tarsal navicular (17.6%), femur (6.65%) and pelvis (1.6%) [41,43].There also appears to be a difference in the distribution of stress fracture location with higher rates observed in females at the sacrum (female: male ratio = 51.1) [4], pelvis (22%), and femur (20%) [44].

Risk factors

Risk factor can broadly be sub-classified as intrinsic or extrinsic. Studies have identified low aerobic fitness [28,44], reduced tibial cross sectional area, low (trabecular and cortical) BMD as well as reduced cortical area of the posterior tibia as potential predisposing factors of fracture. In addition, smoking, previous stress fracture and adverse biomechanics are also recognised as significant contributory risk factors [15,14,19,22,25,28,46]. Similarly, both genetics and ethnicity are also considered influential in the causation of stress fracture, with lower rates seen in African-American populations compared to Caucasian and Asian groups [22,47]. Menstrual irregularity especially late-onset menarche appears to be a risk factor [11,22,26] whilst oestrogen functions contribute to increased bone mass by inhibiting osteoclastogenesis [46] some studies have shown that female athletes who are amenorrheicor oligomenorrheicare at increased risk of stress fracture [11,12,31,44, 48].

Nutritional factors or eating disorders which compromise nutritional intake are considered contributory to the pathophysiology of bone stress injury [22]. Calcium is a mineral building block while vitamin D contributes to both calcium homeostasis and optimises bone turnover and fundamental components of bone metabolism and contributes to favourable bone mineral density. Interestingly, Merkel et al. [7], found that female military recruits who have low iron anaemia are at an increased risk of developing stress fracture.

Extrinsic risk factors include the type of loading as well as the manner and environment in which it is applied. Abrupt increases in the volume, intensity and frequency of high impact physical activities such as running, jogging or hopping have been identified as presenting significant risk [3,6-8,11]. Conducting these forms of impact activity on hard or undulating surfaces as well as over ascending or descending gradients also represents increased risk. Inadequate or inappropriate recovery periods prevent micro cellular adaptation or maturation of newly replaced bone therefore rendering the cortex susceptible to injury [22]. Likewise muscular fatigue from excessive or pro-longed bouts of axial loading leaves the neuro-muscular system vulnerable to delayed or compromised muscle action such that the postulated protective mechanisms, such as the prevention of sheer forces through the tibia, are of less benefit. The altered action of fatigued muscles is likely to contribute to altered lower limb biomechanics and compromised lower limb dynamic

control thereby contributing to compromised mechanical efficiency and ability to disseminate GRF. Consequently, sleep deprivation has also been highlighted as potentially contributory to these potentially avoidable injuries [2,6,49]. Irrespective of fatigue levels lower limb gait pattern and cadence has also been suggested to play a role [9,22,28,32-34].The position, control and timing of foot contact in context to ankle, knee, hip and pelvic mechanics also warrants consideration.

Management of stress fracture

Although, it is not possible to prevent all injuries the management of choice for stress fractures should always be prevention. Prevention strategies may include the development of a screening tool based upon recognition and modification of confirmed risk factors [2]. Effective action may include targeted health promotion strategies including smoking cessation, provision of advice on appropriate dietary intake, avoidance of overtraining as well as the progressive introduction of carefully selected exercise and gait education [10,12,19,22,28].

A multi-factorial approach has been found to be the most effective strategy to the prevention and management of these injuries. This can be considered in four complementary domains. These are; the initial screening of musculoskeletal and health behaviors with subsequent modification of identifiable risk factors, progressive preventative rehabilitation conditioning exercises, complementary pharmacological support and potentially surgical intervention [50]. Essentially the aim of management should be preventative but once injury has been sustained the focus must be on the prevention of further damage, the promotion of optimal healing and the progressive restoration of function [9].

Nutrition

There is conflicting evidence to suggest that high level of calcium (1,500-2000 mg) and vitamin D supplementation (800-1000 IU) may prevent or even contribute to the prevention of stress fractures [51,52]. A randomised study by Lappe et al. [53-59], reported a 20% reduction in incidence following supplementation of 2,000mg elemental calcium in US female military recruits. However, despite these encouraging findings the literature offers conflicting evidence regarding dietary intake and development of stress fracture [22,31].

Pharmacological

Fracture healing and endochondral bone formation is understood to be regulated by bone morphologenic proteins as well as a fibroblast growth factor 2 [60-62] whilst parathyroid hormone, parathyroid hormone -related protein, Wnt proteins and Wnt signalling antagonists are also understood hold active roles in the regulation of bone formation [63-65]. Einhorn et al. [66], described both the timing and effect of pharmacological management on fracture healing. Specifically, parathyroid hormone and anti-sclerostin drugs have been used to accelerate fracture healing through facilitating callus growth, bone mass and mineral content which in turn contributes to increased stiffness and tensile strength. Similarly, bone morphogenetic protein has been used during the inflammatory phase to enhance coupled remodeling thereby again increasing both size and stiffness of

the callus. It is further postulated that these factors have positive influence on the regulation and interaction between different cell and tissue types during the skeletal healing process [66]. Although the pathophysiological mechanisms within the healing process remain unclear, bisphosphonates have also been used in the treatment of stress fractures [67]. Controversially, the lack of food and drug administration approval may be in part due to a suspected association with abnormal long-term bone deposition [68]. Therefore, further study is required before these drugs are utilised in the treatment of stress fracture.

Electrotherapy

Although controversial it has been proposed that the therapeutic application of electrotherapy may enhance fracture healing [69]. Management strategies incorporating the use of electromagnetic fields and low-intensity pulsed ultrasonography have been associated with up to an 80% success rate in the resolution of non-united fractures [70,71]. The analysis of results from in vitro studies has indicated that this may be due to the positive stimulation of protein synthesis in human fibroblasts [72] whilst notably in animal trial slow-intensity pulsed ultrasound has been reported to stimulate fracture healing [73,74]. In addition following randomized, double-blind, controlled clinical trial low intensity therapeutic ultra sound was found to accelerate the normal repair process for fractures of both the tibia and radius [75]. However, the quality of studies in this area is questionable and the findings are considered contradictory. Consequently, meaningful improvements in the stress fracture healing process have yet to be attributed to the application of low-intensity pulsed ultrasound [66-77].

Rehabilitation

Timelines for the return to full weight bearing status vary according to the site and severity (high or low risk) of the fracture (Table 1). The majority of these injuries are successfully managed conservatively [6,7,9.10] however, in order to optimise the management and outcome of the rehabilitation process it is imperative that clinicians have a sound appreciation of the healing process. Essentially, stress fracture healing processes are comparable with those observed in skeletal tissue repair [66] where catabolic follows anabolic activity. Anabolic activity involves increases in tissue volume whilst adjacent to the fracture line; vascular tissue along with cartilaginous callus will form. At the edges of the new cartilage, the periosteum swells and primary bone formation is initiated. Simultaneously, cartilage is generated and cells that go on to form the nascent blood vessels are recruited and differentiate within the surrounding muscles heath before supplying the new bone [78,79]. The cartilaginous extracellular matrix undergoes mineralization and the anabolic phase of fracture repair terminates with chondrocyte apoptosis [80,81]. Then the catabolic activities predominate and are characterized by a reduction in the volume of callus tissues and cartilage reabsorption whilst specific anabolic processes continue. Secondary bone formation is initiated as the cartilage is reabsorbed and primary angiogenesis continues as the nascent bone tissues replace the cartilage. Subsequently, when bone remodeling begins, the first mineralized matrix produced during primary bone formation is reabsorbed by osteoclasts

before the secondary bone, laid down during the period of cartilage reabsorption, is then also reabsorbed. The prolonged reabsorption of callus is characterized by coupled cycles of osteoblast and osteoclast activity in which the callus tissues are remodeled to the bone's original cortical structure. During this period, the marrow space is re-established and the original structure of haematopoietic tissue and bone is regenerated. In the final period of the catabolic phase, vascular remodeling takes place where the increased vascular bed regresses and the high rate of vascular flow returns to its pre-injury level [82,83]. Although these processes take place consecutively, they overlap so as to create a continuum of changing cell populations and signaling processes within the regenerating tissue. The three major biological events of fracture healing are inflammation, endochondral bone formation and coupled remodeling [66]. An appreciation of these physiological processes underpins the design of an effective stress fracture management protocol.

Initial treatment is characterised by management of pain, relative rest and optimal loading in respect to the severity of symptoms, classification and site of the fracture. Mild analgesics as opposed to non-steroidal anti-inflammatory are preferred in the first forty-eight hours. The anti-inflammatory action, by definition will inhibit the initial and key phase of healing thereby ultimately delaying the process and recovery timeline [84]. Notably, Magnusson et al. [85], reported increases in bone mineral density of up to 19% on the site of injury following effective pain management. This observation furthers supports the importance and benefit of appropriate pain modification through the appropriate management of medication and rest. Relative rest and protection of the fracture site is therefore fundamental whilst offloading through ambulation modification is most commonly achieved using crutches. Optimal restoration of bone metabolism through activity modification, offloading the damaged body part and maintaining an unbroken sleep pattern is also an important in the initial stages [2,9,49].

Conditioned skeletal muscle, through its structure and function, can reduce the magnitude of the load delivered to the axial skeleton, thereby acting as an anatomical shock absorber [22,28,86,87]. Therefore muscular strength and conditioning is vital and may progressively be developed through a variety of therapist led modalities [2,22,34]. Graduated progressive axial loading of the injured limb to stimulate or support the pathophysiological processes of bone healing must be achieved without aggravating the injury and therefore requires careful clinical judgement as well as close communication between therapist and patient. Protected weight bearing activity can includeaqua therapy, use of an antigravity treadmill and the progression from cycling through to walking, jogging and eventually running at the end stage [6,10]. Optimal rehabilitation will include consideration of the entire musculo-skeletal system as opposed to focusing purely on the symptomatic fracture site. An appreciation of the inter-connected articular, muscular and neuro-physiological elements of the kinetic chain is fundamental to facilitation of healing, prevention of re-injury, restoration of function and attainment of optimal performance. Consequently, all patients who develop stress fractures of the lower limb should undertake at least a six week progressive neuro-muscular strengthening programme targeting the muscle

groups surrounding the joints both above and below the site of fracture [2,10,22]. Warden et al. [86], found that a "moderate exercise programme" (3 days /week for 5 consecutive weeks) induced advantageous adaptation to bone structure and resulted in a >100 fold increase in fatigue resistance thereby reducing the risk of subsequent stress related injury. This finding supports not only consideration as the basis of a rehabilitation programme but further highlights the protective benefits of graded physical activity on non-injured individuals. Once daily ambulation is pain free, progressive neuro-muscular strength and conditioning should commence in the vertical plane which in turn will facilitate the subsequent introduction of graded axial weight bearing activities. A number of both clinical and laboratory trials have been conducted specifically to identify strategies designed to maximize the effect of exercise on osteoblastic activity with the osteogenic index a recognised biological phenomena designed to predict the outcome of an exercise protocol on bone mass. Prolonged exercise was found to have less effect on mechanically induced bone formation whilst in contrast short periods (5 days/weekx2) of impact activity had a positive contribution on the "normalising" of bone's sensitivity thereby enhancing tolerance to loading [88]. Although, there is no clear consensus on how much load are stimulating of bone formation and accelerates healing process [88,89] it is agreed that appropriately selected progressive physical exercise can have a positive impact on the development of bone health both in the injured and uninjured populations. Progressive appropriate tissue loading is therefore considered sentinel to successful rehabilitation. The practical application of the "Tissue Homeostasis Model" where, as proposed by Dye [90], individuals work within their "envelope of function", is recommended by the authors as an effective approach to the management of bony stress injuries.

This paper does not provide detailed content on rehabilitation protocols, but rather identifies areas considered as key constituents of a rehabilitation programme. Rehabilitation of these injuries should also include assessment of muscular strength endurance training, aerobic fitness, proximal and distal control of the kinetic chain, balance and proprioception training, flexibility, lower limb biomechanics as well as gait education [2,6,9,22,34,87].

Controlled progressive loading complemented by the measured development of these areas is considered to have positive effect on the stimulation of osteoblastic activity (Wolf's law). In turn this will have positive influence on the development of bone density, size, shape and ultimately mechanical strength. Restoration of both neuromuscular control and functional (static and dynamic) stability provide the basis from which occupational orientated training goals may then be made [89].

Surgical

Although most stress fractures heal without complication, some high risk stress fractures (Table 1), are more likely to result in delayed union, non-union or complete fracture and as such require extended periods of reduced weight bearing [10,54] and potentially surgical intervention [55] followed by prolonged therapeutic rehabilitation [91]. The site and extent of stability provided by surgical fixation along with the length of time of reduced mobilization will also affect the patterns of skeletogenic

stem cell differentiation into either chondrocytes or osteoblasts. Extensive cartilage tissue formation has been associated with a less secure fixation whilst increased development of bone tissue is in part attributed to a more secure fixation and therefore the provision of greater stability [56].

Interestingly, when fractures are not stably fixed, angiogenesis is initially increased [57,58] with excessive inter-fragmentary instability impeding cartilage replacement, and subsequent diminishing angiogenesis thereby compromises the new bone from bridging the fracture gap [59]. Therefore, an optimal 'window' of inter-fragmentary motion seems to be needed to enable normal callus to develop and stably bridge a fracture. The tissue source of these cells and their ability to be recruited are dependent on the extent of injury and the stability of the fracture union [7,9,10].

CONCLUSION

Stress fracture, the physiological consequence of a mismatch between applied load and tissue tolerance present far reaching implications for the patient, coach, sports team, military organisation and clinician alike. Irrespective of severity they require extended periods of carefully considered rehabilitation in order to return individuals back to pre-injured status and potentially to reduce the risk of future re-injury. Consequently, there is a need to gain a thorough understanding of these injuries. This paper serves to offer a review of the pathophysiological mechanisms at play as well as to discuss the merits of specific interventions and consider themes of best practice management

AUTHORS' CONTRIBUTIONS:

JS and RH conceived the study, drafted and critically review the manuscript and both authors read and approval final version of the manuscript.

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Email: Jagannath.sharma706@mod.uk
Jagannath.sharma13@gmail.com

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