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Bone stress injuries

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Abstract | Bone stress injuries, including stress fractures, are overuse injuries that lead to substantial morbidity in active individuals. These injuries occur when excessive repetitive loads are introduced to a generally normal skeleton. Although the precise mechanisms for bone stress injuries are not completely understood, the prevailing theory is that an imbalance in bone metabolism favours microdamage accumulation over its removal and replacement with new bone via targeted remodelling. Diagnosis is achieved by a combination of patient history and physical examination, with imaging used for confirmation. Management of bone stress injuries is guided by their location and consequent risk of healing complications. Bone stress injuries at low-risk sites typically heal with activity modification followed by progressive loading and return to activity. Additional treatment approaches include non-weight-bearing immobilization, medications or surgery, but these approaches are usually limited to managing bone stress injuries that occur at high-risk sites. A comprehensive strategy that integrates anatomical, biomechanical and biological risk factors has the potential to improve the understanding of these injuries and aid in their prevention and management.

Stress fractures

Bone stress injuries with radiologically visible sclerosis or fracture line.

Stress reactions

Bone stress injuries without radiologically visible sclerosis or fracture line.

Bone stress injury

Focal failure of bone tissue to repeated loading that results in localized pain and/or an increased risk of complete bone fracture to typically tolerable loads.

Stress

The amount of force experienced per unit area of tissue when an external force is applied.

Strain

The change in the dimensions of bone tissue when stress is applied.

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In 1855, the Prussian military physician Breithaupt described an overuse syndrome presenting as “painful swollen feet associated with marching”¹. The pathology was later referred to as a ‘march fracture’ and radiologically identified as a metatarsal stress fracture². We now know that stress fractures and stress reactions are types of bone stress injury. A bone stress injury is an overuse injury that develops in response to repetitive loads applied to generally normal bone. Bone stress injuries lead to pain and loss of function, and may progress to a complete fracture. This class of injury presents a substantial burden to active individuals given that they frequently recur, often at alternative locations, and invariably require a reduction in loading that curtails participation in physical pursuits. Some bone stress injuries might require surgery to facilitate healing and limit progression to a complete and/or non-union fracture, with avascular necrosis being a potential long-term complication.

Bone is a multifunctional tissue with roles in mineral homeostasis and haematopoiesis, and is also an endocrine organ. However, the mechanical support provided by bone is among its most recognized functions. Bone is repetitively loaded during activity by gravitational forces and muscles. Muscles attach to bones either directly or indirectly via tendons, and bones are used as levers to produce motion at specialized bone-to-bone linkages (that is, joints). Bone is ideally suited to fulfil mechanical roles, as the mineralized extracellular matrix

composition provides substantial strength and rigidity to resist stress and strain, while the organic elements minimize brittleness. However, repetitive loads below the critical threshold required to cause a complete break can create material fatigue in the form of microdamage. The concept of material fatigue is well known in engineering, where it can culminate in catastrophic structural failure. Fortunately, in contrast to inert, non-biological structures, bone is highly dynamic and possesses an ability to self-repair fatigue-induced damage.

Microdamage is a normal phenomenon in bone and stimulates a process called targeted remodelling. Bone typically maintains a balance between damage formation and replacement. However, when there is an imbalance between microdamage formation and its removal and replacement, the prevailing theory is that microdamage can accumulate, extend and/or coalesce to alter local bone strength, contribute to symptoms and increase the risk of complete bone fracture³.

An imbalance between microdamage formation and repair may occur when loading produces damage at a rate exceeding the rate of normal remodelling. This can occur with intense and/or rapid changes in physical activity, such as during training in athletes and military recruits. Bone stress injuries that result from heightened stress and strain owing to loading above habitual levels are sometimes referred to as ‘fatigue fractures’ and are the focus of this Primer. This group of injuries

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includes bone stress injuries that occur in individuals who have heightened loading combined with reduced bone strength (for example, athletes and military recruits with low bone mass).

Injuries with a phenotype similar to a bone stress injury can develop in the absence of heightened loading. This type of injury occurs when normal bone biology is altered, resulting in compromised bone properties and heightened stress and strain in response to normal loads. Scenarios in which this occurs include individuals with osteoporosis or hypophosphatasia, and those taking methotrexate (for rheumatic conditions) or anti-remodelling drugs. An injury developing in these scenarios is often referred to as an insufficiency fracture. As these types of injury are more related to altered bone health and less related to bone loading, this class of injury is not a focus of this Primer. Clinically, bone stress and insufficiency injuries can lie along a spectrum and it may be difficult to discriminate between the two entities in select cases.

Bone stress injuries affect a wide range of individuals and, although clinically identified more than 150 years ago, this class of injury has received limited attention in comparison with traumatic and low-trauma (for example, osteoporotic) fractures. This neglect of bone stress injuries has negatively affected understanding and the prevention and management of bone stress injuries. In this Primer, we review current insights into the epidemiology, risk factors, diagnosis and management of bone stress injuries, and we discuss the impact of these injuries on quality of life. Furthermore, we present a detailed pathophysiological overview of bone turnover, microdamage accumulation and fracture propagation. We provide an overview of both molecular and clinical evidence to allow a comprehensive understanding of bone stress injuries with the aim of accelerating the

clinical translation of basic research to enhance patient care. In addition, we aim to provide an outlook on future research opportunities and challenges to understanding this form of injury.

Epidemiology

Bone stress injuries predominantly occur in response to repeated mechanical loading; accordingly, most of these injuries occur in physically active individuals. Bone stress injuries occur at a rate of 3.2–5.7 cases per 1,000 person-years in military recruits in the USA^{4–6}, and up to 5–10% of new recruits develop a bone stress injury during the initial 2–3 months of basic training^{4,5,7,8}. However, rates vary by country and military branch, possibly owing to, among other factors, differences in training approaches and techniques, and recruit training history and fitness (particularly in conscripts)⁹. The 1-year incidence of bone stress injuries in athletes is lower than in military recruits, at ≤5%^{8,10}, with 1.5 and 5.7 bone stress injuries occurring per 100,000 athlete-exposures in high school and collegiate-level athletes, respectively^{11,12}. The lower incidence in athletes might be due to a less extensive history of physical activity and poorer physical fitness on career entry in some military recruits. The incidence in athletes may be increasing, particularly in paediatric populations¹³. This rising incidence might be due to increased participation in ‘at-risk’ sports and the trend of youth sport specialization, which limits variability in loading and the development of a potentially less robust skeleton^{14,15}.

The activity that an individual participates in influences their risk of bone stress injury. Risk in athletes is greatest in those participating in sports that involve higher impact and repetitive loads, such as cross-country running, gymnastics, basketball, and outdoor and indoor track^{11,12} (FIG. 1). The activity that an individual participates in also influences the locations in which bone stress injuries occur (FIG. 2). Most bone stress injuries occur in highly loaded bones, such as those of the lower extremities and particularly the long bones of the leg (tibia and fibula) and foot (metatarsals). The exact location depends on how the skeleton is loaded, as different physical activities load different bones. For example, the tibia accounts for most bone stress injuries (40%) in cross-country runners whereas most bone stress injuries (51%) in basketball players occur in the metatarsals¹². Individuals who participate in activities that repetitively load the spine (for example, gymnastics, cricket and wrestling) have relatively high incidences of vertebral bone stress injuries (particularly involving the posterior elements of the spine at the pars interarticularis, commonly referred to as a ‘pars defect’ or spondylolysis)^{11,16}. Rowers repetitively load their rib cage during the drive phase of the rowing stroke and are at heightened risk of rib bone stress injuries¹⁷. Throwing athletes are at risk of developing humeral bone stress injuries as they repetitively expose their humerus to significant loads^{18,19}. Similarly, high loading of the forearm and hand in climbing may result in bone stress injuries of the distal radius or fingers (phalanges)²⁰. Athletes with disabilities who participate in adaptive sports have a high prevalence of upper-extremity bone stress injuries because of an increased reliance on the upper body²¹.

Material fatigue

The formation and propagation of cracks in a material due to repeated loading.

Microdamage

Microscopic damage in bone tissue, often in the form of small cracks, in response to repeated stress, which stimulates targeted remodelling.

Targeted remodelling

The coordinated and sequential action of bone-resorbing osteoclasts and bone-forming osteoblasts to remove bone microdamage and replace it with new bone.

Insufficiency fracture

A bone injury due to loads within the normal range being applied to an abnormal bone or a bone with abnormal biology.

In comparison with athletes and military recruits, the overall incidence of bone stress injuries in the general population is low. However, the potential presence of a bone stress injury should be considered in individuals who are not historically active and report recent strenuous, unaccustomed activity. For example, bone stress injuries have been reported in response to heightened occupational loads^{22–25} and in other scenarios of acute change in skeletal loading, such as pregnancy²⁶, around implanted prostheses²⁷, with the introduction of assistive devices or gait aids²⁸ and in response to persistent coughing²⁹.

Bone stress injuries occur 1.8–2.3-fold more often in female than in male athletes and 3.1–3.6-fold more often in female than in male military recruits^{11,12,30–34}. The higher incidence in both female athletes and female military recruits might be partially explained by the association of bone stress injuries with low energy availability, a condition that is typically more prevalent in active women than in men. Sexual dimorphism in the adaptation of bone size relative to body size has also been proposed as a contributing factor^{35,36}. The comparatively higher incidence in female military recruits than athletes might be influenced by sex-neutral training loads (for example, pack weights during rucking) and overstriding during march training causing higher loads to be placed on the skeleton of female military recruits^{37–40}.

Military studies indicate that bone stress injury risk also varies by race and ethnicity. Black individuals have the lowest rate of bone stress injuries^{5,6}. Compared with Black individuals, non-Hispanic white men and women have 59% and 92% higher risk of bone stress injuries, respectively⁶. Hispanic and Asian individuals have a risk intermediate between non-Hispanic white individuals and Black individuals^{6,41}. Differences in bone mass, structure and strength might underscore the racial and

ethnic differences in bone stress injury rates^{42,43}; however, additional studies in multi-ethnic cohorts are needed to comprehensively examine other potential contributors.

Mechanisms/pathophysiology

The pathophysiology of bone stress injuries remains incompletely understood, which impedes the development of preventive and intervention techniques. However, the general consensus is that bone stress injuries result from an imbalance between load-induced microdamage formation and its removal and replacement^{3,44}.

Bone composition

Bone is a highly complex and organized connective tissue that consists mainly of collagen and hydroxyapatite mineral. Bone structure has a hierarchical organization, extending from molecular bonds to macroscopic features (FIG. 3). At the nanoscale, hydroxyapatite crystals are embedded around and within the collagen triple helix and fibrils. An arrangement of mineralized collagen fibrils is stabilized by various types of cross-link. Non-collagenous proteins, although representing only about 2% of bone matrix by weight, are a vital part of physiological processes in bone. These proteins regulate the formation and size of collagen fibres as well as their mineralization, and are crucial for cellular signalling and cell attachment. At the microstructural scale, skeletal tissue is organized as either compact (cortical) or cancellous (trabecular) bone. The distribution of these two types of bone tissue varies considerably between different parts of the skeleton and within a bone.

Compact bone is dense and is composed of osteons and intervening interstitial bone tissue. Osteons are organized in multiple concentric layers of lamellae around a central Haversian canal that encloses blood vessels and nerves (FIG. 3). Primary osteons form by

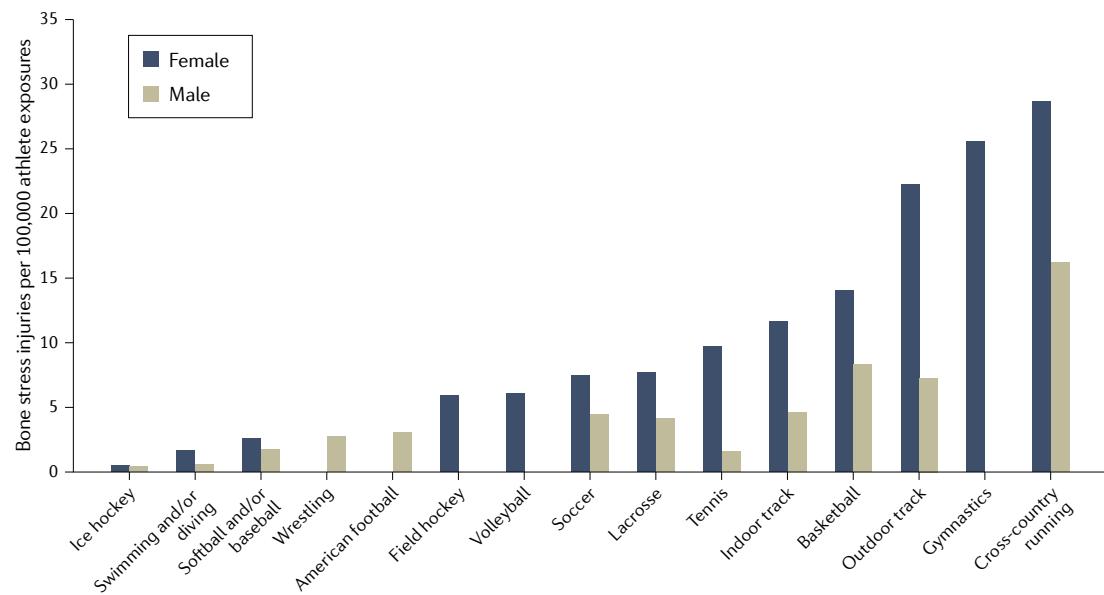


Fig. 1 | Incidence of bone stress injuries in different college sports. Injury risk is greatest in those athletes who participate in sports that involve higher impact and repetitive loads, such as cross-country running, gymnastics, basketball and track and field. Bone stress injuries occur more often in female than in male athletes, which could be partially explained by a higher prevalence of low energy availability in female athletes. Data are from REF.¹².

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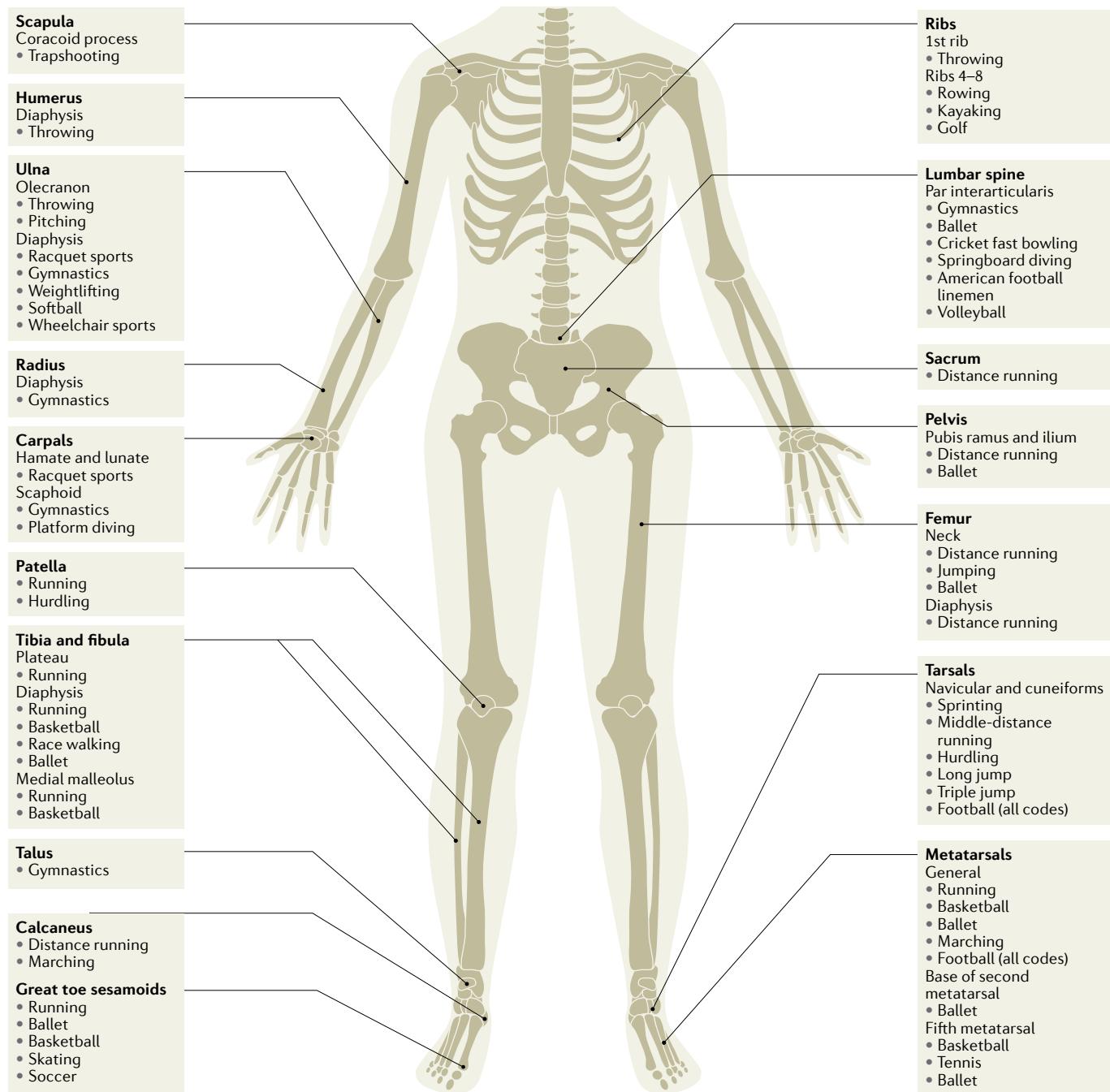


Fig. 2 | Common anatomical sites for bone stress injuries. The typical underlying sports activities associated with each site are indicated. Adapted from REF.²⁰⁹, Springer Nature Limited.

direct lamellar bone formation around vascular channels. Because they are the product of direct formation without preceding resorption, they do not have a cement line and are smaller than secondary osteons. Both of these features make them less effective than secondary osteons at stopping the growth of microcracks. Secondary osteons form as a product of remodelling. As this involves resorption followed by formation, they have a well-defined cement line.

Structurally, secondary osteons contain more lamellae and have larger Haversian canals than primary osteons. Collagen fibres within individual lamellae can be

aligned at different orientations to the bone axis. Two types of alignment exist and may differ by location. In some lamellae, the orientation of collagen fibres changes by 90° from one layer to the next. In other regions, a helicoidal ‘twisted plywood’-type of arrangement exists in which collagen fibres are rotated through 180° from one layer to the next, so that the fibre orientation repeats itself and has a lamellar appearance microscopically¹⁵. Both arrangements can prevent cracks from forming and spreading. The orientation of collagen fibres varies within and between bones and coincides with the distribution of tensile and compressive stresses, thereby

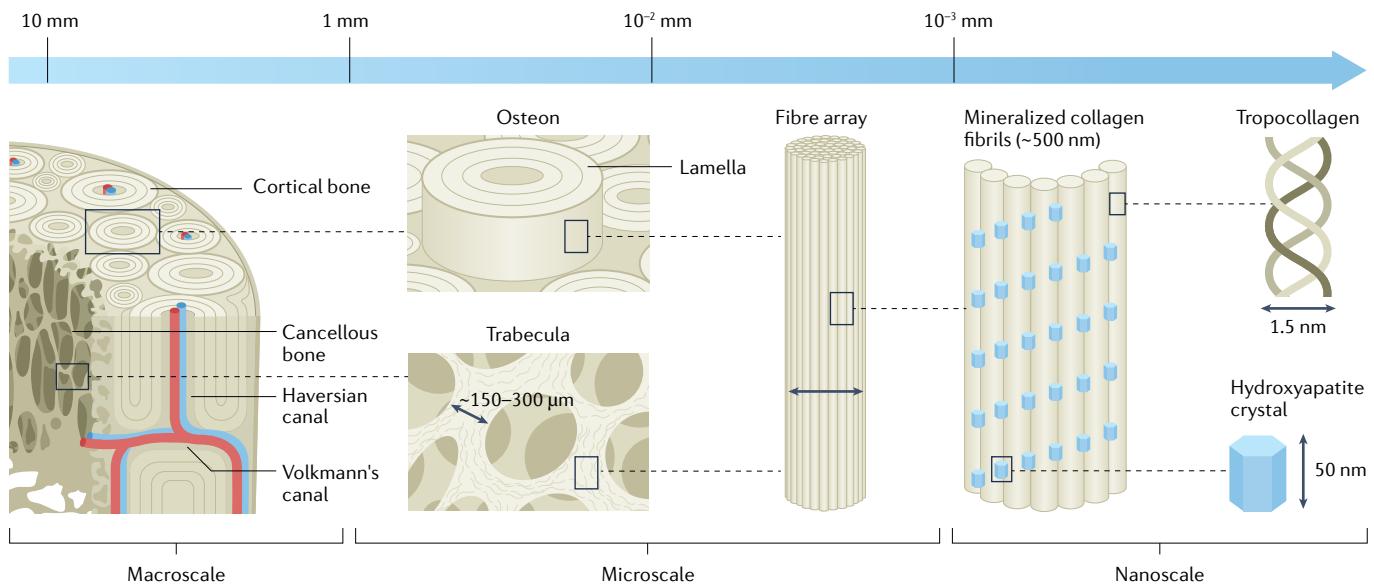


Fig. 3 | Hierarchy of bone structural organization. Bone tissue is organized as either compact or cancellous bone. Compact bone is dense and is composed of osteons and interstitial bone tissue. Cancellous bone is less dense and is composed of a network of individual trabeculae. Osteons are organized in cylindrical structures of lamellae around a central cavity known as the Haversian canal. At the sub-microstructural level, an arrangement of mineralized collagen fibrils is stabilized by various types of cross-link. At the nanoscale, hydroxyapatite crystals are embedded around and within the collagen triple helix and fibrils. Adapted from REF.²¹⁰, CC BY 4.0, and from REF.²¹¹, Springer Nature Limited.

maximizing fracture resistance⁴⁶. Other lamellae are organized circumferentially around the periosteal and endocortical surfaces of cortical bone and the interstitial lamellae that represent the remains of primary and/or secondary osteons. Unlike compact bone, cancellous bone is less dense and is less strong at both compositional and structural levels. Cancellous bone is composed of individual trabeculae, with a higher biological activity and greater potential for remodelling and restructuring than compact bone. Trabeculae typically do not contain osteons, although they can, but often contain hemi-osteons as a result of the remodelling process.

The structural organization of bone is optimized to meet biomechanical demands (stresses and strains) and physiological or metabolic demands (for example, haematopoiesis and mineral storage) while minimizing the amount of bone tissue. Different types of bone serve different primary functions (for example, support, protection, assisting movement, haematopoiesis and mineral storage and release), which is associated with distinct optimization. On the basis of Wolff's Law, bone in a healthy organism adapts to the applied load⁴⁷, a process mediated by bone cells (osteocytes, osteoblasts and osteoclasts) that enables skeletal growth and lifelong regeneration by modelling and remodelling, respectively. In optimal conditions, the structural organization results in an organ designed to resist fracture⁴⁸.

Microdamage

Microdamage in bone is a normal phenomenon that occurs in response to repetitive loading to dissipate energy. Microdamage is present in every human skeleton irrespective of physical activity levels and is caused by loads below the fracture threshold. Microdamage

accumulates with increasing repetitive stress and strain levels, as demonstrated in *in vitro* studies⁴⁹. Biomechanically, microdamage causes a reduction in the structural stiffness and/or the modulus of elasticity of bone tissue^{50,51}. At the microscopic level, microdamage is defined by detectable microcracks in the bone matrix or a complete fracture of trabecular struts⁵². Three main types of microdamage are defined: linear microcracks, diffuse damage and trabecular microfractures⁵³. Linear microcracks are 50–100 μm long in a cross-section of bone and can grow longitudinally in the diaphysis to 1 mm in length. They occur primarily in older, highly mineralized interstitial bone that is under compressive stress^{54–56}. By contrast, diffuse damage represents a collection of many, very small microcracks (<10 μm in length) and is more prevalent under tensile loading than under compressive stress. Interestingly, linear microcracks have been shown to lead to osteocyte apoptosis and activated bone resorption whereas repair of diffuse damage appears to occur without resorption of bone⁵⁷.

Intrinsic and extrinsic toughening mechanisms exist to prevent crack formation and propagation. Intrinsic toughening mechanisms at the level of the mineralized collagen fibril include stretching, through mechanisms during elastic deformation such as sacrificial bonding and dilatational band formation at the crack front^{58,59}. Extrinsic toughening mechanisms take effect after the occurrence of a microcrack and include the lamellar structures and the osteonal margins (that is, the cement lines) causing crack deflection⁶⁰. Microfractures are different from the other types of microdamage, as they are considered to be complete fractures of bony trabeculae. Consequently, the length of a microfracture is defined

by trabecular thickness, which varies between 150 µm and 300 µm in healthy humans but is less in individuals with osteoporosis. In contrast to linear microcracks and diffuse microdamage, microfractures heal either by direct apposition of woven bone or through endochondral healing processes to form a callus, followed by bone remodelling⁵³. Whether microfractures occur acutely or are the result of the evolution of linear or diffuse microdamage is largely unknown.

Bone modelling and remodelling

Two processes that are important in the occurrence and healing of bone stress injury are modelling and remodelling. Bone modelling refers to the spatially independent actions of osteoblasts and osteoclasts, which add or remove tissue (respectively) from an existing bone surface to alter bone shape. The process of bone modelling can be thought of as bone construction (or deconstruction) and is relevant to the adaptation of bone to mechanical loads, particularly during growth. Growth during childhood and adolescence provides a unique opportunity to optimize bone size and strength. During skeletal growth, bone width increases as a result of rapid modelling on the periosteal (outer) surface. Physical activity during youth might contribute to greater cortical area and thickness in response to loads that expand the periosteum while slowing the expansion of the endosteal (inner) layer^{61,62}. Enhanced structural properties increase bone strength and fatigue resistance exponentially in relation to the amount of material added^{63,64}. These benefits of loading when young can persist in the long term, reducing stress and strain for a given load and thereby preventing bone stress injuries^{19,65}. Modelling might also occur as a compensatory response to a developing or established bone stress injury, as a means of stabilizing the injury site.

In contrast to modelling, remodelling is characterized by the temporally and spatially coordinated (or ‘coupled’) actions of osteoclasts and osteoblasts acting sequentially on the same surface. Also, unlike modelling, remodelling does not typically affect bone size and shape and occurs continuously throughout life⁶⁶, although it should be noted that remodelling is generally more active in adolescent than in adult skeletons^{67–69}. Clusters of bone-resorbing osteoclasts and bone-forming osteoblasts arranged within temporary anatomical structures are referred to as basic multicellular units (BMUs). The unique spatial and temporal arrangement of cells within the BMU is crucial, ensuring the coordination of bone remodelling, which occurs in five sequential phases: activation, resorption, reversal, formation and quiescence⁷⁰. Remodelling can be non-targeted, appearing stochastic in terms of location and occurring in response to systemic hormones to enable bone to fulfil its metabolic requirements of releasing calcium and phosphorus into the circulation⁷¹. By contrast, targeted remodelling removes and replaces specific packets of bone and is stimulated by microdamage formation^{72,73}.

Microdamage induces apoptosis (that is, programmed cell death) of local osteocytes embedded in the bone matrix⁷⁴. Once thought to be quiescent cells, osteocytes are now known to be highly active and capable

of modifying the surrounding matrix, sensing and responding to mechanical stimuli and signalling to both osteoblasts and osteoclasts⁷⁵. This signalling is important for the targeted removal of microdamage. Osteocytes are important sources of receptor activator of nuclear factor-κB ligand (RANKL; also known as TNFSF11) and osteoprotegerin (OPG; also known as TNFRSF11B)^{76,77}. RANKL binds to its receptor RANK (also known as TNFRSF11A) on osteoclast precursor cells to trigger their differentiation into osteoclasts. RANKL is also important for maintaining osteoclast activity in mature osteoclasts⁷⁸. By contrast, OPG is a soluble decoy receptor for RANKL and functions to reduce osteoclastogenesis by competitively occupying RANKL-binding sites on precursor and later-stage osteoclasts^{79,80}. By producing RANKL and OPG, osteocytes can positively and negatively regulate bone remodelling. Osteocyte apoptosis in response to microdamage alters the RANKL/OPG ratio in favour of RANKL, resulting in stimulation of osteoclastogenesis and bone resorption^{74,81,82} that leads to the removal of microdamage. Osteoblasts subsequently deposit layers of osteoid (unmineralized bone matrix) on the newly exposed surface that becomes mineralized over time. Some osteoblasts are embedded in the osteoid to become osteocytes.

Fracture propagation and injury development

The occurrence of bone microdamage is not a pathological condition per se. The process may prevent or prolong bone failure by dissipating energy or serving as a stimulus for targeted remodelling, thereby increasing fracture resistance. However, in the presence of an imbalance between microdamage formation and removal, bone stress injuries may occur (FIG. 4). From a simplified viewpoint, bone failure in fatigue follows three stages: crack initiation, crack growth and coalescence⁸³. Initiation of microcracks may be facilitated by lowering intrinsic toughness through changes in bone composition. With growing microdamage, osteocyte death and insufficient bone remodelling, crack growth and coalescence may no longer be arrested by extrinsic toughening mechanisms. The net result is formation of a bone stress injury, and, ultimately with continued substantial loading, a complete bone fracture (FIG. 5). Of note, the third and final stage of bone fatigue failure may not necessarily involve microdamage coalescence, as individual microcracks may grow in length and result in fracture without coalescence⁸⁴.

There is a discrepancy between the loading required to experimentally fatigue a bone *in vitro* and that which results in a bone stress injury *in vivo*. For example, the *in vitro* fatigue life of bone to loading at physiological strains equivalent to those measured in humans during running (~1,200–1,500 microstrain, 0.12–0.15% deformation) ranges from 12 to 37 million loading cycles⁸⁵, which corresponds to several thousand miles of running, but bone stress injuries *in vivo* occur in far shorter distance and time. The reasons for the discrepancy are diverse and may include the fact that running is associated with multi-axial loading (as opposed to uni-axial loading in *in vitro* experiments) and is also coupled with muscle fatigue, which may alter stress and strain⁸⁶.

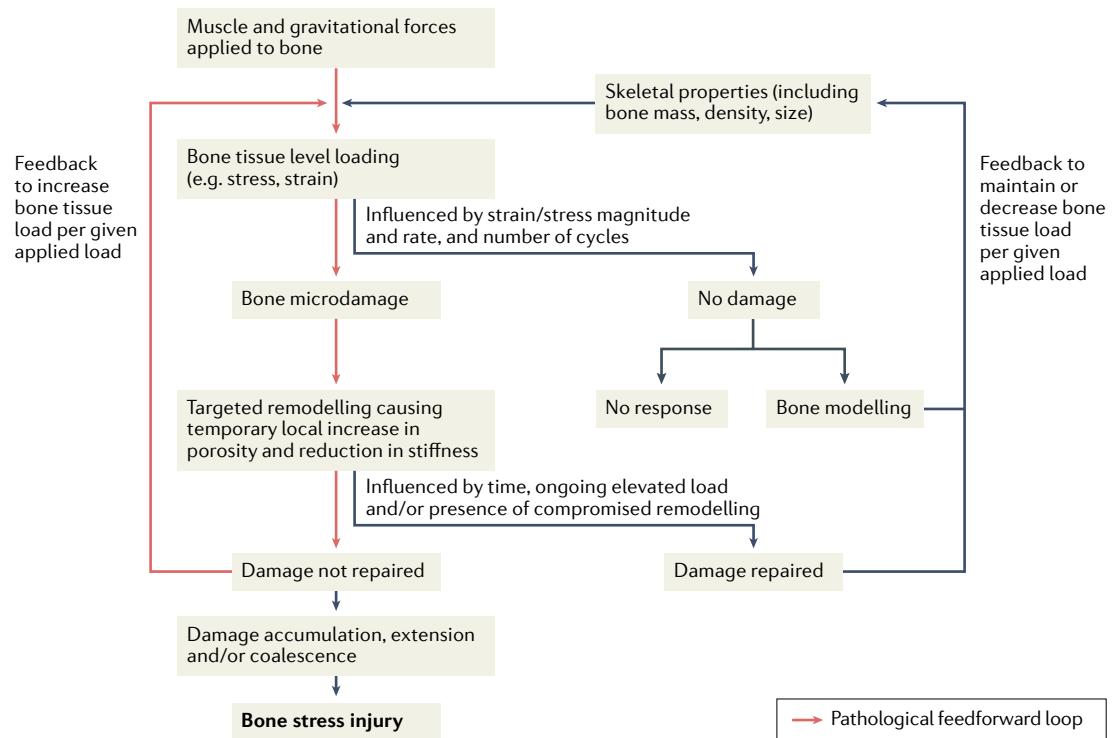


Fig. 4 | Pathogenesis of bone stress injuries. In active individuals, bone is directly or indirectly exposed to repetitive loading. Bone microdamage due to stress and strain is a normal phenomenon and stimulates a process called targeted bone remodelling. Typically, this process results in a positive impact on skeletal properties, ensuring bone strength and higher fracture resistance. When there is an imbalance between microdamage formation and repair, microdamage can accumulate and/or coalesce to alter local bone strength, contribute to symptoms and increase the risk of complete bone fracture.

However, a leading contributor is the process of targeted remodelling, which occurs *in vivo* but not *in vitro*.

Targeted remodelling takes time. Osteoclast activation and bone resorption take ~4 weeks, after which the void is filled with new bone by osteoblasts over the next 3 months. The transition between bone resorption and bone formation generates localized porosity and a reduction in bone strength, creating the potential for a feedforward loop whereby the bone site experiences heightened stress and strain for a given load, which, when coupled with too rapid progression of training, can generate further microdamage formation, its accumulation, and the growth and/or coalescence of cracks³. However, to date, evidence is lacking on how these pathophysiological findings correspond to clinical presentation and subsequent diagnosis.

Bone stress injury healing

The mechanisms of bone stress injury healing are incompletely characterized. Healing may begin by buttressing of the fracture with callus to stabilize the bone⁸⁷. Callus formation may be a response to a periosteal inflammatory reaction. That inflammation plays a part in the process of microfracture repair has been demonstrated in a rat model of ulnar loading, in which stress fracture healing was accompanied by an early upregulation of IL-6 and IL-11, followed by a considerable upregulation of RANKL that coincided with histological evidence of bone remodelling⁸⁸. Concurrently or subsequently, direct remodelling along the fracture line repairs the

damaged area by removing the crack and forming new bone. Direct remodelling occurs in some insufficiency fractures in humans⁸⁹, although the remodelling in some cases may be ineffective. In athletic injuries, remodelling may be slow or difficult to detect before the formation of a complete stress fracture⁹⁰. Interestingly, microscopically assessed biopsy samples of patients with chronic tibial stress fractures showed that the radiographically visible fracture line was filled with low-density bone undergoing intense remodelling rather than being a void filled with unmineralized tissue⁹¹. It is possible that, depending on the stage of a bone stress injury, as well as its location in trabecular or cortical bone, distinct healing mechanisms occur, allowing the repair of microfractures by classical fracture healing (inflammation, callus formation and remodelling) or repair of microcracks by targeted bone remodelling. This assumption suggests that there may be several mechanisms of healing stress injuries, depending on the type of injury and its location⁹².

Risk factors

Knowledge of risk factors for bone stress injuries can guide both injury prevention and management strategies. The large numbers of individuals required to generate adequate statistical power is a primary challenge in the prospective study of bone stress injury risk factors. Prospective studies have been performed in the military, but most studies in athletes use retrospective cross-sectional study designs that cannot infer direct

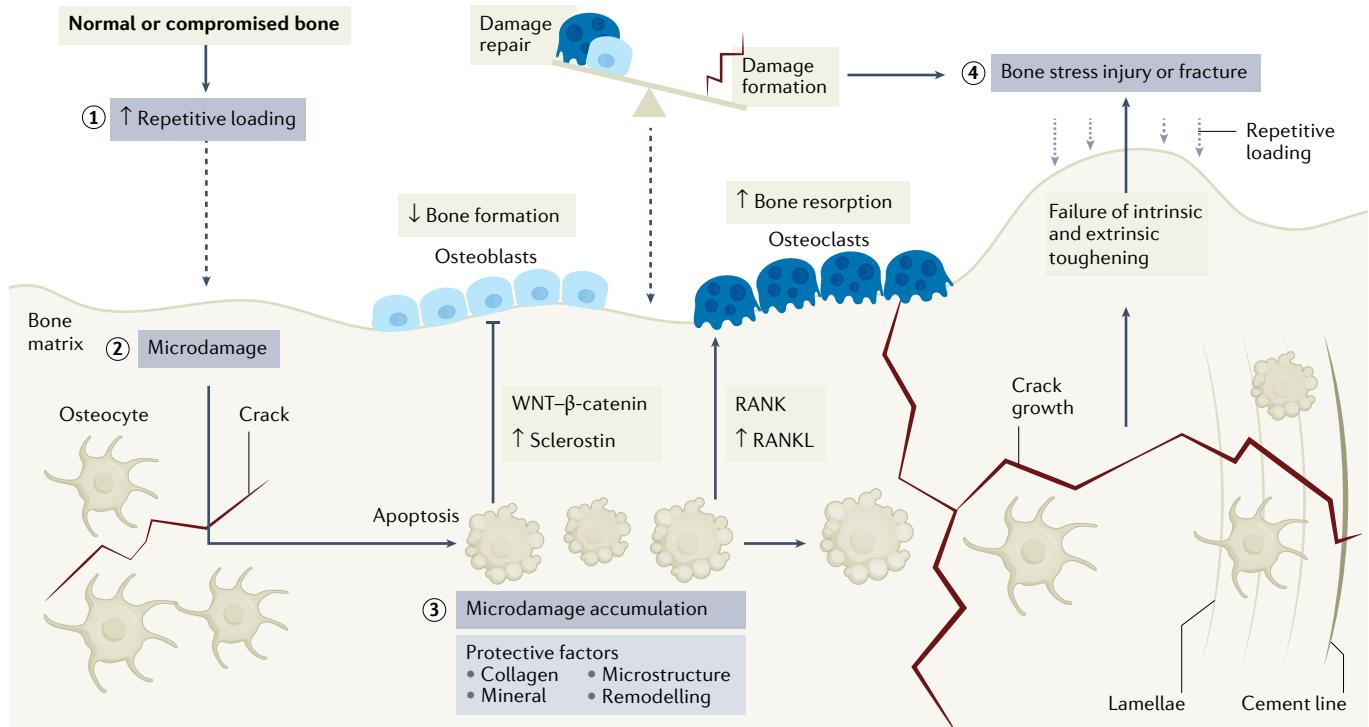


Fig. 5 | Molecular aspects of bone stress injury pathophysiology. Repetitive loading (step 1) on bone tissue leads to microdamage (step 2). Osteocyte apoptosis leads to pro-osteoclastogenic increase in the receptor activator of nuclear factor- κ B ligand (RANKL)/osteoprotegerin (OPG) ratio. If there is an imbalance in bone microdamage accumulation (step 3) over removal via targeted remodelling, a bone stress injury (step 4) may occur. Initiation of nano-cracks may occur by failure of intrinsic toughening mechanisms. With growing microdamage, osteocyte death and insufficient bone remodelling, crack growth and coalescence may no longer be arrested by extrinsic toughening mechanisms, which include the lamellar structures and osteonal margins that normally cause crack deflection. This may result in a complete bone fracture and, potentially, displacement.

causality. Despite difficulty in establishing risk factors, most evidence suggests that the origin of bone stress injuries is multifactorial and that the contributing factors differ between individuals.

For simplicity, risk factors for bone stress injuries may be grouped at the nexus between the loads being applied to a bone and the ability of the bone to resist load and repair microdamage. Most commonly, the load applied to a bone has been estimated from indirect measures, including ground reaction forces and segment accelerations⁹³. However, these metrics may not be accurate surrogates for bone tissue loading. Both internal and external forces contribute to loading at the bone tissue level. For a given applied load, bone strength in the direction of loading influences the stress and strain generated. Skeletal features that influence bone stiffness include the amount (mass), distribution (structure) and quality of bone material. There is evidence that these features are linked to bone stress injury risk and that they are influenced by both non-modifiable and modifiable factors^{94–98}.

Physical activity. Most bone stress injuries occur in the context of high-demand physical activities, but not all activities contribute equally to risk of injury. As mentioned earlier, activities that involve both high numbers of loading repetitions and high loading magnitudes and/or rates have the highest incidences of bone stress injury;

example sports include road and cross-country running, track and field, gymnastics, basketball, lacrosse, soccer and field hockey^{11,12,99}. When an individual presents with symptoms at an ‘at-risk’ anatomical location for their activity, consultation with clinicians who are equipped with knowledge of sports with heightened risk of bone stress injuries may lead to an earlier diagnosis. However, the potential for a bone stress injury to occur at a less common or more unusual site should not be discounted.

Stage of training. The incidence of bone stress injuries varies according to stage of training. Although injury may occur at any time during athletic exposure, in seasonal sports (for example, basketball, soccer and outdoor track) the risk of bone stress injuries may be elevated during the preseason and the transition to the competitive season^{12,100}. These represent times of rapid changes in loading as athletes return from the off-season and increase loading intensity and frequency associated with competition. Other at-risk times include when an athlete returns from injury and when they move up in competition level. Similarly, bone stress injuries in military recruits begin early in training, with incidence increasing 3 weeks after commencing training and peaking after 8 weeks⁷. These peaks in incidence likely coincide with generation of bone fatigue damage resulting from heightened repetitive loading of bone. The bone remodelling that targets newly damaged bone for removal leads

to a temporarily more porous bone and a positive feedback cycle of damage, repair and porosity, ultimately contributing to the development of bone stress injury¹⁰¹.

Biomechanical factors. Movement patterns have the potential to alter the magnitude, rate and direction of bone loading. Runners with a history of a bone stress injury may have greater peak rearfoot eversion and hip adduction^{102–104} and less knee flexion than those without such a history¹⁰⁵. Other variables that have been related to bone stress injuries include altered hip range of motion¹⁰⁶, leg-length discrepancy⁹⁴ and both pes planus (flat foot)¹⁰⁷ and pes cavus (high arch)¹⁰⁸. In the foot, a varus forefoot and limited ankle dorsiflexion are assumed to increase metatarsal loading and thereby increase risk of metatarsal bone stress injuries¹⁰⁹. Runners with a low step rate, irrespective of loading rate, were prospectively found to be at higher risk of bone stress injury¹¹⁰. An intimate mechanical relationship exists between muscle and bone⁹². Muscle loads bone, but there is ongoing debate regarding the contribution of muscle to bone stress injuries. Biomechanical data indicate that most bone loading is muscle-induced^{111,112}; however, experimental and clinical data^{94,96,113,114} suggest a potential protective role of muscle in the risk of bone stress injury. In particular, prospective studies demonstrate that bone stress injury susceptibility is negatively related to muscle size^{94,96,113} and strength¹¹⁴. In addition, muscle fatigue can alter spatial-temporal, kinematic, kinetic and nonlinear running gait parameters, which may modify the direction of bone loading, resulting in an altered strain distribution¹¹⁵.

Environment. Historically, walking and running on harder surfaces was believed to increase the risk of bone stress injury. However, the interaction between surface and injury risk is complex, as leg stiffness rapidly changes depending on the surface¹¹⁶. Ultimately, what may be most important to consider for injury risk is a recent and rapid change to an unaccustomed surface for participation in physical activity or sport. For example, a habitual road runner changing to trail running may be at increased risk of bone stress injury as trail running alters bone strain magnitudes and direction and can accelerate muscle fatigue¹¹⁷.

Shoes and inserts. The role of shoes and inserts (orthotics and insoles) on bone stress injury risk remains a topic of perpetual debate¹¹⁸. Shoes and inserts theoretically alter ground impact forces by acting as filters and influencing motion. Abrupt changes from cushioned shoes to footwear with limited mechanical support may increase the risk of injury, particularly in the metatarsals¹¹⁹. Although footwear influences load rates in runners¹²⁰, further research is needed to characterize whether footwear and change of footwear and/or related inserts can alter risk of bone stress injuries.

Sex and race. As discussed above, women and non-Hispanic white individuals are at greater risk of bone stress injuries than men and non-white individuals, respectively. Differences in anatomy, biomechanics and overall

ability of bone to resist load may contribute to the heightened risk in these groups^{6,8}. In addition, the heightened risk in female athletes might be influenced by a higher prevalence of hormonal disturbance (discussed below).

Early sport specialization. Less participation in physical activities or early specialization in low impact (for example, swimming and cycling) or unidirectional, repetitive loading sports (for example, distance running) during growth might contribute to risk of bone stress injury. Athletes who specialize early in sports with low osteogenic potential might enter adolescence and young adulthood with low bone mass and elevated risk of bone stress injury¹⁵. Studies in both athletic and military populations indicate that individuals with a history of participating in high-impact and multidirectional activities (for example, ball sports) have a lower risk of bone stress injury, likely owing to higher bone mass and the development of a more robust skeletal structure^{14,15,121,122}.

Low energy availability, RED-S and athlete triads. Low energy availability is a major risk factor for bone stress injuries^{41,123–125}. Low energy availability can result from low dietary energy intake and/or excessive energy expenditure and affects bone health and bone stress injury risk in both women and men. Low energy availability often leads to hypogonadism in women (evidenced by menstrual dysfunction such as amenorrhoea) and men (potentially presenting as decreased sexual function and libido)¹²⁶. In addition to decreased oestrogen and testosterone, other hormones, including insulin-like growth factor 1, leptin and triiodothyronine, are down-regulated whereas growth hormone resistance and cortisol levels increase. This complex constellation of decreased energy availability and hormonal disruptions negatively affects bone density, remodelling capacity and fracture resistance^{127–129}. Low energy availability, menstrual dysfunction and low bone mineral density are the three components of the female athlete triad, a syndrome that is associated with an increased risk of bone stress injury¹³⁰. The male athlete triad has similar criteria but replaces menstrual dysfunction with functional hypothalamic hypogonadism¹³¹. The inclusive term relative energy deficiency in sport (RED-S) was defined by the International Olympic Committee (IOC) as the potential consequences of low energy availability on health and physical performance in both men and women^{125,126}. Although consequences of low energy availability on health can be observed in both men and women, the effects are better described in women, including elevated risk of decreased bone mineral density¹³² and impaired bone microarchitecture¹³³.

Calcium and vitamin D. Calcium combines with phosphate to form hydroxyapatite crystals to endow bone rigidity. Active vitamin D (also known as calcitriol or 1,25-dihydroxycholecalciferol) promotes calcium absorption in the gut and reabsorption in the kidneys. Low levels of both vitamin D and calcium have been linked to low bone strength and increased risk of bone stress injuries^{134–136}. Female distance runners who consumed less than 800 mg of calcium daily had

an almost sixfold higher bone stress injury rate than those who consumed more than 1,500 mg daily¹³⁶, and in a case-control study of 1,200 white military recruits, low vitamin D levels were significantly associated with bone stress injuries¹³⁷. The risk of bone stress injury in young female athletes was reduced for those in the highest quintile of vitamin D intake¹³⁵. Furthermore, in 3,700 military recruits, risk of bone stress injuries was reduced by 20% after daily supplementation with vitamin D (800 IU) and calcium (2,000 mg)¹³⁴.

Genetic factors. There are well-established genetic factors that have a considerable influence on bone mass, size and strength^{6,42,138,139}. Thus, it is reasonable to assume that genetic factors contribute to bone stress injury risk; however, differences based on race and ethnicity are not well described. Polymorphisms in *P2RX7*, which encodes the purinergic receptor P2X7, are a potential predisposing factor in the development of bone stress injuries¹⁴⁰. In addition, positive family history may predispose to a bone stress injury⁹⁹. The question remains as to how to clinically use information regarding potential genetic predisposition.

Medications. Corticosteroids are the most prominent example of medications that are associated with impaired bone health. Bone stress injury risk has been associated with not only the intake of corticosteroids¹⁴¹ but also endogenous cortisol excess (hypercortisolism)¹⁴². Prolonged use of NSAIDs may also be associated with increased risk of bone stress injuries, as demonstrated in a cohort of more than 1 million military recruits¹⁴³.

Sleep disorders and psychological factors. The contribution of psychological factors to bone stress injuries is not fully understood. Psychological stress may directly affect bone remodelling but other mechanisms (for example, change in muscle factors and biomechanics) may also account for an increased risk of injury¹⁴⁴. Aspects of sleep, such as quality and duration, are likely to influence bone stress injury risk but remain poorly understood. One interventional study in the Israeli military instituted lifestyle and training guidelines that included 6 h minimum of sleep, which contributed to a 62% reduction in bone stress injuries¹²¹.

Diagnosis, screening and prevention

Diagnosis

Early identification of a bone stress injury is important to reduce risk of progression to a complete bone fracture and to expedite a return to activity. Diagnosis is achieved by a combination of patient history and physical examination, with imaging used for confirmation and to grade the injury and guide management.

The potential presence of a bone stress injury should always be considered in the differential diagnosis of a patient, but suspicion is raised in the presence of key risk factors including participation in an 'at-risk' activity, whether the individual has a history of a previous bone stress injury, their physical activity levels and the presence of indicators of RED-S and the female or male athlete triad. In terms of activity levels, attention should

be paid to changes in the previous 4–6 weeks, as there is usually a delay between a change in activity and the development of symptoms of bone stress injury. Changes in activity may include a large change in a single training feature, such as training duration, frequency, intensity or type, or small simultaneous changes in multiple training features. A review of training logs, including volume, intensity and perceived effort, can be informative. In addition, loading arising from activities outside of formal training, such as occupational and recreational or leisure time loads (for example, recent physical work or hiking), should be considered.

Pain is the most important diagnostic feature on physical examination, although its features and nature show variability between patients. Although they may vary in symptoms, most bone stress injuries are normally pain-free when unloaded, but advanced bone stress injuries can be painful at rest, including at night. Pain can range in severity from a mild diffuse ache after activity or a specific amount of activity, to localized sharp pain that is aggravated every time a load is applied to the bone. Mild pain may occur more in the presence of a low-grade bone stress injury, whereas severe pain may more frequently occur with a stress fracture in which the mechanical properties of the bone are more significantly compromised. The cardinal sign of a bone stress injury is the presence of localized bone tenderness that is aggravated by loading and that does not 'warm up' as activity continues.

Tenderness associated with a bone stress injury is readily palpated at subcutaneous sites (for example, tibial and metatarsal diaphyses and tarsal bones). Local swelling, redness and warmth may also be evident at these locations. At deeper sites covered by heavy musculature (for example, the femoral neck and shaft), symptoms are often less localized and more complex. Clinical diagnosis of a bone stress injury at deeper skeletal sites may be facilitated by specific bone loading tests, including hopping on the affected limb for lower extremity injuries¹⁴⁵, the fulcrum test for the femoral diaphysis or shaft¹⁴⁶, or the squeeze test for the calcaneus¹⁴⁷. In a 2021 study, sensitivity of the hopping test for tibial stress fractures was 100% and specificity was 45%, indicating that a negative test result may aid in ruling out these fractures¹⁴⁸. By contrast, a vibrating tuning fork localized over the bone has little utility as a diagnostic tool¹⁴⁹. The differential diagnosis of a bone stress injury is broad and varies on the basis of injury location. Differential diagnoses may include tendinopathy, muscle strain, ligament sprain, neoplasms, osteomyelitis or arthritic processes.

Bone stress injuries can be diagnosed clinically without imaging^{148,150}. In many clinical situations, plain radiography (that is, without other techniques, such as CT) is standard practice to rule out sinister pathology (for example, infection or bone malignancy), but it lacks the sensitivity to detect bone stress injuries and does not show bone oedema. In some cases, periosteal callus, cortical thickening or sclerosis may be evident in the absence of a radiologically visible fracture line, but these features typically appear only after notable time for healing¹⁵⁰. The visibility of a distinct bone defect by plain radiography can be indicative of a very high-risk bone

Table 1 | Risk classification of bone stress injuries

Skeletal region	Bone sites	
	Low-risk ^a	High-risk ^b
Upper extremities	Humerus, forearm, hand	NA
Thoracic bones	Rib	NA
Pelvic girdle	Sacrum, pubic bone	Lumbar spine including pars interarticularis (spondylolysis)
Thigh	Femoral shaft	Femoral neck
Knee	NA	Patella, tibial plateau
Leg	Posteromedial tibia, fibula	Anterior tibia, medial malleolus
Foot	1st to 4th metatarsal shaft, calcaneus	2nd and 5th metatarsal base, great toe sesamoid, talus, navicular bone

NA, not applicable. ^aLow-risk bone stress injuries usually heal without major complication.

^bHigh-risk bone stress injury locations include bone sites that can have high risk of delayed union, non-union, complete fracture, re-fracture or failure to timely return to sports.

stress injury, such as an anterior tibial stress fracture where the radiological appearance is often referred to as a ‘dreaded black line’. Advanced diagnostic imaging studies are recommended if a high-risk bone stress injury is suspected, for differential diagnoses when a patient fails to respond to initial treatment, and in time-sensitive situations such as imminent high-level competition (TABLE 1). Methods of imaging bone stress injuries include triple phase technetium-99m polyphosphate bone scan (scintigraphy), ultrasonography, CT and MRI^{151–154}. Scintigraphy was historically considered to be the most reliable imaging modality for diagnosis owing to high sensitivity to the hyperaemia and increased bone turnover associated with bone stress injury. However, in recent years, the low specificity of scintigraphic bone scans and their associated use of ionizing radiation has led to MRI, particularly fat-suppressed sequences, becoming the imaging modality of choice¹⁵².

MRI can reveal bone oedema from (interstitial) fluid accumulation¹⁵⁵. The typical signal characteristic is a diffuse, irregular and sometimes large hyperintense oedema in fat-suppressed (T2-weighted) imaging, with corresponding hypointense signal on T1-weighted images (FIG. 6). In high-grade injuries (defined below), a radiological fracture line is present. Periosteal reactions and adjacent soft tissue inflammation are commonly seen, and their presence is a further helpful discriminating feature from other diagnoses. Nevertheless, MRI may also provide false positives; that is, evidence of oedema in the absence of symptoms of bone stress injury¹⁵⁶.

Unfortunately, limited MRI access in many areas in the world means that diagnosis is based on clinical features^{148,150}. An alternative approach is to use ultrasonography, which may be available at the point of care. However, ultrasonography possesses limitations, such as being highly user dependent, limited to relatively superficial sites and with questionable sensitivity to subtle pathology.

Numerous radiographic grading systems are used to assess the severity of a bone stress injury^{157–161} (FIG. 7). The system published in 1995 by Fredericson et al.¹⁶¹ for tibial bone stress injuries is one of the most widely used classifications. This system describes a pathological

continuum ranging from low- to high-grade injuries according to MRI signs. Since then, other classification systems have been introduced, including MRI-based classifications proposed by Arendt et al.¹⁶⁰, Nattiv et al.¹⁵⁸ and Rohen-Aquinilla et al.¹⁵⁹. In addition, Kaeding and Miller¹⁵⁷ described a classification system that added clinical features to the imaging findings. Classifying bone stress injuries seems to have value for clinicians, as a recent systematic review and meta-analysis found that classification systems may be associated with injury severity and healing time¹⁵², although this is not always the case¹⁶².

Stress fractures^{152,160} can be detected as a hypointense fracture line on MRI or when the imaging slice coincides with the fracture location on CT. As this overlap is not always guaranteed, despite excellent osseous imaging, CT is not currently recommended for most cases owing to ionizing radiation exposure and a preponderance of false negative findings^{154,162}. An innovation in orthopaedic research is the use of a cone-beam CT, but its utility has yet to be fully established¹⁵³.

Screening

Although bone microdamage can be visualized using microscopy, no current imaging tool directly measures the amount of microdamage⁴⁴. Furthermore, direct measurement of stress and strain during *in vivo* activity is highly invasive and therefore not routinely feasible or practical. Developments in musculoskeletal modelling to incorporate biomechanical data such as kinematics and kinetics combined with finite element models may improve the estimation of bone stresses and strains and the individualization of safe training practices, but they currently lack universal practicality in the field^{15,87,111}. Current challenges in screening for bone stress injuries highlight the value of early diagnosis of symptomatic injuries at a low-grade stage to avoid progression to a complete fracture.

In the absence of objective screening tools, a clinical algorithm to identify individuals at risk may be most useful in daily clinical practice¹⁶³. Some promising algorithms based on the most important risk factors outlined above have been reported^{121,163,164}, but no algorithm has been successfully adopted for screening in daily clinical practice. Inadequate load monitoring, multifactorial aetiology and individual-specific anatomical, biomechanical and biological features are some of the difficulties faced in developing a screening tool.

Screening of bone characteristics may aid in the identification of individuals at risk of bone stress injury. Biochemical parameters to be observed may include serum 25-hydroxycholecalciferol, calcium, phosphate, osteocalcin, bone-specific alkaline phosphatase, parathyroid hormone, procollagen type I N-terminal propeptide, C-terminal telopeptide of type 1 collagen, urinary calcium/creatinine ratio and deoxypyridinoline cross-links^{165,166}. For decades, dual-energy X-ray absorptiometry (DXA) has been the standard technique to characterize bone health. DXA produces a 2D estimate of areal bone mineral density in g/cm². As DXA does not measure bone geometry or microstructure, it is an inadequate modality to determine the

true relationship of bone quantity and quality to risk of bone stress injury. High-resolution peripheral quantitative computed tomography (HR-pQCT) is an advance that allows 3D imaging and separate quantification of volumetric bone mineral density (in mg/cm³), bone microarchitecture and micro-finite element (μ FE) estimates of bone strength of peripheral bones. Although it is currently only a research tool, reference databases are available to express outcomes relative to expected norms¹⁶⁷. Some but not all studies indicate a relationship between bone mineral density or microarchitecture and bone stress injuries^{94,124,168–170}. Currently, there are no recommendations to use DXA or HR-pQCT on a routine basis, although their use might be reasonable in specific populations.

Prevention

In the absence of an ability to detect microdamage accumulation, prevention is primarily based on identifying modifiable risk factors. A bone stress injury occurs when cumulative loading exceeds the bone's ability to resist damage¹⁵. Consequently, preventive measures rely mostly on either optimizing load⁸⁷ or increasing bone loading capacity. In athletes and military recruits, physical activities to which individuals are unaccustomed are the most important risk factor^{171,172}. In running, a careful systematic increase in volume or speed may represent key factors in the prevention of bone stress injuries. The value of other training features, such as periodization or a targeted strength training programme, has yet to be determined, but they are presumed to be important¹⁷³. In addition, optimization of bone health is likely to be valuable for injury prevention. This approach includes the identification and treatment of low energy availability and specific nutritional deficits, as outlined above.

As nutritional deficits and other risk factors are continually being identified, awareness needs to be raised among athletes, parents, coaches and medical professionals. In a 2015 study, only 37% of 931 physicians had heard of the female athlete triad¹⁷⁴. The following may sound trivial but is in fact very important: maintaining adequate energy availability and normal hormonal function are key bone stress injury preventive measures for women and men. However, a consensus on recommended energy levels has not yet been reached, and cut-off values on BMI for participation in organized sports are predominantly not applied. Furthermore, early activity in high-impact, multidirectional sports such as basketball and soccer during youth have been proposed to reduce risk of future bone stress injury, particularly when there are 2 or more years of participation before puberty^{122,175}. Adequate vitamin D levels, which are achieved from the combination of sunlight exposure, diet and supplemental forms, might aid in the prevention or treatment of bone stress injuries, as discussed below.

Management

General guidelines

Bone stress injury management is guided by injury location. Bone stress injuries are generally classified as low-risk or high-risk based on the bone affected and location within the bone^{176,177} (TABLE 1). Although this classification is broad and may partly lack scientific evidence, it is a useful guide for clinicians who are faced with the question of choosing the optimal treatment strategy. Low-risk bone stress injuries occur on 'compressive' surfaces and usually heal without major complication. Typical low-risk injury sites include the second and third metatarsal shaft, posteromedial tibia, fibula, humeral shaft and ribs¹⁷⁷. By contrast, high-risk

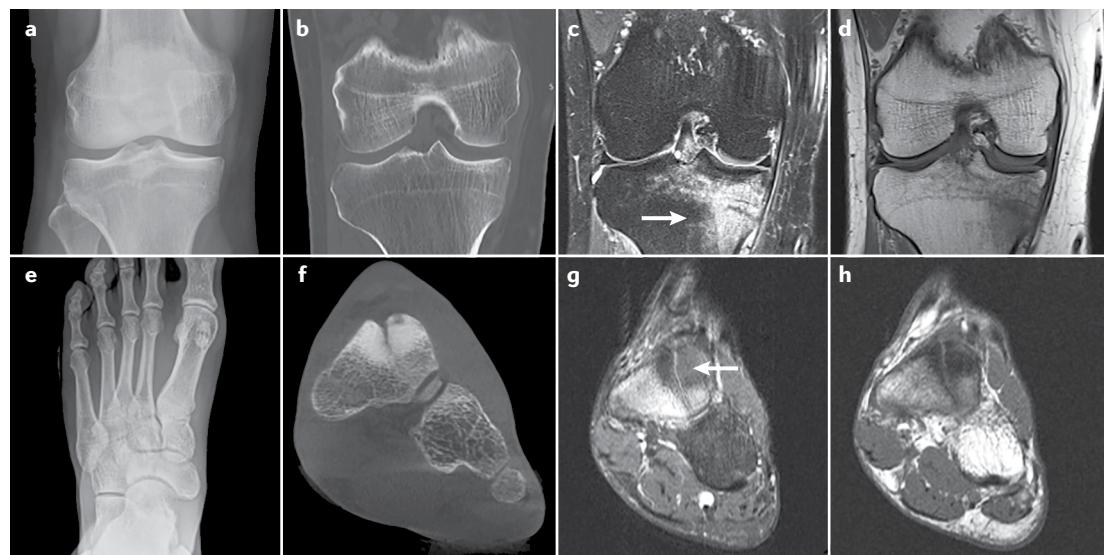


Fig. 6 | Imaging modalities for exemplary bone stress injuries. **a–d** | Bone stress injury to the medial tibial head. **e–h** | Bone stress injury to the os naviculare. Plain radiographs (parts **a** and **e**) are insensitive to detect bone stress injuries, but periosteal callus or cortical thickening can be indicative of a bone stress injury. CT (parts **b** and **f**) is rarely recommended but provides excellent osseous imaging. To date, MRI is the modality of choice. The typical signal characteristic is a hyperintense oedema (arrow) in fat-suppressed (T2-weighted) imaging (parts **c** and **g**) with corresponding hypointense signal on T1-weighted images (parts **d** and **h**). Anterior–posterior view is depicted in parts **a–e** and coronal view in parts **f–h**.

	Fredericson et al. (1995) ^a	Arendt et al. (2003)	Nattiv et al. (2013)	Rohena-Quiniquilla et al. (2018) ^b	Kaeding and Miller (2013)
Stress reaction	Mild to moderate periosteal oedema on T2; normal marrow on T1 and T2	STIR-positive	Mild marrow or periosteal oedema on T2; T1 normal	Endosteal marrow oedema ≤ 6 mm; no fracture line	Imaging evidence of stress fracture; no fracture line; no pain
	Moderate to severe periosteal oedema on T2; marrow oedema on T2	STIR-positive; T2-positive	Moderate marrow or periosteal oedema and T2-positive; T1 normal	Endosteal marrow oedema ≥ 6 mm; no fracture line	Imaging evidence of stress fracture; no fracture line; pain
	Moderate to severe periosteal oedema on T2; marrow oedema on T1 and T2	STIR-positive; T1- and T2-positive	Severe marrow or periosteal oedema on T1 and T2		
Stress fracture	Moderate to severe periosteal oedema on T2; marrow oedema on T1 and T2; visible fracture line	Visible fracture line on T1 or T2	Severe marrow or periosteal oedema on T2 and T1; visible fracture line on T1 or T2	Fx $< 50\%$ of femoral neck width	Non-displaced fracture
				Fx $\geq 50\%$ of femoral neck width	Displaced fracture (≥ 2 mm)
					Non-union

■ Grade 1 ■ Grade 2 ■ Grade 3 ■ Grade 4 ■ Grade 5

Fig. 7 | Overview of commonly used MRI-based classification systems for bone stress injuries. Numerous grading systems for bone stress injuries have been proposed. The Fredericson classification for tibial bone stress injuries is commonly adopted. Other systems have been introduced, including classifications proposed by Arendt et al.¹⁶⁰, Nattiv et al.¹⁵⁸, Rohena-Quiniquilla et al.¹⁵⁹ and Kaeding and Miller¹⁵⁷. Fx, fracture; STIR, short tau inversion recovery. ^aTibia only. ^bFemoral neck only. Adapted with permission from REF¹⁵², Sage Publications Inc.

bone stress injuries need special attention as they are prone to delayed union, non-healing, complete fracture, re-fracture or failure to (timely) return to sports¹⁷⁶. Although the underlying reasons have yet to be established, many high-risk injuries share common features, including high tensile rather than compressive forces, low blood supply and occurrence in weight-bearing bones. Typical high-risk injury sites include the base of the fifth metatarsal, hallux sesamoid, talus, medial malleolus, tarsal navicular, anterior tibia, patella and femoral neck¹⁷⁶. The management of a bone stress injury also includes identifying risk factors to develop an individualized programme that is conducive to healing, minimizes re-injury risk and facilitates safe return to activity. The three components of treatment include the following: first, determining initial strategy to allow for effective bone remodelling and healing (for example, surgical management versus non-operative treatment); second, a progressive loading programme to provide appropriate mechanical stress to bone and address modifiable biomechanical impairments; and third, a structured plan to allow return to activity. In each phase of treatment, the goal is to maintain a pain-free status to ensure bone stress injury healing.

Owing to the multifactorial aetiology of each bone stress injury and the goals of a patient, it is important to identify and address each risk factor at an individual level. All patients with bone stress injury should have lifestyle factors addressed to support bone health, including promoting appropriate nutrition, quality sleep and methods to reduce psychological stress¹²¹. Medications

might be considered in patients with impaired bone health or specific biological risk factors. Selective use of low-intensity pulsed ultrasound therapy, pulsed electromagnetic field, capacitively coupled electric field therapy, extracorporeal shockwave procedures or orthobiologics might be used owing to high patient safety, although there remains limited research to document efficacy of these approaches. Surgery might be considered when treatment is unsuccessful with non-operative management approaches or in select cases, such as some high-risk bone stress injuries.

Protected weight bearing and loading restriction

Activity restriction or modification is necessary to allow bone to initiate repair of damage. The decision on the use of crutches or immobilization is based on the anatomical location of the injury or pain with weight bearing^{87,178}. The combined use of a (tall) boot immobilizer is recommended for injuries to the fifth metatarsal and tarsal navicular, to ensure that no passive indirect traction from tendons compromises bone healing¹⁷⁹. Non-weight-bearing immobilization has traditionally been prescribed for about 6 weeks in many cases of high-risk bone stress injuries.

By contrast, low-risk bone stress injury to areas of compressive force on the long bones (for example, the femur, tibia, fibula and metatarsal bones) typically do not require weight-bearing restriction to facilitate healing unless pain is provoked with weight bearing. The presence of a fracture line, concern for delayed union or non-union, and other clinical situations in which

an individual might not comply with activity modifications, are other considerations for prescribing strict non-weight-bearing status^{87,177}. However, current guidelines support individualized decision-making by considering factors such as injury location, grade of injury, prior injuries, pre-injury training loads, age, competition level, patient compliance and hormonal status^{109,152,178}. Furthermore, patients with a bone stress injury in a high-risk location might benefit from referral to a specialist who has advanced knowledge in optimizing management of these injuries. Upper-extremity bone stress injuries are less commonly observed than those in the lower extremities, and management descriptors are limited, although similar principles on the use of splints, arm sling or other protective measures apply²¹.

Pain management

Pain can be a useful symptom that helps the patient and clinician to monitor healing response and guides what activities are safe to be performed at each stage of healing, which is important, as being pain-free is an excellent guide for gradual return to sports^{87,178}. Medications to treat pain associated with bone stress injuries are prescribed at the discretion of the clinician but, if possible, the use of NSAIDs should be avoided owing to an unfavourable risk/benefit ratio¹⁸⁰. An observational study in the military suggests that prior use of NSAIDs increases risk of bone stress injury, providing further support for avoiding such medications when treating a known bone stress injury¹⁴³.

Medications

The management of a bone stress injury and associated concerns of impaired bone health are primarily addressed through non-pharmacological strategies. Common targets for pharmacological treatment may improve with treatment of the low energy availability state through the combination of increasing energy intake and reducing exercise expenditure^{126,130}. In select cases of female athletes with persistent hypo-oestrogenism and associated oligo-amenorrhoeic state, use of transdermal oestrogen replacement therapy is considered an effective medical treatment. A common application is transdermal 17 β -oestradiol with cyclic oral progesterone, which improves bone mineral density and microarchitecture in athletes with oligo-amenorrhoea¹⁸¹. In male athletes, low testosterone levels may influence bone health; however, testosterone replacement therapy is rarely prescribed as a therapeutic agent for many reasons, including safety and human performance benefits with testosterone. In short, hormonal dysfunction in female and male athletes requires a thorough evaluation and the underlying cause should be addressed. In-depth discussion of this topic^{125,126,181} is beyond the scope of this Primer. Clinicians who do not have experience in treating these conditions are advised to consult with an endocrinologist or sports medicine clinician who is familiar with evaluating and treating these issues.

Bisphosphonates and RANKL antibodies, although commonly used in osteoporosis management, are not among the standard approaches for treating bone stress injuries¹⁸². Teriparatide and abaloparatide are two

parathyroid hormone-related protein analogues that are selectively used in managing bone stress injuries associated with low bone density. Use of this class of medication is supported by biological plausibility to promote bone healing and more global skeletal changes by targeting the parathyroid hormone 1 receptor and stimulating osteoblasts and increasing their longevity¹⁸². Experimental studies demonstrate that teriparatide may accelerate bone remodelling whereas the bisphosphonate alendronate delays bone remodelling in stress fractures¹⁸². Treatment with the sclerostin antibody romosozumab has been approved for severe postmenopausal osteoporosis but evidence is lacking for its use in bone stress injuries. The use of pharmacotherapy is not among the standard treatment approaches to date but may be considered in select patients (for example, those with underlying bone disease or when first-line treatment is unsuccessful). In all cases, medical decision-making should be ethically justified and strict compliance needs to be given to the world anti-doping rules in athletes. In addition, none of these medications is recommended for young individuals with open growth plates. Bisphosphonates, with their long half-lives, should not typically be prescribed to women in the reproductive years, owing to teratogenic risks in pregnancy.

Nutrition and the role of calcium and vitamin D

Bone healing requires optimization of both macronutrients and micronutrients that contribute to bone remodelling and support general physiology. Maintaining adequate energy availability through regular meals supports production of metabolic and reproductive hormones that promote bone healing^{125–130}. Patients identified as having suboptimal nutrition should meet a registered dietitian to obtain nutritional support. Patients with recognized disordered eating or an eating disorder should also be referred to clinicians who can assemble a multidisciplinary team to support healthy eating behaviours along with identification of associated psychological and medical conditions including depression^{125,126,130}.

Supplemental calcium¹³⁴ and higher milk consumption¹³⁶ may prevent bone stress injuries. However, the optimal dose of calcium to treat and prevent bone stress injuries has not been conclusively demonstrated. In general, dietary intake should be encouraged, as calcium-rich foods have good bioavailability, contain protein and phosphorus, and contribute to caloric needs to support bone health¹³⁶. Intake and supplement use should be spaced throughout the day, as optimal absorption of calcium may decrease in individual servings exceeding 500 mg (REF.¹⁸³). Similarly to calcium, the optimal intake of vitamin D has not been defined for bone stress injury healing and prevention. Both supplementation and higher total daily intake of vitamin D reduce risk of bone stress injuries^{134,135}. Although there is biological plausibility that achieving higher serum 25-hydroxyvitamin D (25(OH)D) levels might be helpful in management and prevention of bone stress injuries, the available evidence is insufficient to support higher intake for management of this form of injury¹⁸⁴. As a general recommendation, 25(OH)D levels should, at a minimum, exceed 20 ng/ml

or 50 nmol/l (REF.¹⁸⁵). Optimal serum levels and recommendations for supplementation in athletes, however, are a subject of debate^{185–188}.

Physical therapy

Physical therapy is commonly used in managing bone stress injuries. The goal of treatment is to address impairments identified as contributing to risk of injury, including deficits in range of motion, strength, motor control and flexibility¹⁷⁸. Use of crutches and offloading may result in muscle loss, and impairments in range of motion that are common following immobilization should be addressed. Gait retraining may be considered for runners who have repeated bone stress injuries^{87,178}.

Ultrasound, electric field and extracorporeal shockwave therapy

The use of externally introduced stimuli has been superficially studied in the management of bone stress injuries. Preclinical and preliminary clinical support exists for using low-intensity pulsed ultrasonography in managing bone stress injuries, but a pilot randomized trial did not find a benefit on recovery from low-risk tibial, metatarsal and fibular bone stress injuries¹⁸⁹. Despite lacking high-level evidence of efficacy, low-intensity pulsed ultrasound therapy is used in clinical management of bone stress injuries. Similarly, in a randomized controlled study of tibial bone stress injuries, capacitively coupled electric field therapy did not induce faster healing across all injuries, although higher-grade injuries healed faster with this treatment¹⁹⁰. Also, the application of pulsed electromagnetic fields is not fully established in clinical routine¹⁹¹. No high-level studies have been performed to evaluate the efficacy of extracorporeal shockwave therapy; however, resolution of non-union with this approach in delayed union of stress fractures in athletes has been documented in two case series^{192,193}.

Surgical management and orthobiologics

Choosing between non-surgical and surgical management relies on many individual factors, including bone site, level of sports performance and patient preference. Regardless of whether surgical care is provided, an individualized treatment approach requires shared decision-making. Ultimately, surgery is required for a minority of bone stress injuries.

Current published recommendations on surgical treatment are mostly driven by the location of injury and the patient's level of activity. In general, low-risk bone stress injuries can be treated non-surgically, with exceptions for displaced or non-union fractures. By contrast, high-risk bone stress injuries require a much more nuanced approach. In 2015, a systematic review indicated better outcomes for navicular and fifth metatarsal bone stress injuries when treated surgically, but the certainty of the evidence was low¹⁹⁴. Navicular bone stress injuries may be managed without surgery depending on the extent of injury^{195,196}. Recognition that non-surgical treatment may require a prolonged time to return to sports may factor into electing surgical treatment for selective populations (for example, elite athletes)¹⁹⁵. Fifth metatarsal bone stress injuries are often

addressed surgically in competitive athletes and the most common procedure is intramedullary screw fixation¹⁹⁷. Special attention must also be given to bone stress injuries of the femoral neck — a situation that may require prophylactic or therapeutic internal fixation in advanced non-displaced or displaced injuries, respectively¹⁵⁹. Among the most difficult injuries to address are those to the anterior tibia with a 'dreaded black line'. These injuries can be successfully treated with intramedullary nailing or use of tension plating, while recognizing the risk of surgical complications¹⁹⁸. Overall, decisions regarding timing for surgical management lack strong evidence to guide whether surgery should be offered as a first-line treatment or only after failed non-surgical treatment. The above-mentioned examples clearly demonstrate that bone stress injuries require a highly individualized treatment approach.

One area of clinical growth and research interest is the application of orthobiologics to aid in bone stress injury healing or in combination with surgical management. The term orthobiologics refers to a heterogeneous group of substances used to promote tissue healing and regeneration. Although orthobiologics might have great potential in management of bone stress injuries, barriers limiting widespread use include inconsistent regulation and variability in characterization, which in turn may explain the inconclusive clinical evidence with these substances¹⁹⁹. Bone grafts have value in non-union fractures and could be considered to augment surgical management of bone stress injury²⁰⁰. Various autologous and allogenic types of bone graft as well as synthetic bone graft alternatives are available²⁰⁰. However, although bone grafting procedures are generally safe, strong evidence to support their use in management of bone stress injuries has yet to be shown. Nevertheless, given the individualized treatment approach of surgical management, with every patient and case being considered as unique, the potential utility of bone grafting and other orthobiologic approaches should be acknowledged. Other orthobiologics that have been used for treatment of bone stress injuries include bone marrow aspirate concentrate, bone morphogenetic protein and bone matrix, platelet-rich plasma and platelet-derived growth factor²⁰⁰. Research on orthobiologic agents using consistent reporting measures may help to inform future clinical use¹⁹⁹.

Return to sports

For most low-risk bone stress injuries, a gradual return to sports activities can be initiated once the athlete is pain-free during daily activities⁸⁷. By contrast, high-risk injuries may require special attention, and initial treatment recommendations are encouraged before any kind of return to sports activity is allowed. In selected high-risk cases, clearance to start a return to activity may even be allowed only after repeated imaging demonstrates cortical bridging or other signs of bone healing. Several return-to-sport protocols have been published^{178,201} but the optimal strategy requires individualized decision-making^{202,203}. A previous history of bone stress injury is the most universal risk factor for a subsequent bone stress injury, which further suggests

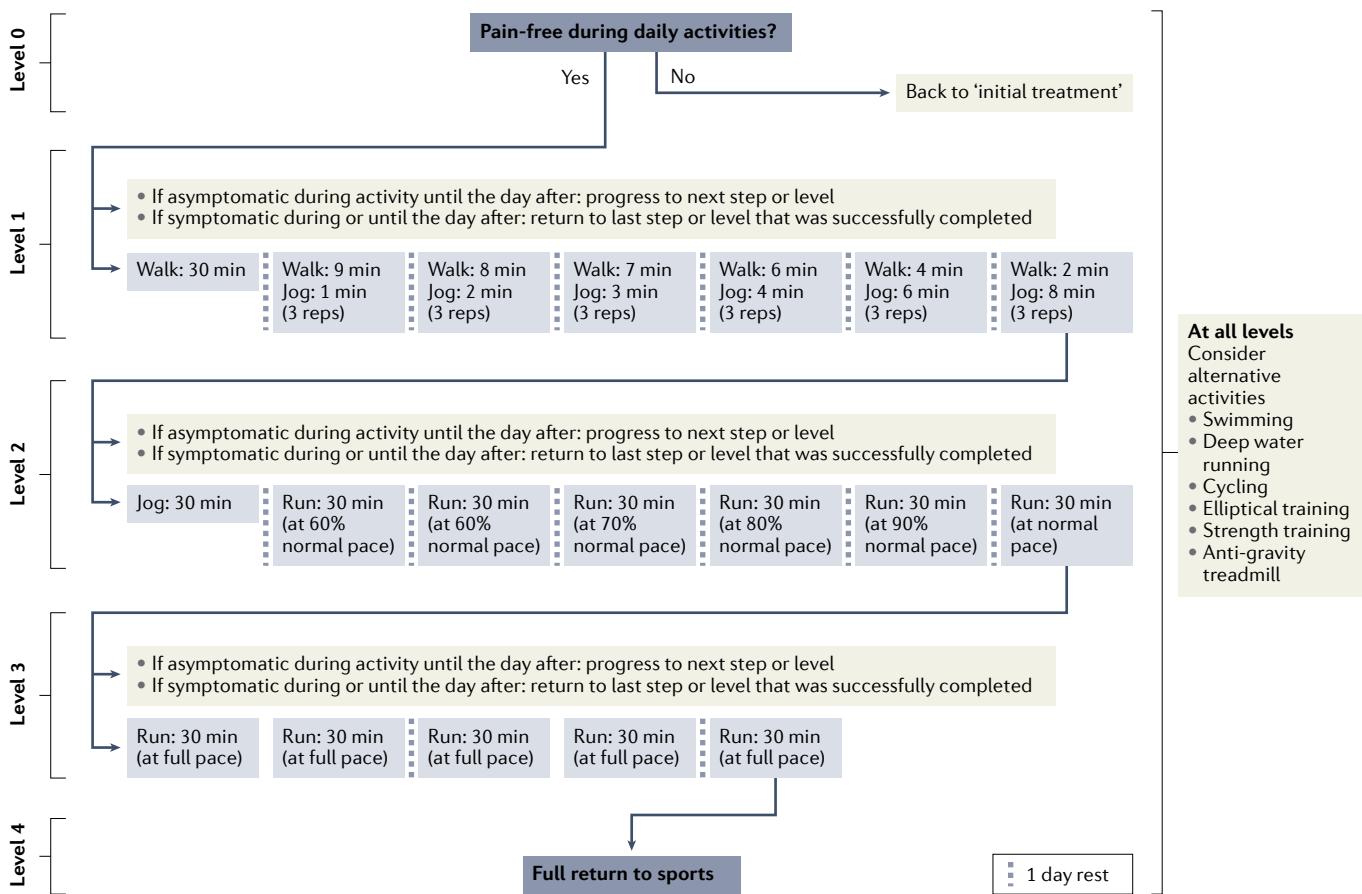


Fig. 8 | Protocol for return to running after a bone stress injury. According to the recommended protocol¹⁷⁸, patients must be pain-free during and after activities to progress between different activity intensity levels. Activity is increased gradually and progress is assessed on a daily basis. Jogging is running at 50% of normal running pace. Alternative sports with lower impact, such as cycling, pool running or swimming, can be a useful addition.

a need for improved understanding of optimal loading and return to sports²⁰². An example programme guided by pain provocation¹⁷⁸ is shown in FIG. 8. At all rehabilitation stages, patients need to be pain-free during and after activities. As many patients are unlikely to tolerate several weeks or months of inactivity, alternative sports with less impact, such as cycling, pool running or swimming, offer good alternatives⁸⁷.

Quality of life

Fractures to bone, whether atraumatic or traumatic, adversely affect quality of life. Just as with other musculoskeletal conditions²⁰⁴, bone stress injuries might lead to pain at sites exposed to mechanical force. This pain might result in restrictions of movement-related activities with, sometimes even worse, loss of social participation and happiness²⁰⁵. In military recruits, bone stress injuries are associated with increased risk of discharge from military service²⁰⁶. In athletes, bone stress injuries might result in considerable absence from sports participation and could be season-ending^{100,152}. Of note, absence from training or competition can be career-ending for elite athletes, with associated financial implications. From a public health standpoint, physical inactivity should be avoided, so ideally injuries that prevent activity should

be minimized²⁰⁷. Prevention and effective management of bone stress injuries are as important for people who are exercising for health benefits as for those aiming for sporting performance. This approach is also important because sports participation may be an important source of mental as well as physical health in active individuals. Besides psychological considerations, inactivity leads to detraining of muscles and cardiopulmonary organs. If detected and managed early enough, most patients can make a complete recovery from a bone stress injury¹⁵². Failure to diagnose or treat, however, might worsen the patient's condition. Undetected bone stress injuries might lead to serious complications, including complete bone fracture, delayed union, non-union, avascular necrosis and immobility^{176,208}.

Outlook

Underlying conditions that predispose to bone stress injuries are complex and heterogeneous. A multifactorial strategy that integrates anatomical, biomechanical and biological risk factors has the potential to provide a more comprehensive understanding of these injuries. Despite major improvements in understanding of bone biology, the exact pathogenesis of bone stress injuries has yet to be established. Because substantial gaps remain

in our understanding of the underlying contributions to injury and fracture occurrence, translation of knowledge into clinical practice faces challenges. For example, material and biological properties differ considerably in trabecular and cortical bone, but bone stress injuries are seen in both types of bone and do not have precise treatment plans based on bone composition. Individualized treatment is crucial to optimize outcomes and to avoid under- or over-treatment. Non-invasive strategies (such as extracorporeal shockwave therapy), the role of orthobiologics and both patient selection and techniques for surgical treatment should be studied more extensively. High-quality clinical trials are warranted with the aim of elucidating optimal treatment strategies. These trials are of major importance, as numerous claims and promises have been made with regard to multiple aspects of sports medicine and lifestyle health but these often lack strong evidence of efficacy.

Growth in our understanding of evaluation, management and prevention of bone stress injuries may result from technological advances. For example, substantial improvements in imaging have been achieved in recent years. Future studies could make use of these possibilities, and future research directions may include finite

element analysis, wearable technology and big data analyses. Furthermore, whether through technological advances or alternative approaches, researchers would benefit from methods to non-invasively monitor or measure bone stress, bone strain and microdamage accumulation. Scholars and clinicians should give attention to the multifactorial components of bone quality, as the ability to withstand fracturing comprises a collection of histological features. In this way, biomechanical, nutritional, pharmacological and other interventions aimed at strengthening bone might successfully aid in the treatment and prevention of bone stress injuries. Finally, and arguably of the greatest importance, is implementation of known lifestyle factors that may reduce the burden of bone stress injury and fractures. Safe spaces for physical activity and sport, appropriate nutrition and early detection of impaired bone health concerns may provide primary prevention. In this sense, government and organizational policy should heed the lessons from lifestyle factors demonstrated to have positive effects on bone health such as promoting physical education in early life⁶⁵.

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