A Meta-Analysis of the Prevalence of Lower Limb Asymptomatic Bone Stress Injuries in Athletes and Military Personnel.

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Abstract

Bone stress injuries (BSI) appear to be widely accepted throughout the medical and sports world, although the importance of asymptomatic injuries remain unclear and their clinical relevance questionable.

Objectives: To determine the prevalence of asymptomatic BSI in the lower limb using a systematic review of the published literature, secondly to identify any differences between athletic and military populations in the prevalence of lower limb asymptomatic BSI and finally to highlight the locations in the lower limb with the highest prevalence.

Subjects and methods: An electronic database search was conducted using two databases: PubMed and Medline. Two observers independently systematically reviewed these data, assessing the studies against pre-determined criteria. The number of subjects BSI, location and imaging modalities were subsequently extracted from the selected studies. A mixed model analysis with random effect was used to calculate prevalence rates, confidence intervals and p values.

Results: The overall prevalence rate of asymptomatic BSI was 27/100 from all studies (military, athletes and civilian). Athletes had a significantly higher prevalence of asymptomatic BSI 75/100 than military personnel 28/100 ($p= 0.0065$), although the overall rates of BSI were not significantly different between these populations. The tibia was the most prevalent site for both symptomatic and asymptomatic BSI with 9.3 and 7.7 per 100 patients respectively and there was a significant difference between symptomatic (0.3/100) and asymptomatic (28/100) BSI in the tarsal bones ($p=0.049$) and in the fibula, 2.4/100 symptomatic and 6.8/100 asymptomatic ($p=0.024$).

Conclusion: Although a number of studies identified the existence of asymptomatic BSI, most failed to provide adequate follow-up in order for their clinical significance to be properly assessed and thus it is difficult to postulate the clinical significance of the 27/100 prevalence rate given a lack of empirical evidence. The higher prevalence of asymptomatic BSI in athletes is probably multifactorial with training history, motivation, fitness levels and sampling bias all possibly explaining some or all of this higher rate.

In summary this review has identified a clear gap in the literature for a large robust study examining asymptomatic BSI with clinical follow up in order to clearly establish the role of asymptomatic BSI.

Acknowledgements

A major project like this is never the work of any one person and as a mark of thanks I would like to acknowledge both the individuals and organisations for their contributions.

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Abbreviations

99mTc = Technetium -99m

CT = Computer Tomography

BME = Bone Marrow Edema (also known as Bone Marrow Oedema)

BSI = Bone Stress Injury

FOV = Field of View

FSE = Fast Spin Echo

Gd-DTPA = Gadolinium Diethylenetriamineentaacetic acid

MR = Magnetic Resonance

MRI = Magnetic Resonance Imaging

mSv = Millisievert

MT = Metatarsal

MTSS = Medial Tibial Stress Syndrome

RCT = Randomised Control Trial

ROI = Region of Interest

SE = Spin Echo

SF = Stress Fracture

STIR = Short Tau Inversion Recovery

T = Tesla

T1 = Longitudinal Recovery

T2 – Transverse Recovery

TE = Time to Echo

TI = Inversion Time

TR = Time to Repeat

US – Ultrasound

Introduction

The term bone stress injury (BSI) is used to encompass a wide range of bone injuries caused by repeated mechanical stresses that can result in a partial or complete fracture (Kiuru, Pihlajamaki, & Ahovuo, 2003; Markey, 1987; Martin & McCulloch, 1987) and can be either symptomatic or asymptomatic.

Symptomatic Bone Stress Injuries

The majority of BSI reports that appear throughout the literature present with pain, and in particular in response to exercise (Clement et al., 1993) for which there are a number of reasons for this. Firstly, retrospective studies where the evidence is already captured make the reporting much simpler (Arendt, Agel, Heikes, & Griffiths, 2003). Secondly, it is easier and more cost effective to study samples that are known to have symptoms as they are more likely to have a BSI and thirdly the ethical considerations of potentially irradiating participants who may well be asymptomatic are significant. Thirdly gaining ethical approval for such a study, especially when little is known about the clinical relevance of asymptomatic BSI, is therefore difficult, particularly if ionising imaging modalities are being utilised.

The relationship between the 'bone strain continuum' and pain depicted in Figure 1 provides a useful guide when thinking about BSI (Bennell & Brunker, 2005). Patients present at various stages along this continuum: from completely asymptomatic through to mild symptomatic bone stress and to full-blown stress fractures and beyond (Fullerton & Snowdy, 1988).

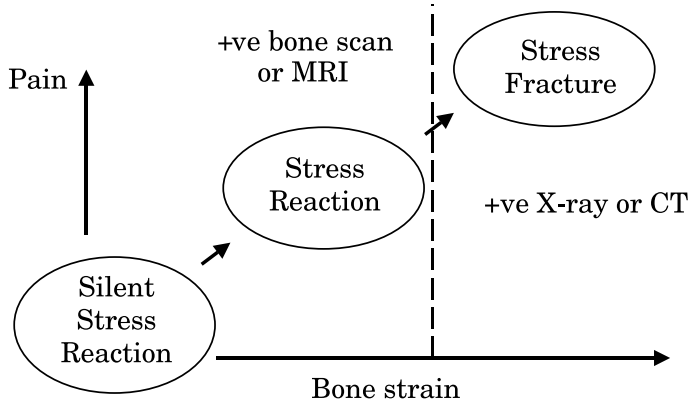


Figure 1: A graph depicting the 'bone strain continuum' and its relationship to pain and diagnostic findings (Bennell & Brunker, 2005, p. 175).

Asymptomatic Bone Stress Injuries

Asymptomatic BSIs are defined as BSI that are detected incidentally through medical imaging without clinical symptoms (Groshar, Lam, Even-Sapir, Israel, & Front, 1985). This type of injury has had much less attention within the world of research. This is in part due to the way in which BSI research has been conducted and reported as previously noted. It could be argued that it is difficult to image what is unknown, however there have been a number of studies examining symptomatic BSI which have noted incidental findings in the form of asymptomatic BSI (Ruohola, Kiuru, & Pihlajamaki, 2006). Furthermore there has been an increase in prospective studies imaging physically active asymptomatic sample populations with MRI, whilst this is expensive it has presented positive findings. Their appearance on medical imaging are identical to symptomatic BSI, but often occur as lower grade lesions, (Figure 2 for MRI), but they can also appear as higher grade changes such as fracture lines and callus (Kiuru et al., 2003; Matheson et al., 1987a). On bone scintigraphy they appear as hotspots again usually as lower grade BSIs. The lesions can appear as multiple foci or as solitary lesions on the ipsilateral and/or contralateral side (Hod et al., 2006; Kuusela, 1984; Nussbaum, Treves, & Micheli, 1988; Zwas, Elkanovitch, & Frank, 1987).

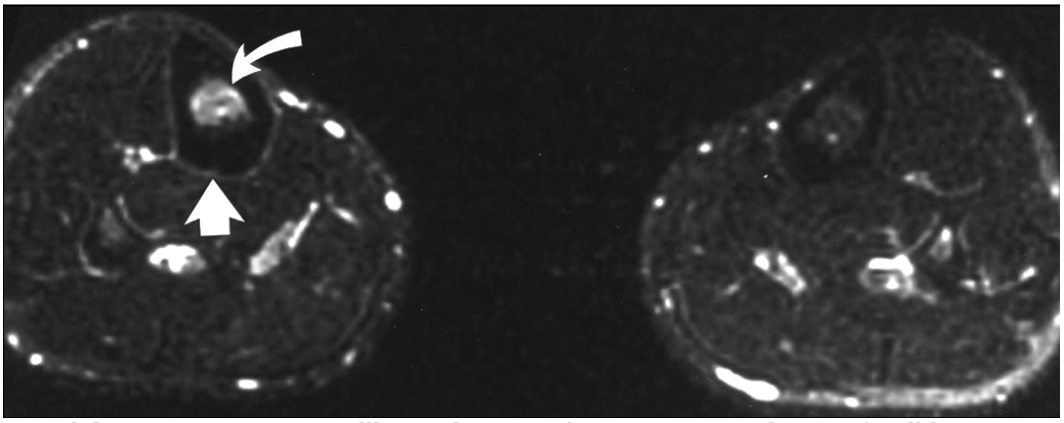


Figure 2: An axial MRI T2 FS sequence illustrating a grade 2 asymptomatic BSI of a tibia. This MRI sequence demonstrates a grade 2 BSI (Fredericson, Bergman, Hoffman, and Dillingham, (1995) grading system) on the right tibia with periosteal oedema posteriorly (straight arrow) and BME (curved arrow). Note the left is normal (Bergman, Fredericson, Ho, & Matheson, 2004, p. 637).

Similarly to symptomatic, asymptomatic individuals also report a history of increased biomechanical stress rather than trauma. This is important, as this systematic review is not examining occult fractures from a trauma, which according to Yao, Johnson, Gentili, Lee, and Seeger, (1998) can take on a similar appearance on MRI as bone bruises or BME in their low grade form and as such will exclude them during the data collection process using special exclusion criteria.

The clinical relevance of these asymptomatic lesions has been in dispute. Evidence from Chisin, Peyser, and Milgrom, (1995) and Gofrit and Livneh, (1994) suggest these are incidental findings of no significance and that any increased uptake/signal on imaging is normal physiological adaptive remodelling in response to increased stress and not BSI.

However there is also a significant and growing body of evidence to suggest the opposite, with varying degrees of clinical relevance (Groshar et al., 1985). A study with 340 conscripts provided has evidence to suggest they are a precursor to high grade BSI and that if training is continued they can develop into symptomatic BSI with some even noting fracture lines and callus formation on asymptomatic sites (Kiuru et al., 2003). Roub et al., (1979) published a continuum of bone response to stress, Figure 3 which illustrates the 'grey area' of symptomatic and asymptomatic BSI between numbers 3 and 4.

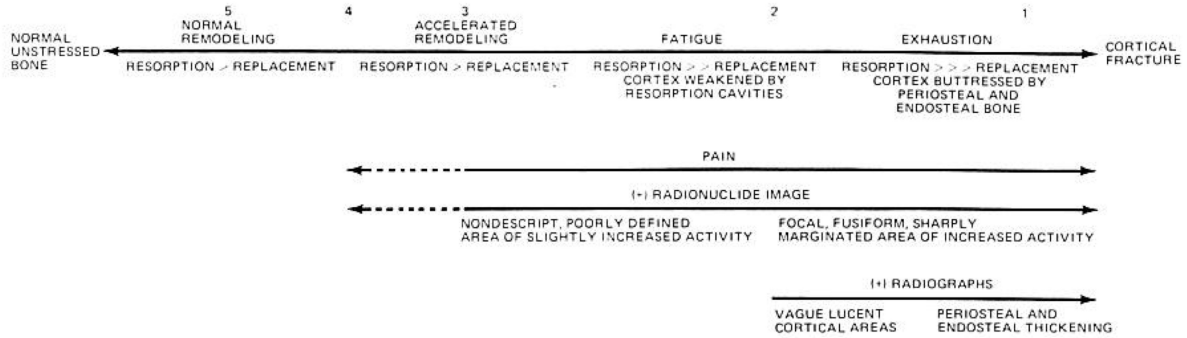


Figure 3: A diagram depicting the continuum of bone in response to varying levels of stress and its relation to pain and radionuclide images and radiographs
(Roub et al., 1979, p. 436).

A gap in the literature?

BSI, once limited to military personnel, has with the growth of competitive sports, become a widespread problem amongst athletes too. There are high costs, both financially and professionally to the military and athletes alike and furthermore it is a concern of a wider number of people and organisations including: clinicians, sponsors and other stakeholders. For example in the American military it was estimated that annual costs of $1.85 USD (United States Dollar) were a result of BSIs in 2,000 female marine recruits (Subcommittee on Body Composition, 1998). A multiple intervention strategy to reduce overuse injuries in particular femoral neck BSI demonstrated that the interventions appear to have reduced the number of BSI of the femoral neck by 75 and calculated that $5.3 USD million were saved (Scott et al., 2012). Extrapolate that figure to incorporate BSI throughout the skeleton and across the globe the figure would be astronomical and provides a real insight to the impact of this injury. These costs to the military can be broken down into discrete areas. For example: the cost to recruit a replacement solider, medical expenses including treatment (sometimes surgery), rehabilitation, salary during injury, rehabilitation and on occasion severance pay (Scott et al., 2012) as the occurrence of BSI can result in early discharge during marine-corps basic training (Reis, Trone, Macera, & Rauh, 2007).

With athletes this is less tangible, depending on if they have sports contracts, however athletes may lose fitness and or miss competitions, which could ultimately result in premature retirement (Knapp & Garrett, 1997).

Consequently, because of these costs within the physical performance domain there has been a vast amount of research in this field. The majority of published studies focus on symptomatic BSI with asymptomatic the focus of a growing minority. Despite the number of studies there is a lack of coherence in: study design, terminology, grading systems, imaging modalities etc. This has led to confusion within the physical performance domain, of the diagnosis, management, and treatment and in particular the clinical significance of asymptomatic BSI. This thesis will systematically examine the current literature on asymptomatic BSI, presenting a general prevalence rate and finally will attempt to assess the importance to a range of populations of this rate, adding to the knowledge base of what appears to be a relatively under reported injury.

Review of the Literature

History

19th Century

The first recorded BSI was in 1855 in military personnel who presented with painful swollen feet after long periods of marching (Morris, 1968). Breithaupt, a Prussian military physician, termed this *'Fussgeschwulst'* (foot swelling or tumour) thinking the condition was a traumatic inflammatory reaction in the tendon sheaths (Morris, 1968).

Twenty-two years later in 1877, Weisbach's studies (as cited in Morris, 1968) led him to believe that the lesion was in the ligaments and termed the condition *'syndesmitis metatarsea'* and later still Pauzat (1887) reported (as cited in Morris, 1968) occurrence was not limited to the second metatarsal and noted that they were able to palpate periosteal proliferation on the second, third and fourth metatarsals (Morris, 1968).

Wilhelm Rontgen's discovery of X-rays in 1895 enabled Stechow (as cited in Morris, 1968) to provide the first radiographic evidence that a metatarsal fracture (Figure 4) was the cause of these lesions, which in 1897 became known as the 'March Fractures' (Morris, 1968). Radiographic evidence revolutionised the ability to research this injury in more detail than ever before.

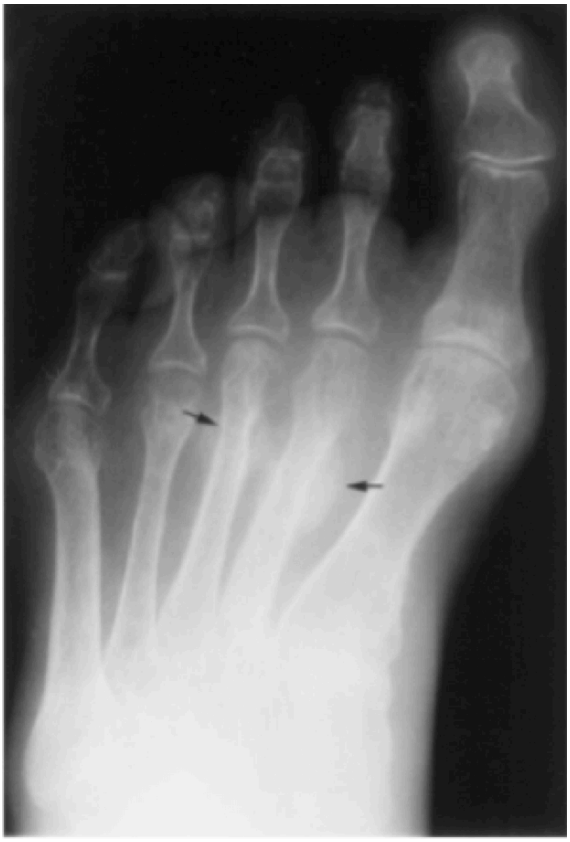


Figure 4: A radiograph of stress fractures to the second and third metatarsal in a runner. Note the periosteal reaction but no fracture is seen (arrows) (Boden, Osbahr, & Jimenez, 2001, p. 109).

20th Century

For many years this injury remained confined to military personnel and as X-ray became increasingly utilised a greater knowledge was gained including the occurrence in other bones (Morris, 1968). The first BSIs in civilians were confirmed by Deutschlander in 1921 in six women (Brukner, Bennell, & Matheson, 1999). With the advent of competitive sports it has since become a widespread problem amongst athletes (Bennell, Malcolm, Thomas, Wark, & Brunker, 1996a; Matheson et al., 1987b). However it was almost one century after its first diagnosis, in 1956 that the first athletes were reported with this injury (Devas & Sweetnam, 1956). As professional sport continues to increase in popularity, with large amounts of training similar to that previously seen only in the military, the problem has exacerbated. Recreational sport has also become increasingly popular in civilian populations which is reflected in the incidence of BSI within the general population. The military have also changed the type of training from marching to more running based activities, mirroring that of professional athletes (Kiuru et al., 2003; Markey, 1987). BSIs

have been compared in military personal to athletes and although some clinical differences were noted, essentially the pathology was the same (McBryde, 1976).

However it is the advancements in medical imaging such as bone scintigraphy, Computer Tomography (CT), Magnetic Resonance Imaging (MRI) that has allowed researchers to delve deeper into BSI pathogenesis and presentation.

In the 1980s and 1990s interest continued to grow in both recreational and professional sport, which fuelled an interest and real need to identify possible risk factors and implement modifications in an attempt to reduce BSI (Bennell, Matheson, Meeuwisse, & Brukner, 1999). The biggest studies have been undertaken in military medicine, these have been instrumental in developing much of what is known about BSI (Gofrit & Livneh, 1994; Milgrom et al., 1985b). This investment is primarily financially motivated and aims to reduce the number of recruits lost to BSI (Subcommittee on Body Composition, 1998).

21st Century

In the last 13 years scientific advances in imaging have meant that MRI – the current gold standard has become increasingly available to all, resulting in quicker diagnosis and therefore improved recovery. More powerful computer processing and technology advances have also allowed better computer modelling with regard to biomechanical modelling (Crossley, Bennell, Wrigley, & Oakes, 1999) and gene analysis (Yanovich et al., 2012) all of which have offered an excellent platform for further research to be undertaken, extending the knowledge base.

Terminology of Bone Stress Injuries

The terminology of this injury has undergone many transformations since it was first reported in 1855, resulting with inconsistent definitions across the literature. As noted above, there was an initial failure to understand the true nature of the pathogenesis of this injury. Consequently in the beginning definitions attempted to describe the aetiology, of which there were a myriad:

- fussgeschwulst,
- syndesmitis metatarsea,
- march fracture,

- Deutschlander's disease,
- pied force,
- overload fracture,
- wear-and-tear fracture,
- recruit's disease,
- periostitis ab exercitio,
- osteopathia itineraria,
- soldier's fracture,
- spontaneous fracture,
- pseudo fracture,
- insidious fracture,
- creeping fracture
- crack fracture,
- exhaustion fracture

(Brukner et al., 1999).

As understanding improved the terms *'fatigue fracture'* and *'stress fracture'* appear to be the most popular and used interchangeably within literature over the last few decades. However Matheson et al. (1987a, p. 72) attempted to explain the problems with these terms and to quote:

Since the term 'stress fracture' implies an all or nothing phenomenon, it limits the understanding of the bone response to loading at points below the yield strength.

Stress reaction is another term used increasingly to describe low-grade bone stress injuries, where the bone is weakened but the continuity is not disrupted (Jones, Harris, Vinh, & Clint, 1989).

For the purposes of this study the term Bone Stress Injury (BSI) will be used. Coined by both Markey, (1987) and later Kiuru et al., (2003), it encompasses the wider spectrum of bone injuries caused by repeated mechanical stress. It reflects the true dynamic response of bone to stress and is more inclusive of the bone changes within the continuum, from early remodelling to frank fracture (Kiuru et al., 2003; Matheson et al., 1987b). BSI can

be classified further for the purpose of treatment and management if required. Whilst the author does not wish to offend previously published research, for the sake of consistency and simplicity in this paper the term stress fracture and fatigue fracture will be changed to the umbrella term of BSI.

Other Terminology

Confusingly there are many terms 'loosely' connected to BSI that change over time, making it difficult to draw solid conclusions from both the older and newer research and include:

- insufficiency fracture
- medial tibial stress syndrome (MTSS)
- traction periostitis
- shin splint

Insufficiency fractures occur when pre-weakened bone (from old age, drugs or other medical conditions) fail under normal amounts of physiological stress, whereas a true BSI occurs when an excessive amount of normal stress is applied to normal bone (Kiuru et al., 2003; Matheson et al., 1987b).

Traction periostitis is another term used interchangeably with MTSS, confusingly BSI has been reported in patients with MTSS with local resorption around the MTSS site (Moen, Tol, Weir, Steunbrink, & De Winter, 2009).

A shin splint is a non-specific term, pertaining to activity related pain in the shin, from a wide range of conditions (Bradshaw, Hislop, & Hutchinson, 2006). Broadly there are three common problems: bone stress, chronic compartment & MTSS and a range of less common causes all of which have been placed under the umbrella term of shin splints (Bradshaw et al., 2006).

Whilst the American Medical Association (American Medical Association, 1966) reported that shin splints should be limited to musculo-tendinous inflammation and not incorporate BSI, throughout the literature there have been tenuous links between 'shin splints' and BSI, with a number of authors relating them to part of the bone stress continuum.

Originally a negative plain radiograph diagnosed shin splints. In one study, possible lower limb injuries were radiographed throughout 12 weeks upon which if no positive lesion presented it was deemed a shin splint (Aoki, Yasuda, Tohyama, Ito, & Minami, 2004). Furthermore this study used MRI as a comparison. They found it possible to differentiate between the two, where shin splints were reported to having linear abnormally high signal on T2 fat saturated sequence along the medial posterior surface of the tibia or medial bone marrow, whereas a BSI has abnormally wide signal in bone marrow (Aoki et al., 2004).

As mentioned shin splints are thought to be caused by musculo-tendinous inflammation from excessive use of foot flexors (American Medical Association, 1966). Contentiously one of the possible causes of BSI is fatigued muscle and which may suggest that they are related. However in order to avoid potential contamination of results none of these terms will be included in this study, but are hereby mentioned as they maybe an interesting area for further study.

The Incidence Rates of BSI

Across the physical performance domains there have been large variations in the incidence of BSI in the lower extremity. In athletes, the incidence of BSI varies from: 8.7% in a study of runners (Nattiv, 2000); 21.1% - 31.1% in track and field athletes (Bennell et al., 1996a; Johnson, Weiss, & Wheeler, 1994); 9.9% in elite gymnasts (Dixon & Fricker, 1993). The incidence of BSI in the military has an even wider range from: 1.1% (Pester & Smith, 1992) and 3.4% (Brudvig, Gudger, & Obermeyer, 1983) to 31% (Milgrom et al., 1985a).

There is also significant variation between male and female incidence in military studies. Brudvig et al., (1983) reported an incidence of 0.9% and 3.4% for males and females respectively. Whilst Jones, Bovee, Harris, and Cowan (1993) found an incidence of 2.4% for males but 12.3% in females and later still Armstrong, Rue, Wilckens, and Frassica (2004) reported 2.3% in males and 8.4% in females.

There also appear to be international differences: Milgrom et al. (1985a) reported 'unusually high incidences' of 31% of recruits found with BSI amongst Israeli soldiers. In contrast, published incidences in American soldiers have been between 1.1% (Pester &

Smith, 1992) and 3.4% in female recruits and 0.9% for their male counterparts (Brudvig et al., 1983).

It was proposed that a possible cause of this high incidence in Israeli recruits was related to the study design as they studied prospectively and "included scrupulous follow-up" of all participants until the subjects had completed their training (Milgrom et al., 1985a). Whereas in America the majority of military studies are retrospective and the incidence is calculated by relying on self-reporting (Brudvig et al., 1983).

Furthermore it was suggested that education was another factor in high incidence rates (Milgrom et al., 1985a). In the Milgrom et al. (1985a) study all the participating recruits and staff were informed of the objectives of their investigation including an explanation of what BSIs were, including possible presenting symptoms, resulting in all medical staff having a high index of suspicion when they examined or interviewed all the recruits every three weeks throughout the study.

The primary tool for evaluating BSI was bone scintigraphy in the Milgrom et al. (1985a) study, although radiographs were also utilized to a much lesser degree. They did not however use a second modality to confirm the existence of all the lesions visualised on bone scintigraphy, which may have potentially resulted in a higher incidence being reported. Brudvig et al. (1983), Pester and Smith (1992) and Provost and Morris (1969) primarily used radiographs, with its lower sensitivity to diagnose BSI, and only used bone scintigraphy in limited cases, possibly reducing the incidence rate.

The literature has consistently reported that bone scintigraphy has a much higher sensitivity to BSI than radiographs, resulting in a higher likelihood of BSI being diagnosed. In one study it was reported that X-ray confirmed the presence of BSI in only 20% of cases when compared to bone scintigraphy results (Milgrom et al., 1985a). Furthermore, in the Milgrom et al. (1985a) study, bone scintigraphy of the whole body was performed on every symptomatic patient. This included high-resolution imaging of the pelvis and lower limb, which invariably found BSI at additional sites that may or may not have been symptomatic (Milgrom et al., 1985a) and the actual training involved may have increased the risk of BSI as the distribution of BSI throughout the training, as according to Milgrom et al. (1985a) it was significantly different from the pattern seen in American recruits.

This theory may be supported by the evidence that the American soldiers appeared to sustain their BSI injuries earlier in the training programme (Greaney et al., 1983).

These large variations across both athletic and military domains may be the result of a number of factors including: level and type of activity, level of fitness, the sensitivity of clinical and imaging examinations and variations in terminology and methodology. Therefore it is difficult to compare the incidence rates between military personnel and athletes without further examination of the data. The size and methodology used in the various investigative studies lend themselves to bias. For example, military studies have access to larger, more closely matched cohorts potentially reducing bias and possibly producing more statistically reliable results.

Distribution of BSI throughout the Skeleton

The distribution of BSI reported throughout the literature appears to have shifted with changes to: equipment, training and the development of medical imaging (Kiuru et al., 2003; Markey, 1987). Initially studies before and during World War II described this injury being 'reserved to the foot' of soldiers, in particular the metatarsals and as such was coined *'March fracture'* (Bernstein & Stone, 1944; Hartley, 1943).

There have been many changes in training regimes but none more so than the move from drilling exercises and parades on paved surfaces to marching and running (Giladi, Ahronson, Stein, Danon, & Milgrom, 1985), thus significantly increasing the fitness levels of soldiers, enabling them to run faster, harder and more regularly. An increased awareness of, equipment changes, principally to footwear, have also enabled soldiers to sustain a greater level of training than was previously possible. Finally the significant developments in medical imaging and the greatly increased sensitivity of the various imaging techniques have enabled the reporting of subtler and possibly asymptomatic BSI (Brukner et al., 1999).

By the 1960s a changing trend was observed in the distribution of BSI, with a decrease of metatarsal BSI: 51% (Blickenstaff & Morris, 1966) 38.7% (Darby, 1967) and an increase of tibial BSI: 17% (Blickenstaff & Morris, 1966) 13.3% (Darby, 1967). In the 1970s metatarsal BSI still remained the most prevalent in military personnel, whilst fibulae BSI were more prevalent in athletes (McBryde, 1976). Later studies further support these

shifts and by the 1980s the increase in tibial and femoral BSI was accompanied by a further reduction in BSI in the feet: One study reported that only 2% of BSI occurred in the feet, whilst 71% presented in the tibia and 25% in the femur (Giladi et al., 1985). Whilst another study reported 49.1% of BSI in the tibia of Canadian athletes, 34.1% in the feet and 7.2% in the femur (Matheson et al., 1987b). In the last 30 years this distribution has been mobile: Papalada et al. (2012) reported 51% in the tibia, 1% in the femur and 40% in feet of track and field athletes. In addition, the sex of the participant also has a bearing on the distribution as well as the incidence as previously noted. Pester and Smith (1992) reported the distribution of BSI of males and females recruits as follows: MT, 66% (M) 31% (F) calcaneal 20% (M) 39% (F) and lower leg 13% (M) 27% (F).

While this thesis is solely examining BSI in the lower limb (femur to toes), BSI can occur almost anywhere within the skeleton if a repetitive stress placed upon it exceeds the bone's strength. Examples include: vertebral BSI, common in cricket bowlers (Ranson, Burnett, & Kerslake, 2010), rib BSI are frequently in rowers (Hickey, Fricker, & McDonald, 1997), the ulna in weightlifters (Hamilton, 1984), whilst humeri BSI are common in tennis players (Lee et al., 2006) and finally pelvic BSI are often related to running so both track and field athletes and military personnel are at increased risk (Kiuru et al., 2003; Matheson et al., 1987b).

Normal Anatomy of Bone

The skeletal system consists of bone, a specialised connective tissue accompanied by cartilage (Saladin & Porth, 1998). Bone is a living, metabolically dynamic tissue undergoing constant formation, resorption and remodelling which four bone matrix cells are responsible (Saladin & Porth, 1998).

Osteogenic (Osteoprogenitor cells): develop from embryonic mesenchyme, although they are slightly more specialised and have reduced development potential. They appear in the endosteum, inner periosteum and haversian canals (Figure 5).

Osteoblasts: known as the 'building cells', are immature bone cells, they are different from the osteogenic cell, and their main job is to synthesise and secrete bones organic matrix (Figure 5).

Osteocytes: Once osteoblasts deposit matrix (which is the intercellular substance of the bone tissue) they become trapped within lacunae or small spaces. From this point they cease producing matrix and begin maintenance, ensuring the equilibrium of calcium and phosphate between blood and bone (Figure 5).

Osteoclasts: These cells originate from the fusion of monocytes and are responsible for shaping the bone (bone resorption). Osteoclasts dissolve the bone by secreting acids and enzymes that break down the organic matter of salts and the matrix and release minerals into blood plasma (Figure 5).

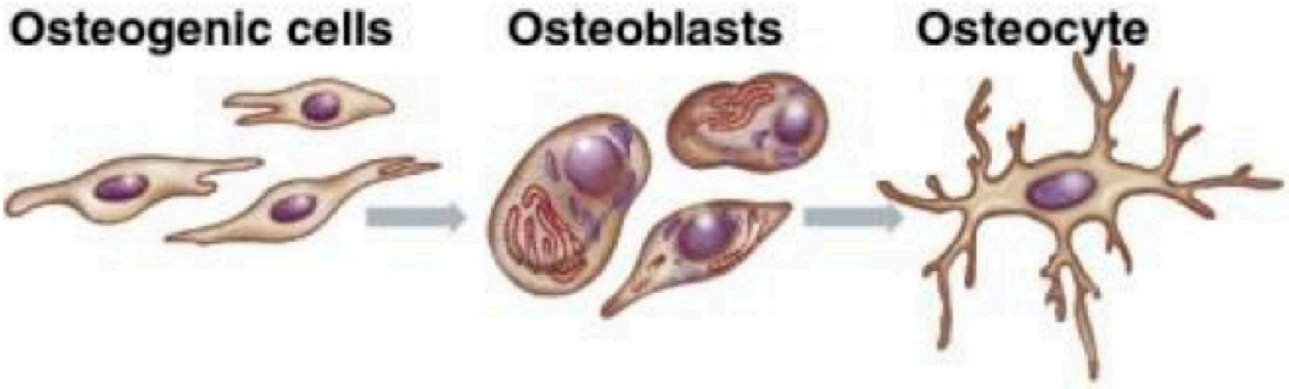


Figure 5: An illustration of Osteogenic, Osteoblast and Osteocyte cells (Saladin & Porth, 1998, p. 232).

These bone cells are responsible for regulating bone metabolism in response to various extrinsic signals – more specifically for this paper, 'stress' (Saladin & Porth, 1998). The hormone cytokine growth factor modulate cellular activity, cell differentiation and intra cellular communication (Heymann & Roussellem, 2000). At a macroscopic level the bone is divided into two types: compact and cancellous.

Compact (cortical) bone accounts for 80% of the skeleton (Brukner et al., 1999) and forms the outer layer. Microscopically bone is made up of both organic and inorganic matter. Approximately 25% is organic, including extracellular matter (protein fibres like collagen) and the aforementioned cells, all of which aid flexibility and tensile strength. A further 50% is composed of inorganic components, 85% hydroxyapatite (a mineral salt), 10% calcium carbonate and the remainder combines magnesium, sodium, potassium, fluoride, sulfate, carbonate and hydroxyl ions to give bone its rigidity and the final 25% is water (Saladin & Porth, 1998).

Osteons make up two thirds of adult cortical bone, with each osteon consisting of a central haversian canal containing small blood vessels and nerve fibres, surrounding this are concentric layers of lamella, (Figure 6). This arrangement provides strength and support for the vast majority of bone mass (Brukner et al., 1999). Lamellae are highly organised densely packed collagen fibrils that are present in both compact and cancellous bone. On the outer border of the lamellae are lacunae (small cavities) and situated in each one is an osteocyte. Canaliculi are small channels that project outwards from each lacunae and form a network, connecting adjacent lamellae's lacunae and the haversian canal (Brukner et al., 1999). A thin layer of organic matrix (cement) separates each osteon (Figure 7). It is thought that BSIs initiate through these lines initially (Buckwater, Glimcher, Cooper, & Recker, 1995).

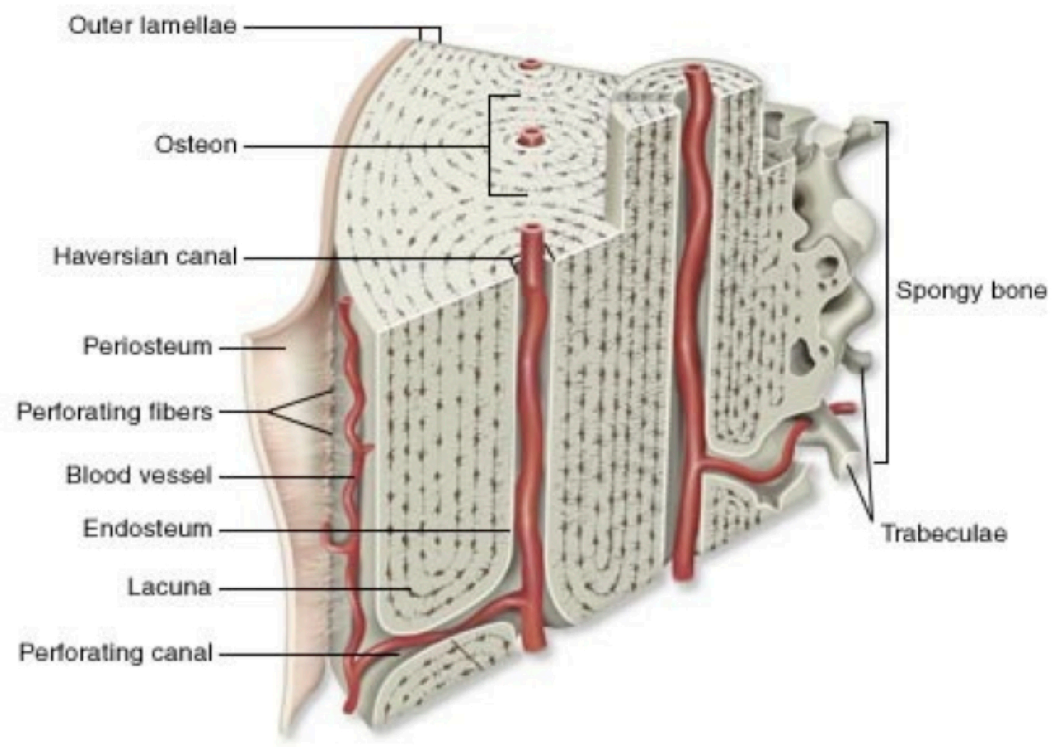


Figure 6: A three dimensional illustration of the structure of compact bone (Saladin & Porth, 1998, p. 235).

Cancellous (trabecular) bone in contrast makes up the other 20% of the total skeleton (Brukner et al., 1999) it is lighter and less stiff but weaker due to its lattice architecture, called trabeculae with a honeycomb appearance (Seeley, Stephens, & Tate, 2000). The

architecture of cancellous bone means it has a greater surface area than compact bone, making it more suitable for metabolic activity (Saladin & Porth, 1998). Microscopically cancellous bone is similar to compact bone, with its matrix arranged in lamellae, however there are fewer osteons as they are not required to the same degree as the osteocytes are close to the blood in the marrow (Saladin & Porth, 1998).

Cancellous bone is highly vascular and has bone marrow situated within the spaces of the trabeculae (Saladin & Porth, 1998). There are two types of marrow: haematopoietically active red marrow (where red blood cells are produced) and haematopoietically inactive yellow marrow (Saladin & Porth, 1998). The ratio of red and yellow marrow within cancellous bone is determined by the age of the individual and at birth is filled with red marrow, however over time this slowly replaced with yellow marrow and this change is normally complete by around 30 years (Figure 8) (Vogler & Murphy, 1988).

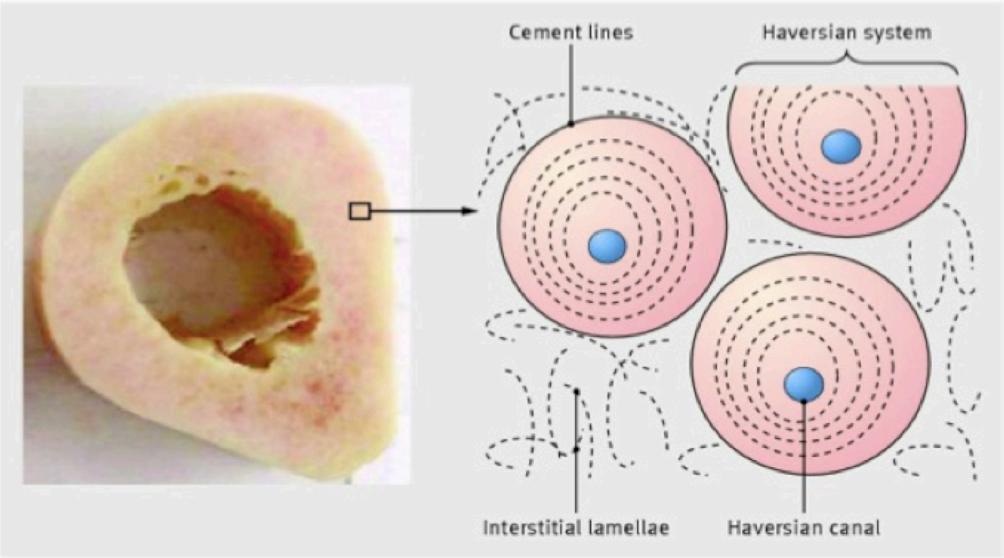


Figure 7: An image depicting the composition of mature bone.
Note the bone is composed of oriented collagen fibres arranged in sheets known as lamellae. In cortical bone the collagen fibres are arranged in concentric rings or harversian systems, which in turn are surrounded by cement lines. These are areas of relative weakness, where stress fractures can propagate (Pegrum, Crisp, & Padhiar, 2012, p. 7).

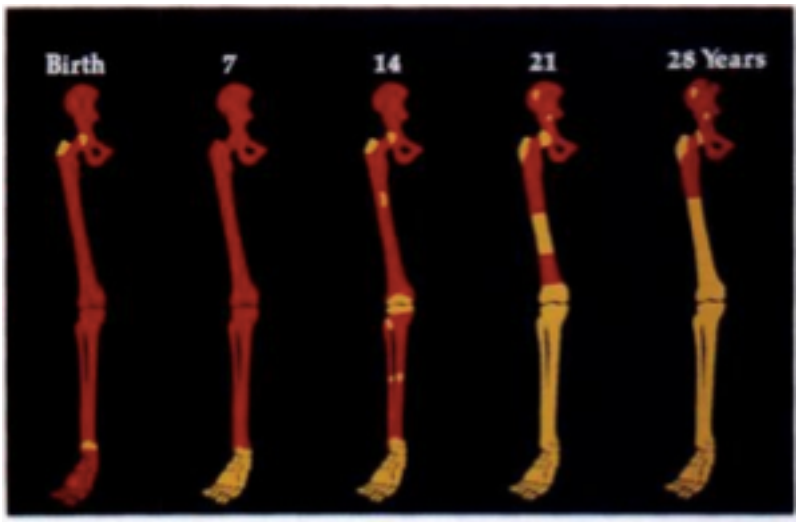


Figure 8: An illustration demonstrating the distribution of red and yellow bone marrow
Note the changing distribution of red and yellow bone marrow conversion through the first 30 years of life (Vogler & Murphy, 1988, p. 680).

Physiology of Normal Bone

Very little was understood about bone before Julius Wolff published his seminal work in 1892 on bone 'transformation', known today as bone modelling and remodelling. Wolff's (1892) law, stated below, was the result of 25 years work in orthopaedics and skeletal anatomy:

Every change in the form and function of a bone or their function alone is followed by certain definite changes in their internal conformation in accordance with mathematical laws
Wolff as cited in (Frost, 1994, p. 175).

In simple terms bone will model and remodel in accordance with the stress placed upon it in order to maintain its integrity.

Remodelling of bone…. occurs in response to physical stresses or to the lack of them – in that bone is deposited in sites subjected to stress and is reabsorbed from where there is little stress

(Salter, 1970, p. 7).

Wolff's law forms the foundation of normal bone physiology and the pathogenesis of BSI

There are six fundamental steps which bone undergoes when exposed to (increased) activity or stress (Kini & Nandeesh, 2012):

1. Quiescence or period of rest
2. Activation Phase - Osteocytes sense increasing physical stress being placed upon them.
3. Resorption Phase - Osteoclasts remove bone material that is damaged or not strong enough. This liberates minerals and other molecules stored within the bone matrix (resorption) and takes approximately ten days.
4. Reversal Phase – A change from bone resorption to bone formation commences. Upon completion of this resorption process, cavities are found to house mononuclear cells such as monocytes and osteocytes which have become liberated from the bone matrix.
5. Formation Phase - Osteoblast precursor cells appear which morph into mature osteoblasts to form new stronger bone (they produce the organic component of bone 'osteoid' – from collagen). Minerals start to crystallise around the collagen scaffold to form hydroxyapatite.
6. Mineralization: Many osteoblasts become embedded within the matrix and change into osteocytes (Kini & Nandeesh, 2012).

The process of resorption leaves behind a weakened bone. If bone is put under repeated stress during this vulnerable time, the resultant weakened bone may undergo internal damage possibly resulting in BSI (Brukner et al., 1999).

Pathogenesis

It is widely accepted that the bone undergoes adaptive changes as a result of stress at a cellular level (Wolff's Law). The pathogenesis of BSI appears to result from an unsuccessful adaptation of bone to a change in its environment, although the exact initiation process in unclear (Bennell, Malcolm, Wark, & Brunker, 1996b).

There are two physiological processes which are thought to do so: firstly, remodelling (Philipson & Parker, 2009) and secondly, micro-damage production (Datir, Saini, Connell, & Saifuddin, 2007). Figure 9 graphically represents the two processes that are believed to result in BSI.

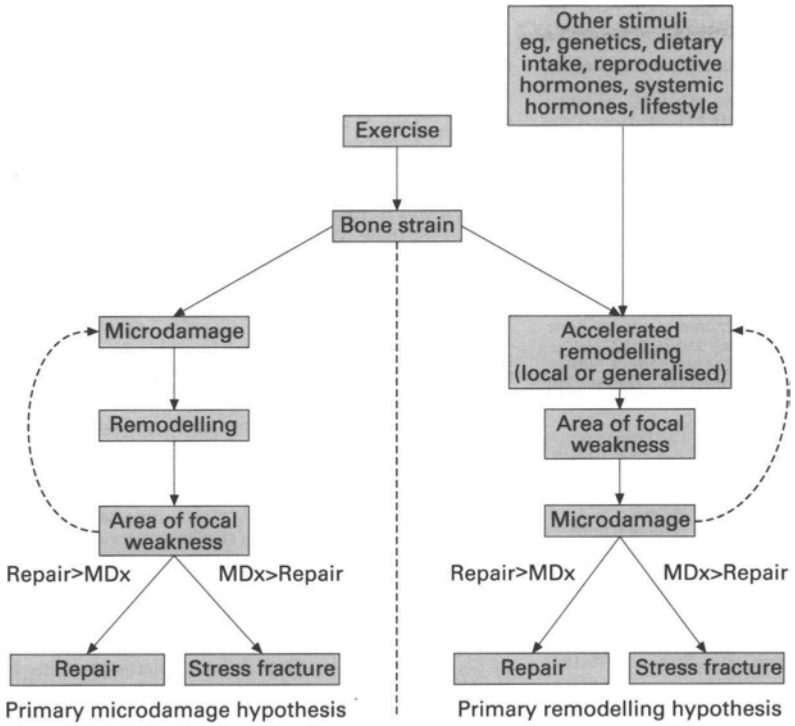


Figure 9: A dynamic representation of two possible mechanisms for BSI development. The primary micro-damage hypothesis and the primary remodelling hypothesis (Bennell et al., 1996b, p. 203).

Theory One - Accelerated Remodelling

An important concept is that stress fracture is an accelerated example of bone remodelling, thus making it a process, not an occurrence (McBryde, 1976, p. 212).

This theory proposes that a positive shift in stress, through extensive training for example, results in osteoclastic and osteoblastic activity being increased to improve the strength of the bone (Kiuru, Niva, Reponen, & Pihlajamaki, 2005).

Philipson and Parker (2009) suggest that the lag between old bone being reabsorbed by osteoclasts and new stronger bone being formed by osteoblasts creates a vulnerable, temporarily weakened bone. The bone typically takes one to two weeks to 'catch up' and

if the stress continues during this 'weakened' period, damage can result (Brukner et al., 1999). This delicate balance between stress and recovery may result in micro-damage within the bone matrix. This damage can propagate (Figure 10 & 11) and coalesce potentially leading to a BSI (Pegrum et al., 2012).

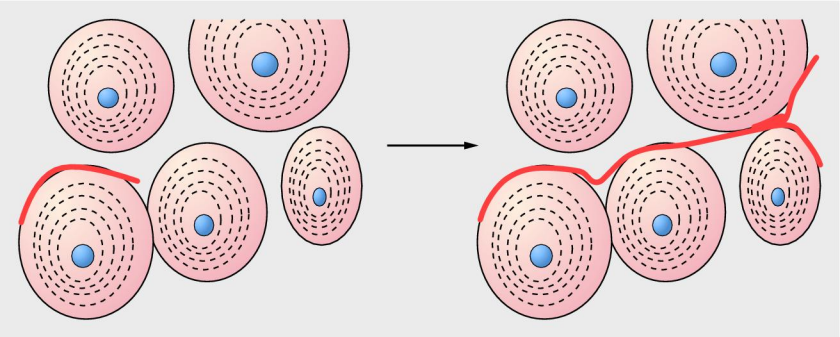


Figure 10: A schematic diagram to illustrate how cracks in bone arise and propagate with repetitive cyclical loading.
The red line demonstrates the path the path. Clinically important cracks or BSIs occur when propagation outstrips repair (Pegrum et al., 2012, p. 7).

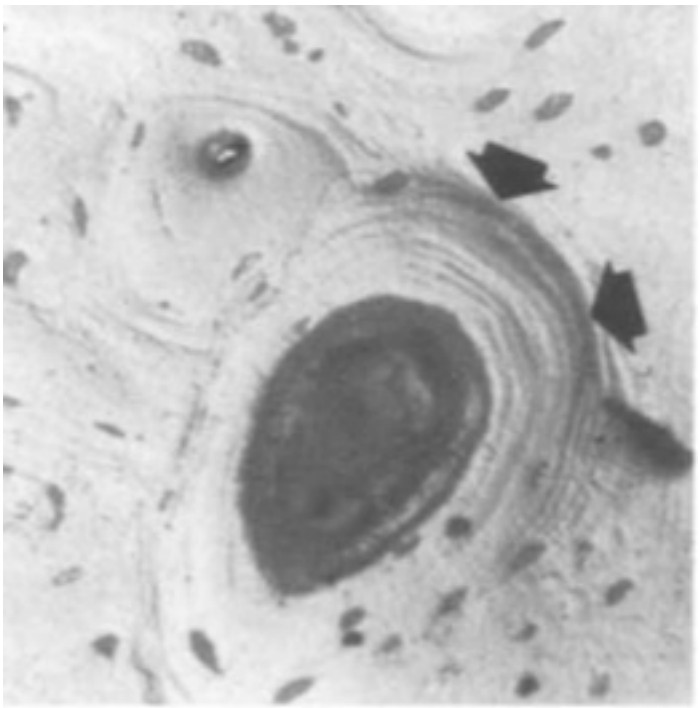


Figure 11: A photomicrograph of micro-damage to bone.
Observed the damage in the cement lines of a compact bone in a test specimen indicated by the arrows (Schaffler, Radin, & Burr, 1989, p. 12).

The amount of damage caused by stress during this vulnerable stage is determined by a number of risk factors discussed later, however the continuum shown in Figure 12 suggests that the training load is the biggest contributing factor in this process (Blackman, 2010).

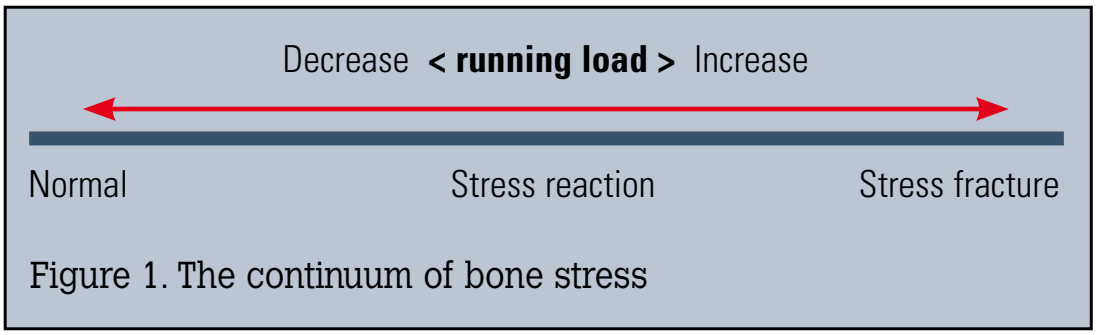


Figure 12: A diagram demonstrating the continuum of BSI.
Note increased stress being proportional to the risk of injury, with normal bone at one end of the spectrum with 'normal activity' whilst a big increase in activity or stress is associated with BSI (labelled here as 'stress fracture'). Please note this is a schematic representation of the BSI continuum and no figures have been assigned to the model (Blackman, 2010, p. 25).

Theory Two - Micro-damage

The second theory suggests that micro-damage initiates the osteoclastic response. The process involves an area of bone becoming 'maximally stressed', which subsequently causes an area of micro-damage. This area of micro-damage sends out chemical messages to commence bone remodelling (Bennell et al., 1996b). The osteoclasts then begin their role of bone reabsorption, which temporarily weakens the bone, peaking at approximately 21 days (Datir et al., 2007). Simultaneously, but at a decreased rate, osteoblastic rebuilding occurs, unfortunately osteoclastic reabsorption outstrips osteoblastic production, which ultimately means that if the repetitive stress occurs a BSI may result.

Regardless of the initiating factor, histological samples from Sweet and Allman (1971) provide a time line of events. Symptoms commence with localised pain and tenderness in the presence of stress or activity and osteoclastic resorption. Within a few days the cortex will become riddled with 'holes' (resorption cavities), (Figure 13 and Figure 14) for a period of 2-3 weeks. Periosteal reinforcement begins two weeks after the initial stress and peaks 6 weeks later, (Figure 15). After three to four weeks the cavities begin to fill with new bone, but this process can take several months to complete. This time line suggests that bone is at its most vulnerable and most likely to fracture if stress continues in the third week of this cycle (Sweet & Allman, 1971).

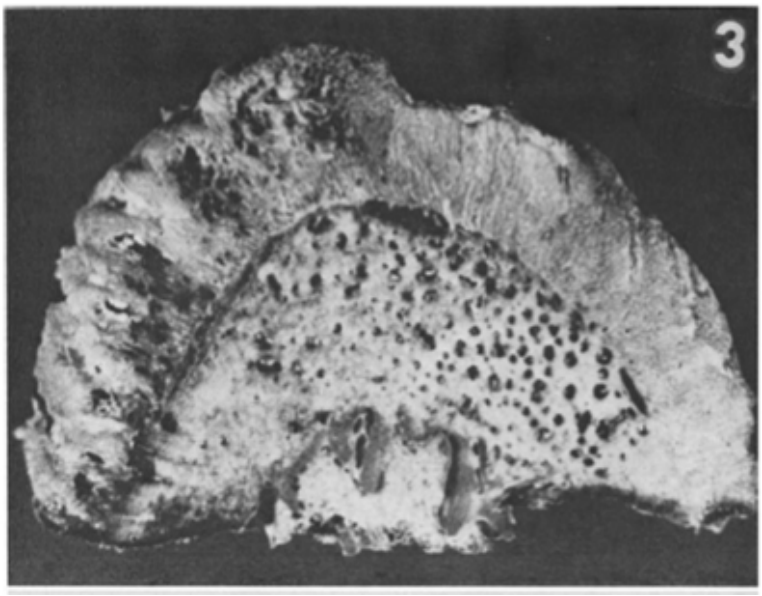


Figure 13: A cross sectional sample of a tibial cortex with the characteristic appearance of a periosteal reaction.
Note the left of the cortex of this section is riddled with 'multiple holes' (Sweet & Allman, 1971, p. 690).

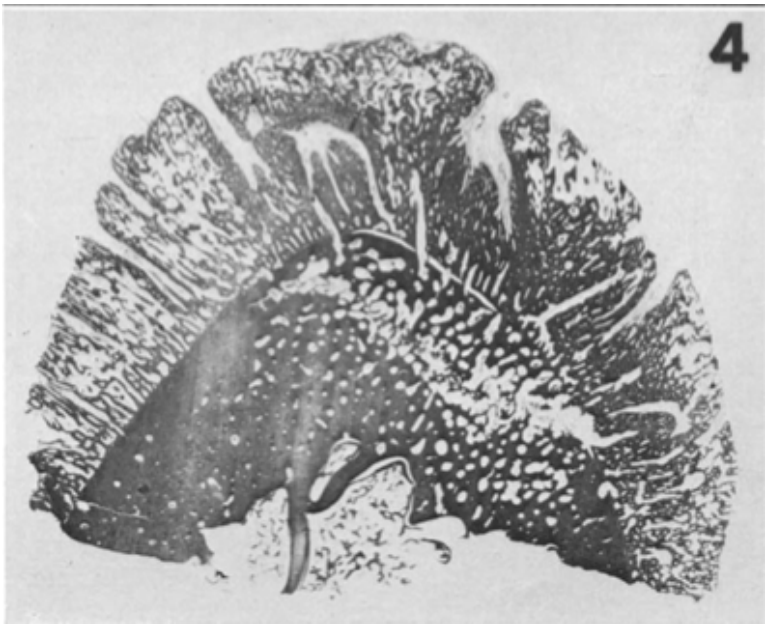


Figure 14: An x-ray taken from a cross sectional sample of a tibial cortex with multiple holes merging into a confluent lytic defect in the cortex.
The lytic defect represents the areas of cortical osteoclastic resorption. This is the radiolucent area on a radiograph, however it is often concealed by the periosteal reaction seen here as radial type streamers laid down to reinforce the weak bone (Sweet & Allman, 1971, p. 690).

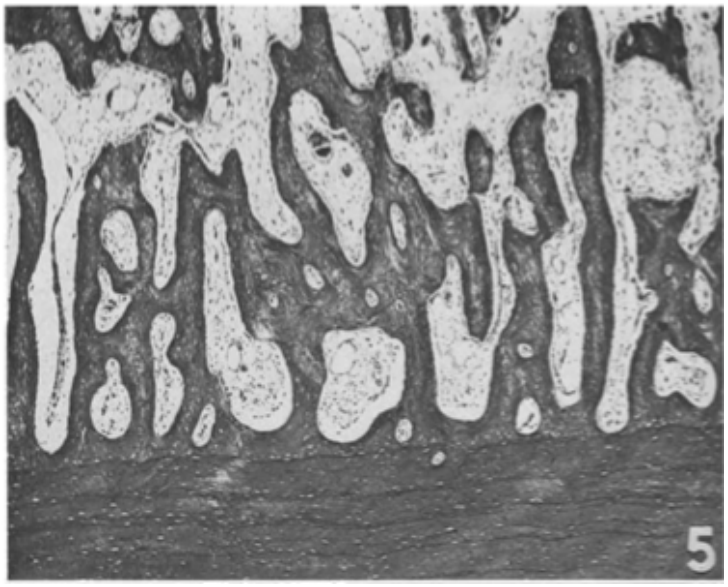


Figure 15: A microscopic image illustrating the radial streamers of periosteal new bone in contrast to circumferential lamellar of undisturbed bone cortex
(Sweet & Allman, 1971, p. 691).

Knowledge of the pathogenesis behind BSI is constantly evolving as new techniques and research is undertaken and highlighted by papers such as Brock et al., (2013), which proposed a new technique of imaging the micro-damage in bone. Until this new technique, X-ray micro-computed tomography had been the closest scientists could get.

However using transmission X-ray microscopy has allowed nano-scale visualization. The images produced by Brock et al. (2013) enable visualisation of damage in bone at a resolution of 30 nanometres. Instead of seeing new surfaces formed by damage, or cracks, as was expected, the researchers observed damage in the cellular structures (Brock et al., 2013). In conclusion the body's own self-preservation mechanism, trying to cope with the stress, may ultimately be the cause of BSI.

Biomechanics

Stress can be defined as the force or load applied to bone. This may arise from muscular action or more commonly weight-bearing activity (Anderson, 1990). A traumatic fracture requires a single high magnitude stress, whilst the stress to induce a BSI has multiple repetitions at less magnitude, which surpass the remodelling process (Figure 16) (Reeder, Dick, Atkins, Pribis, & Martinez, 1996). This suggests that higher stresses require fewer cycles to cause a breakdown in the bone remodelling process to result in a BSI. It also suggests that a minimum stress level is required to inhibit the remodelling process and below this level there is no risk of BSI (Reeder et al., 1996).

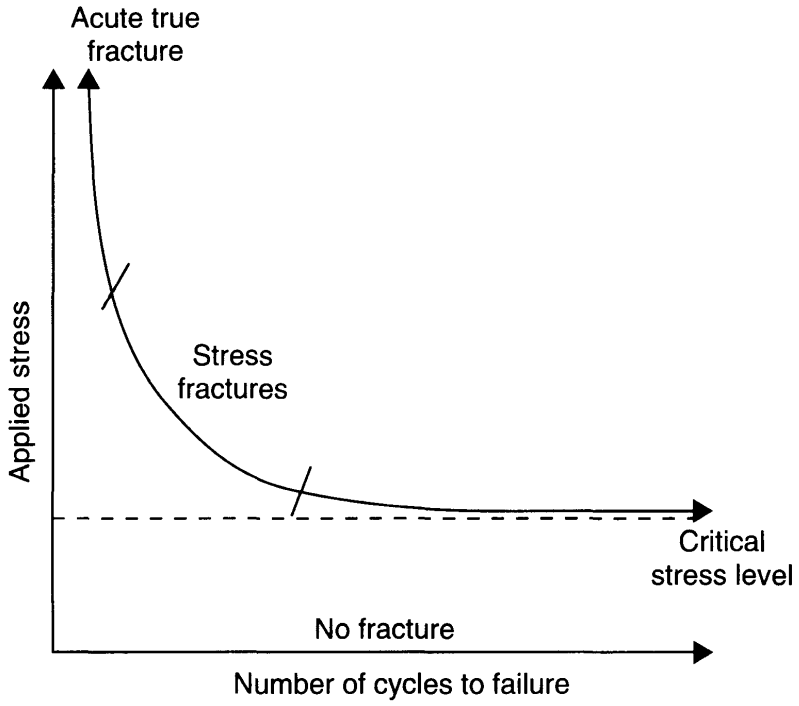


Figure 16: A graph demonstrating the fatigue curve in association to bone stress.
As the level of stress is increased, fewer cycles are required to produce fracture. As the number of cycles increase, less stress per cycle is required to produce fracture (Reeder et al., 1996, p. 201).

Clinical Diagnosis

Active involvement of a multidisciplinary team, including expert medical personnel to support the athlete or soldier is crucial (Kiely, 2011). Unfortunately in professional sports the focus is too often on getting the athletes back to play as soon as possible rather than ensuring they are fully recovered (Carmont, Mei-Dan, & Bennell, 2009; Philipson & Parker, 2009).

A thorough patient history and clinical examination with a high index of suspicion for BSI are the fundamental basis for diagnosis of BSI (Reeder et al., 1996). This can be complimented with medical imaging to grade the extent of the injury (Arendt & Griffiths, 1997). A typical history of a BSI will involve pain during increased activity, which if continued worsens over time (Anderson & Greenspan, 1996). At the beginning pain subsides upon rest but if the activity is continued, pain will remain during rest (Anderson & Greenspan, 1996). Symptoms are usually general, rarely abrupt and are not always helpful in localising the lesion as pain can often be referred (McBryde, 1976). Occasionally, patients experience little or no pain and do not present until after the BSI has displaced although this is rare (Luchini, Sarokhan, & Micheli, 1980).

There have been a plethora of papers on BSI risk factors particularly aimed at military but also in the athletic community and the results of these should be at the forefront of the medical support team's mind.

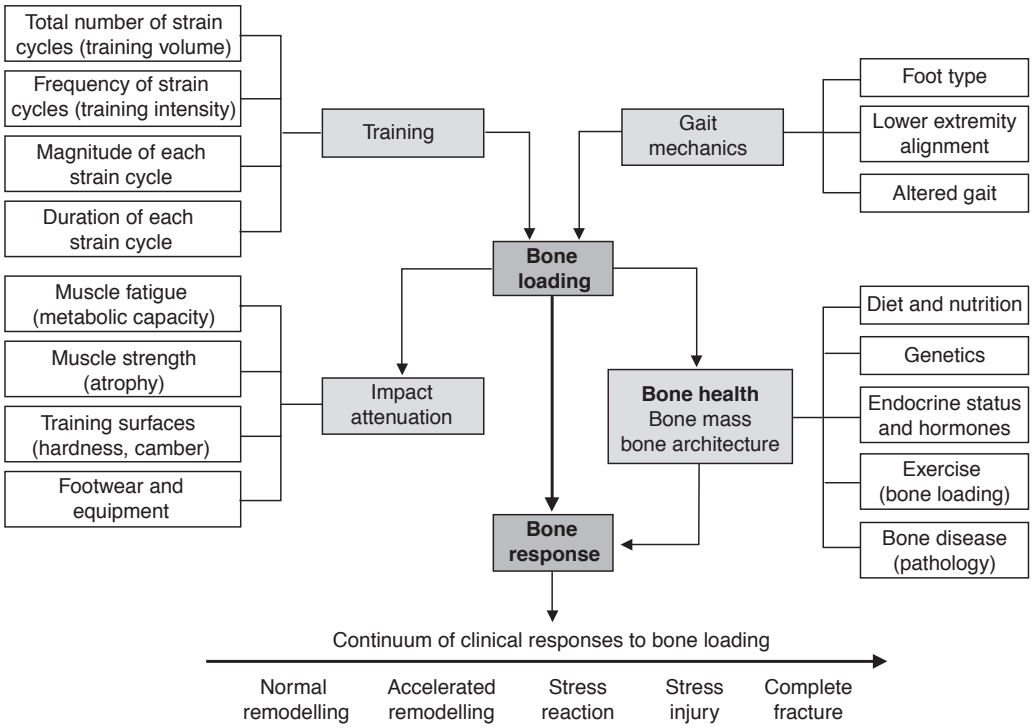


Figure 17: A flowchart to illustrate the contribution of risk factors to BSI pathogenesis. Note how the complex interplaying nature of these risk factors produce bone response (Bennell et al., 1999, p. 96).

The interplaying nature of BSI risk factors is a complex science; Figure 17 gives a simplistic view. For example training influences bone loading, however four factors affect bone loading (Bennell et al., 1999).

Diagnostic Imaging

Since its introduction in 1895 the revolutionary introduction of diagnostic imaging has become the cornerstone of diagnosis and management of BSI. Earlier diagnosis of BSI has allowed research to push the boundaries of our understanding with regards to its pathogenesis, risk factors etc., and has allowed medicine on occasion to discover sub-clinical changes using such techniques. The only drawback of these advances in imaging is the vast variation it has on research results, which vary considerably between X-ray, bone scintigraphy, CT, US and MRI.

Radiography

Radiography was the first imaging modality to be developed back in 1895 and used to diagnose BSI in the feet of soldiers (Blickenstaff & Morris, 1966). This relatively cost effective, and widely available tool maintained its primary position in the diagnosis of BSI

for over seven decades, giving a unique insight into BSI, which no other science could offer.

The appearance on radiographs, like the continuum, changes depending on the extent of the injury (Fullerton & Snowdy, 1988). Most BSIs are diagnosed before they displace, and typically the appearance would be less severe, either as a increased density subchondral line indicating a mild periosteal reaction (Figures 18) (Yoon, Yoo, Yoon, & Kim, 2012) or slightly more marked medullary sclerosis and periosteal new-bone formation or callus which demonstrates more macroscopic bone healing (Figure 4) (Boden et al., 2001). This is characterised by local increased bone thickening over a symptomatic site and typically takes 2-3 weeks to appear on X-ray post injury (Savoca, 1971; Sweet & Allman, 1971).

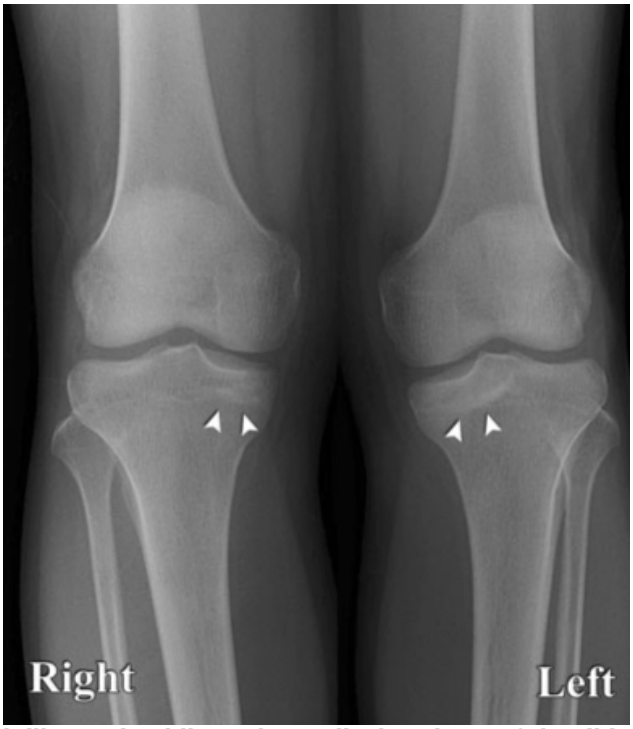


Figure 18: A plain radiograph illustrating bilateral non-displaced BSI of the tibia.
The arrowheads point to the linear increased density subchondral sclerosis (Yoon et al., 2012, p. 946).

At the most severe end of the spectrum the BSI will fracture completely and subsequently displace. Figure 19 is an example of this in the femoral neck.

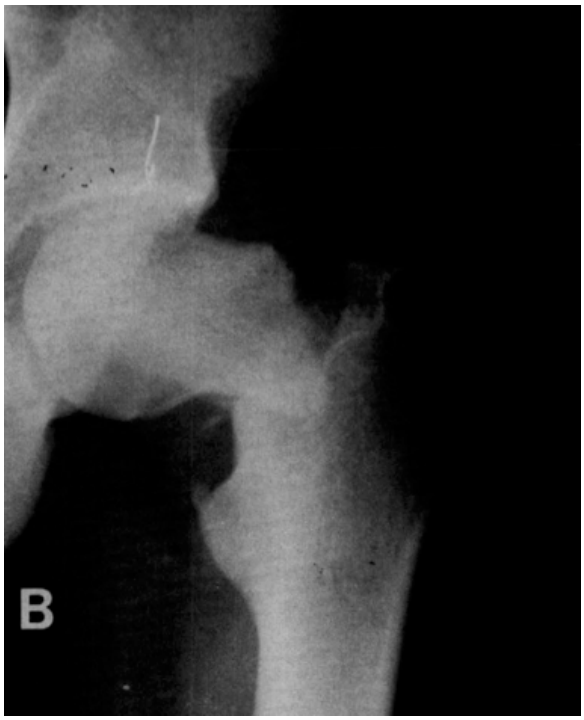


Figure 19: A displaced fracture to neck of femur.
This injury is progressed from a BSI to a complete displaced fracture of the neck of femur (Fullerton & Snowdy, 1988, p. 368).

Subsequently when new imaging modalities such as bone scintigraphy were developed, it became evident that that there was a delay in the pathological presentation on radiographs (Boden et al., 2001, p. 109). Once this delay or time lag, became evident, more caution was used when evaluating radiographs to look for BSI (Zwas et al., 1987). Bone scintigraphy proved that radiographs were unable to offer up-to date physiology and or pathophysiology (Zwas et al., 1987). This is not surprising considering the early stages of the pathological process is on a microscopic level (Zwas et al., 1987). As a result plain radiographs often reported that acute BSI were normal, when bone scintigraphy proved that this was not the case (Geslien, Thrall, & Espinosa, 1976). Consequently these false negatives caused complications that have been career ending for military personnel and professional athletes alike (Geslien et al., 1976; Greaney et al., 1983). Figure 20 demonstrates the spectrum of pathophysiological changes with BSI, compared to the imaging and clinical findings.

Tomography (moving radiographs) (Blickenstaff & Morris, 1966; Lappe, Stegman, & Recker, 2001; Nattiv, 2000) and Macrographs (magnified views) (Meurman & Elfving, 1980b) were used for a time before bone scintigraphy CT and MRI became the principle

choices. These were helpful in diagnosing difficult stress fractures, particularly in the tarsal bones and if the fracture is positioned in a non-trans-axial plane (Figure 25).

According to Sofka (2006) most institutions still use plain radiographs as the initial tool. However Matheson et al. (1987b) noted a reduction in the number of plain radiographs performed in 1987 which they suggest reflects the "growing loss of faith" in the accuracy this modality and in current practice, particularly with high performance athletes this is not routine, instead they are fast tracked to MRI (P. Wheeler, Personal communications, January 10, 2012).

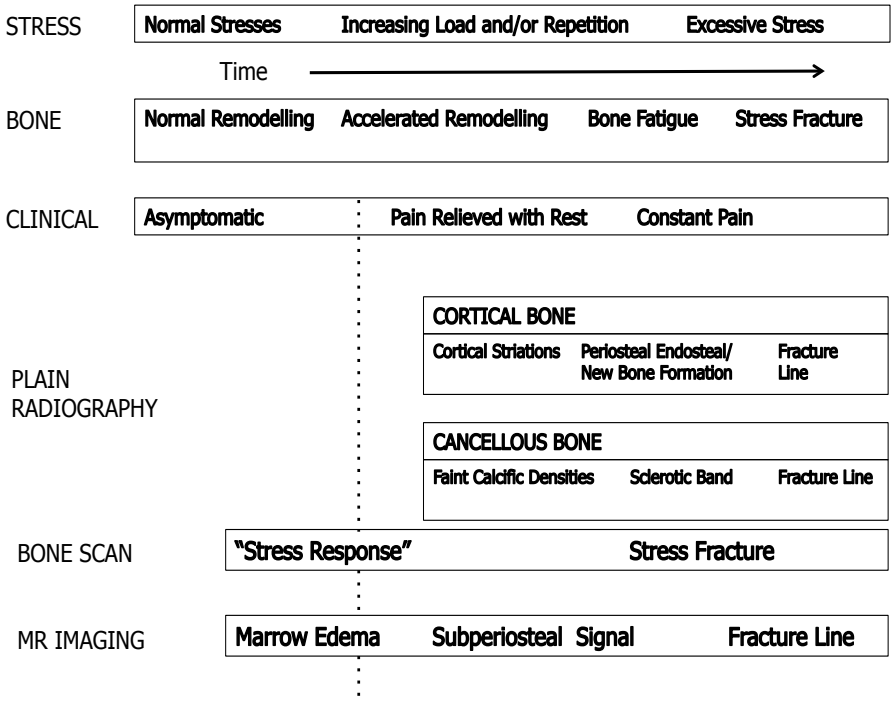


Figure 20: A diagram illustrating the spectrum of BSIs against imaging and clinical symptoms (Anderson & Greenspan, 1996, p. 3).

The low sensitivity and specificity of radiography has been well documented, with a number of reports claiming that a significant number BSI failed to present on plain radiographs (Bennell et al., 1996a; Greaney et al., 1983). Hallel, Amit, and Segal (1976) reported that it often took up to two weeks for callus to form before BSI was visible. Matheson et al. (1987b) concurred with this in their study of 320 athletes, recording that

after one week of pain fewer than 10% of patients had their BSI picked up in plain film radiographs.

In this current review examining asymptomatic BSI, plain radiography is not a suitable imaging modality as the literature appears to demonstrate, that it is only able to diagnose BSI once they have become symptomatic, given the significant time delay involved in periosteal reaction (Anderson & Greenspan, 1996). The exception to the rule may be Luchini et al. (1980), as they provided radiographic evidence of callus formation around the site of an acutely displaced femur (stress) fracture which had until that point been asymptomatic.

Bone Scintigraphy

In 1971 a new radiopharmaceutical complex ^{99m}Tc was introduced, to image bone physiology (Subramanian & McAfee, 1971). By injecting the patient with the radioactive pharmaceutical ^{99m}Tc-labelled methylene diphosphonic acid (MDP) allowed us to utilise the intrinsic nature of bone to image potential BSI. BSIs result in part by accelerated remodelling. This remodelling requires increased blood-flow and/or metabolic activity. Once radionuclides are injected into the patient, they are flood any areas of increased remodelling bone and are visualised as an area of increased uptake. This technique increased both the sensitivity and speed of diagnoses (Subramanian & McAfee, 1971) and supported by an early study by Geslien et al. (1976) found that scintigraphy detected BSI 118 of 188 BSI several weeks prior to X-ray, which they noted was particularly useful as 20% were in sites of high risk of non union.

When bone scintigraphy is used to evaluate BSI, a 3-phase bone scintigraphy is performed (Rupani, Holder, Espinola, & Engin, 1985). Phase 1 is taken directly after the injection and illustrates early blood flow (vascularity), phase 2 (blood pool phase) is imaged at 5-7 minutes post injection and demonstrates any soft tissue involvement such as the surrounding muscles and the third (delayed) phase is taken between 2-4 hours post injection, when most of the radioisotope has been metabolised. The third phase is the most useful in diagnosing BSI as it reflects the osteoblastic response to stress (Rupani et al., 1985).

Acute and chronic BSIs can be differentiated by their appearance on the three phases, with acute showing on all three phases whilst chronic only appear on the third phase (Nikpoor, 2009). Normally healing BSIs are seen on bone scintigraphy up to between 3-6 months as the uptake on delayed images decreases. In addition as BSIs resolve they become less fusiform and narrower and less focused, (Figure 21 & 22), note minimal uptake can still be visible at 8-10 months as bone remodelling often lags behind 'clinical resolution' of symptoms (Rupani et al., 1985).

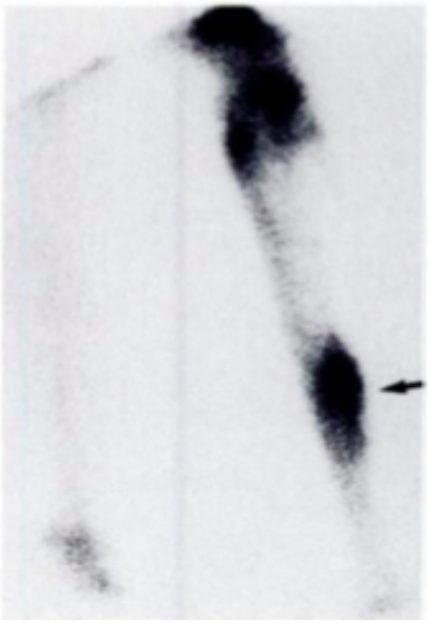


Figure 21: A lower leg bone scintigram of a symptomatic runner at initial examination. Delayed image, lateral view. 3+ fusiform activity in the mid-posterior tibial cortex (arrow) (Rupani et al., 1985, p. 195).

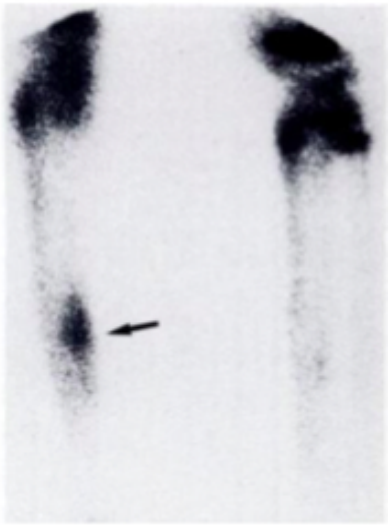


Figure 22: A follow up lower leg bone scintigram of a runner 7 weeks later
Delayed image. 2+ activity at the site of stress fracture (arrow), consistent with healing (Rupani et al., 1985, p. 195).

The radiation dose is between 3-5 mSv, comparable to a single radiograph, but plain radiography often requires multiple views/images, resulting in an overall higher dose, or the equivalent of approximately twice the annual background radiation dose (Kanstrup, 1997).

Bone scintigraphy enabled researchers to explore new ground and subsequently Zwas et al. (1987) published a classification system for BSI using this. The system evaluated the severity of a lesion with increased activity into four grades (Figure 23). Their aim was to improve early diagnosis and increasing accuracy by defining the clinical presentation. It was envisaged that it would enable prompt and effective management and treatment. Where applicable preventing progression of lesions and their results appear to support this (Zwas et al., 1987). The importance of early detection and grading became even clearer with an article by Geslien et al. (1976) showing lower disability and complications rates when using this system.

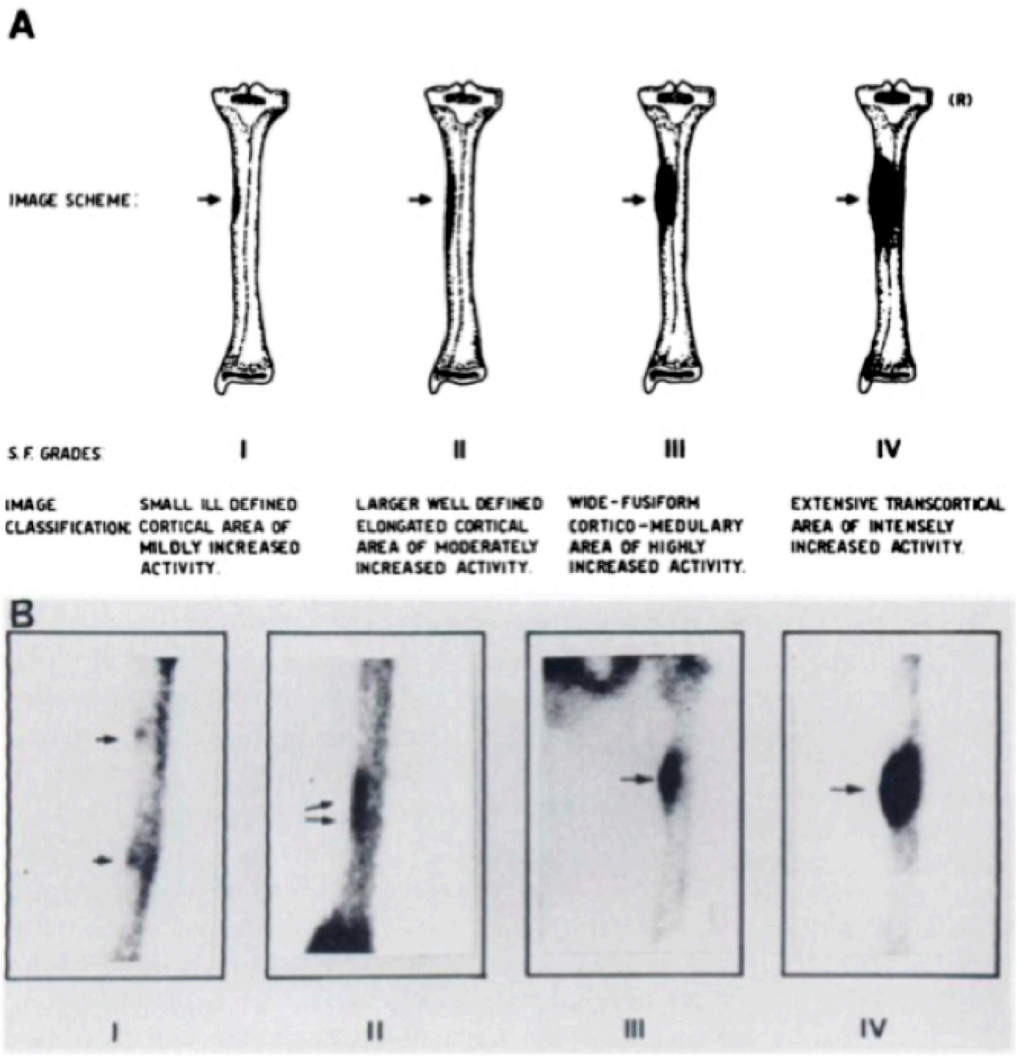


Figure 23: (A) A schematic representation of the four grades of BSI (B) Bone scintigraphy images transposed on to this grading system.
The BSI in evolution with clear differences in Grade - I-IV (Zwas et al., 1987, p. 453).

The incredible sensitivity of bone scintigraphy not only enables the detection of BSI lesions as early as 1-day post injury, but clearly shows some lesions without symptoms. These asymptomatic BSI were incidental findings and only discovered because of the way bone scintigraphy is used, routinely imaging both lower limbs from pelvis to feet (Giladi et al., 1985). Most of the early literature suggested that these were false positives and of no clinical relevance, suggesting the increased uptake was just a 'normal' physiological response to stress not a pathological response (Chisin et al., 1995; Gofrit & Livneh, 1994; Roub et al., 1979). However some authors believe that asymptomatic BSI may be of clinical relevance, showing that asymptomatic lesions can progress to painful lesions

(Groshar et al., 1985). Despite these incidental findings being noted in a number of papers very little published work has been dedicated to examine this finding prospectively.

Further advances in bone scintigraphy involved single photon emission computer tomography (SPECT). This has improved the contrast resolution, sensitivity, specificity and localisation of smaller stress fractures and is particularly effective at differentiating between soft tissue and bone and for this reason is utilised in the spine and pelvis and improves the spatial localisation of uptake in the femoral neck (Bryant, Song, Banks, Bui-Mansfield, & Bradley, 2008).

Although bone scintigraphy is known to have a high sensitivity, it has poor specificity in comparison to MRI (Gaeta et al., 2005). Two studies reported false-negative bone scintigraphy results when compared to MRI (Milgrom et al., 1985a;Wen, Propeck, & Singh, 2003). Another drawback of bone scintigraphy, as noted earlier, is its inability to readily distinguish between older BSI when symptoms have ceased and newer BSI (Nielsen et al., 1991; Rupani et al., 1985). The combination of this, the reduced specificity, radiation dose, it's invasiveness and the lack of ability to perform follow up has resulted in bone scintigraphy becoming superseded by MRI as the preferred imaging modality for BSI (Fredericson, Jennings, Beaulieu, & Matheson, 2006).

Computer Tomography (CT)

Hounsfield was an electrical engineer who helped develop what he originally termed "Computer transverse axial scanning (tomography)" which is now known as computed tomography (CT), in a paper in 1973 (Hounsfield, 1973).

CT uses X-radiation, which is projected from an X-ray tube through the patient as it rotates around a gantry. The attenuated rays are measured as they pass through the individual onto a bank of detectors. These measurements are then reconstructed providing 3D information of the area of interest (Euclid, 2008).

CT technology is constantly evolving, from a single slice per rotation machine, to 64 slice scanner which produces 64 slices per rotation (Euclid, 2008). These leaps in technology allow sub millimetre isometric voxels which provides exquisitely clear images but also

provides enough data to reformat the slices into multi planar reconstructions in a matter of seconds (Euclid, 2008).

Similarly to plain radiography, CT relies on bone healing and macroscopic bone changes to demonstrate BSI, rather than bone scintigraphy, which detects lesion activity (Sofka, 2006). Imaging characteristics include: medullary sclerosis, periosteal reaction, sclerotic fracture lines and callus formation, but these can take a number of weeks to appear (Figure 24 & 25) (Feydy et al., 1998).

When compared to other imaging modalities whilst CT can image osseous changes, it has a limited ability to demonstrate the 'activity' of BSI lesions. For example, actively acute lesions and quiescent or chronic lesions have few distinguishing features between them when compared to other modalities, whilst bone scintigraphy is able to demonstrate bone turnover and MRI can show bone marrow oedema (Sofka, 2006).

A further study by Gaeta et al. (2005) compared CT and MRI in the diagnosis of BSI. They found that CT was superior and was able to depict osteopenia, one of the earliest stages of the bone response to stress in symptomatic patients, whilst MRI remained negative.

Despite the fine bone detail provided by CT, it uses X-radiation, which has an associated risk of cancer. This varies greatly in the age and sex of the patient, the type of scanner and the scan being performed (Einstein, Henzlova, & Rajagopalan, 2007), which needs to be considered and justified before requesting such a scan. Therefore this is a significant drawback in comparison to MRI, which is non-ionizing (Moran, Evans, & Hadad, 2008). Subsequently CT is only used in a number of indications, firstly when an individual has contraindications for MRI for example a pacemaker, intra-orbital metallic foreign bodies and secondly in diagnosing longitudinal BSI of the tibia (Feydy et al., 1998).

Some studies have reported that CT may be particularly useful for imaging BSI of the pars interarticularis situated in the spine, but only in comparison to plain radiography (Sofka, 2006) and as the current thesis is only focused on the lower extremity, it is less relevant in this review.

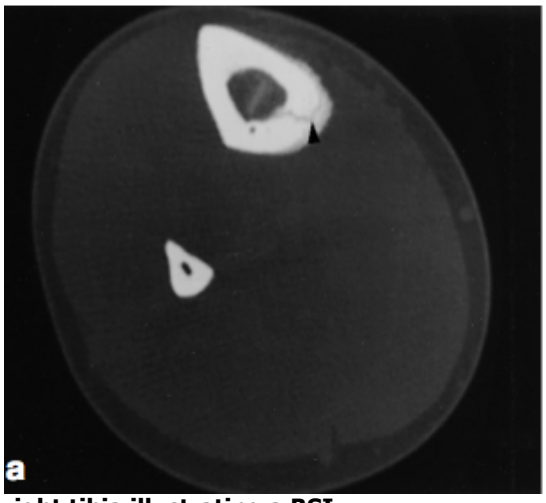


Figure 24: An axial CT slice of a right tibia illustrating a BSI.
An 18 year old runner presented with lower leg pain presented, note a thin posterior transcortical line of tibial (black arrowhead) with periosteal and endosteal callus at the fracture site (Feydy et al., 1998, p. 600).

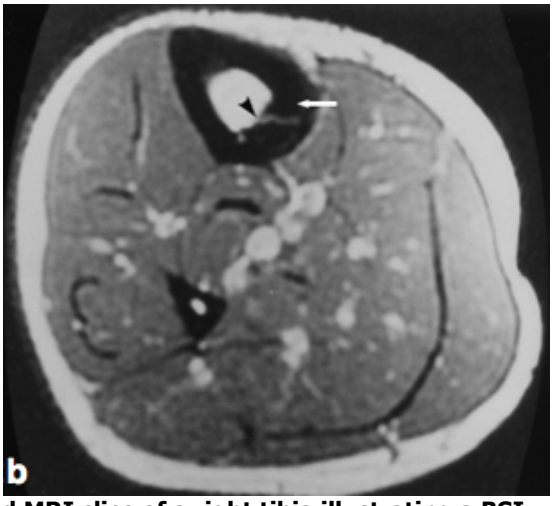


Figure 25: An axial T1 weighted MRI slice of a right tibia illustrating a BSI.
This slice was taken from the same runner at the same level, also depicting the thin cortical fracture line with an intermediate signal (black arrow head), however the periosteal callus (white arrow) is less conspicuous than with CT (Feydy et al., 1998, p. 600).

Magnetic Resonance Imaging (MRI)

In 1971, Damadian discovered it was possible to visualise differences between normal and pathological tissues in mice by measuring the tissues' T1 relaxation times using a nuclear magnetic resonance device (now know as MRI) (McRobbie, Moore, Graves, & Prince, 2007). In 2003 Mansfield and Lauterbur won the Nobel Prize for developing MRI for medical purposes (McRobbie et al., 2007) enabling it to be used in hospitals and medical centres worldwide. In 1986 the first report on MRI as an imaging tool for the diagnosis of

BSI was published (Stafford, Rosenthal, Gebhardt, Brady, & Scott, 1986) and MRI is now recognised as the gold standard for musculoskeletal imaging (McRobbie et al., 2007).

MRI uses the body's naturally abundant hydrogen nuclei to produce 3D images. Different tissues throughout the body have different quantities of hydrogen, which in turn produce different signal intensities. These differences produce image contrasts between various tissues and can be further enhanced and manipulated using different imaging techniques or pulse sequences (McRobbie et al., 2007).

T1 weighted images afford detailed anatomical information where fluid is low signal (black) (unless flowing into the image i.e. blood), fat based tissue gives a high signal (bright white) and water based tissues give a medium signal intensity (mid grey). This sequence is used to evaluate the anatomical dimensions of the injury as they delineate the boundaries between tissue types (Figure 26C) (McRobbie et al., 2007).

T2 weighted images are known as 'pathology scans' because of the appearance of high signal from abnormal fluid contrasting against the (darker) low signal normal tissue (Figure 26B). A fat saturation (FS) pulse can be added to either sequence; when added to a T2 it simply nulls the fat so the fluid is (bright) high signal, while all other tissues remain a variety of darker greys (low signal). A short tau inversion recovery (STIR) is an alternative to a T2FS, which also demonstrates fluids having the highest signal whilst all tissues with the same T1 as fat will be suppressed (Figure 26A) (McRobbie et al., 2007).

Pathological processes often induce an increased blood supply and or oedema, both of which affect the tissue contrast (McRobbie et al., 2007). The resultant signal intensity can be manipulated by these various image or pulse sequences to either increase or decrease the signal (McRobbie et al., 2007).

Initially in BSI, as the bone undergoes its stress response, bone marrow oedema and hyperaemia develop as part of the pathological process, both of which can be visualised on an a STIR (Figure 26A) or T2 FS. If the bone continues to be stressed the bone architecture will begin to fail and depending on the grade of injury this will be visible on T2 first (Figure 26B) then T1 (Figure 26C) (Arendt et al., 2003).

It has be suggested that bone marrow oedema (BME) is one of the first and most common findings in BSI and reported in 97.2 % of subjects in one study as positive for BME on MRI (Ishibashi et al., 2002). However BME has also been reported in asymptomatic personnel with altered biomechanical stress. But Kiuru et al. (2005) concluded that asymptomatic BME was of no clinical significance from results of their prospective military study, which highlights a clear disagreement on this area throughout the literature.

To quote Arendt and Griffiths, (1997 p. 292):

With the advent of MR imaging, understanding of stress fractures and stress phenomena of bone has increased dramatically, and the focus has begun more on the bone marrow abnormalities that can be seen on MR images following repetitive trauma.

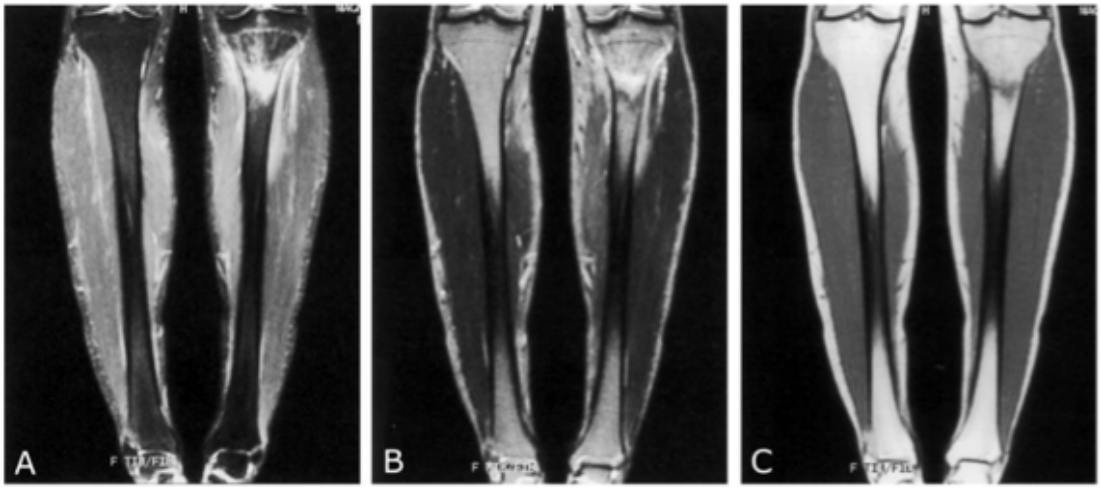


Figure 26: Three different weighted coronal MRI sequences of a female runner's tibia.
(A) The STIR sequence, demonstrates obvious increased signal in the proximal the left tibial metaphyseal region. (B) The T2-weighted image shows a linear low-intensity signal, the cortex is violated, the line is irregular in nature, excluding a true cortical stress injury to bone. (C) The T1-weighted sequence shows a decreased signal over the left proximal tibia. These images confirm a high grade stress injury to bone, consistent with a diagnosis of grade 3 stress injury (Arendt et al., 2003, p. 964).

MRI is non-invasive (unless a contrast agent is administered) and is now the cornerstone of musculoskeletal imaging owing to its high specificity and sensitivity without exposing individuals to harmful ionising radiation. It is quicker than a bone scintigraphy and offers detailed anatomical information on localised soft tissue in multiple planes, which can be particularly helpful in excluding other potential causes of localised pain (Datir et al., 2007).

MRI provides both anatomical and physiological information from visual evidence of subtle bone marrow signal changes on STIR and T2 sequences to frank low signal lines indicative of fractures (Kiuru, Pihlajamaki, Perkio, & Ahovuo, 2001). Furthermore it has been noted that using MRI for the diagnosis of BSI allows earlier treatment and a more favourable outcome (Major, 2006).

There are a number of negative aspects of using MRI, with cost proving a barrier for many. Although MRI is an expensive modality anecdotal evidence suggests that at elite level sport many athletes have medical insurance built in to their programme or membership potentially reducing this problem. Furthermore a large number of military facilities, according to the number of research articles published, appear to have the MRI scanners. General access has also increased considerably since its introduction with a large global increase in the number of operational MRI scanners with the number of MRI per million population (Chung et al., 2011)

Another disadvantage is the inferior imaging of cortical bone compared to CT (Feydy et al., 1998). CT is dependent on attenuation of X-rays through tissues, whereas MRI utilises the abundance of hydrogen atoms (Feydy et al., 1998). In cortical bone there are very few hydrogen atoms in comparison to cancellous bone, soft tissue and fluids within the body, resulting in less signal (McRobbie et al., 2007).

Claustrophobia is an issue for some patients using MRI and some metal implants (pacemakers, aneurysms clips, heart valves) and foreign bodies are contraindicated for MRI (Shellock, 2010). In order to reduce this problem biomedical companies are developing implants that are MRI compatible and to ensure safety all patients are screened prior to entering the magnet for any of these contraindications (Shellock, 2010).

It is generally accepted that MRI is the 'gold standard' for the assessment of BSI. It has greater sensitivity and higher specificity than bone scintigraphy (Gaeta et al., 2005) and it provides the most comprehensive evaluation of BSI by demonstrating morphological and functional information of bone (Moran et al., 2008).

When clinically evaluating patients with recurrent symptoms, it is important to know at what stage the initial BSI would have dispersed on imaging. Slocum, Gorman, Puckett, and Jones (1997) performed a study of ten non-displaced compressive-side femoral neck

BSIs. The results demonstrated that 90% of cases take up to 6 months for increased signal in STIR sequences to resolve. This lag shows the importance of MR image interpretation, with patients with recurrent pain and this knowledge gives medical personnel a guide when clinically assessing patients with recurrent symptoms and interpreting MR images. To conclude a diffuse hyper-intensity seen on STIR image more than six months since the primary insult is indicative of a new BSI (Slocum et al., 1997).

Within MRI there are further considerations: firstly, the strength of the magnet and secondly where the contrast is administered. Clinical field strengths vary from 0.2T -3T, however most clinical systems are 1.5T (McRobbie et al., 2007). The main advantages of 1.5T magnets include: being less prone to artefacts, are cheaper to run and generally have more universal imaging capabilities. More recently the introduction of 3T offers improved signal to noise ratio, which is particularly useful in musculo-skeletal imaging (MSK) imaging. A small study in 2011 compared the 1.5T and 3T in BSI of the foot, reporting that whilst 3T had slightly better resolution to 1.5T, when looking at oedema there was no noteworthy difference when examining the sensitivity of BME in BSI (Sormaala, Ruohola, Mattila, & Koskinen, 2011).

MRI specificity is so high, it can classify whether a BSI of the neck of femur is a compression or tension type (Pihlajamäki, Ruohola, Kiuru, & Visuri, 2006a) the latter of which is more unstable (Devas, 1965). This concurs with Shin, Morin, Gorman, Jones, and Lapinsky (1996) who reported that positive scans could be evident after 6 days from onset of symptoms, thus allowing a more complex classification of risk and therefore a more accurate diagnosis and treatment.

A further advantage of MRI is its ability to image surrounding tissue and adjacent structures when compared to bone scintigraphy, which only images the actual skeleton (Dobrindt et al., 2012).

In summary, MRI is the gold standard tool for imaging BSI, providing clinicians with a comprehensive evaluation of both bone morphology and function with a high degree of sensitivity, specificity without ionising radiation.

Ultrasound (US)

This modality uses sound waves to obtain images, whereby a probe is placed on the affected body part and sound waves are transmitted through this area. As the sound waves travel through the body they hit different tissues and some of them bounce back and are detected by the probe. The machine then calculates the distance from the probe to the various tissue structures and then displays these echoes using distance and intensity to produce a 2D image (Hofer, 2013).

Originally therapeutic US aided diagnosis in BSI as patients with BSI had pain when the therapeutic US probe was placed on the injured area (DeLacerda, 1981). Unfortunately it was only useful in the early stages of BSI, where the damaged periosteum in early stress fractures absorbed the US energy and subsequently converted to heat and eventually manifested into pain and has a reported accuracy of 96% (Moss & Mowat, 1983). In comparison an uninjured 'complete' periosteum or injured with callus formation does not allow propagation of sound in the same manner and therefore no heat and pain (Moss & Mowat, 1983), however further radiological assessment is required to confirm this finding.

This has been superseded by diagnostic US and has many advantages: it is widely available, relatively inexpensive, portable, non-ionising and can be performed quickly and dynamically (Papalada et al., 2012).

There are some significant limitations of this modality: firstly it has limited penetration power reducing the areas it can image and more importantly it is highly operator dependent, meaning inexperienced operators can misdiagnose injuries (Farkash, Naftal, Deranza, & Blankstein, 2008). As US waves cannot pass through bone, only the outer surface of the bone can be imaged whilst internal detail remains undetectable (Bodner, Stockl, Fierlinger, Schocke, & Bernathova, 2005). Thus US is more suited to imaging superficial structures such as the tibia and feet, where the large difference in the acoustic impedance of bone and soft tissue structures give a strong echo, allowing any disruption in the periosteum to become evident (Van Holsbeeck & Introcaso, 2001). Normal cortices appear linear and echogenic (have a bright high signal) and any disruption will appear hypo echoic (low signal) (Figure 27). Low grade BSIs are often subtle with no obvious break within the cortex and US has been reported to visualise these more subtle signs in

the lower limb (Bodner et al., 2005). Periosteal thickening or elevation and hyper echoic swelling in the soft tissues have all been reported using US (Bodner et al., 2005).

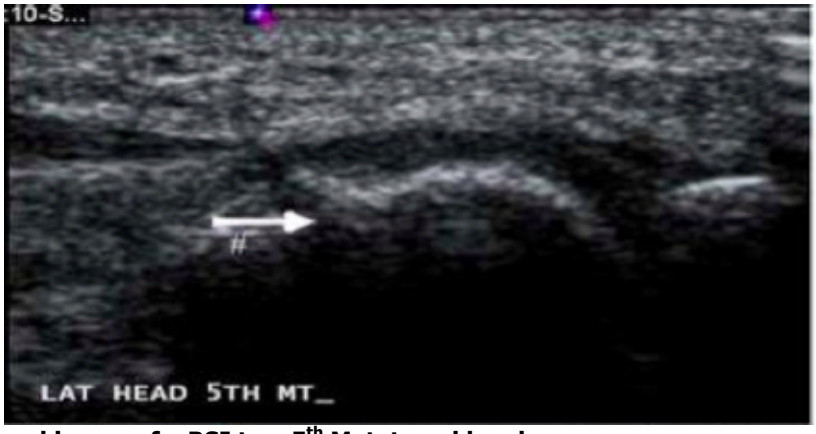


Figure 3: An ultrasound image of a BSI to a 5th Metatarsal head.
A clear break in the cortical bone (arrowed) with accompanied periosteal reaction (Jones & Philips, 2010, p. 4).

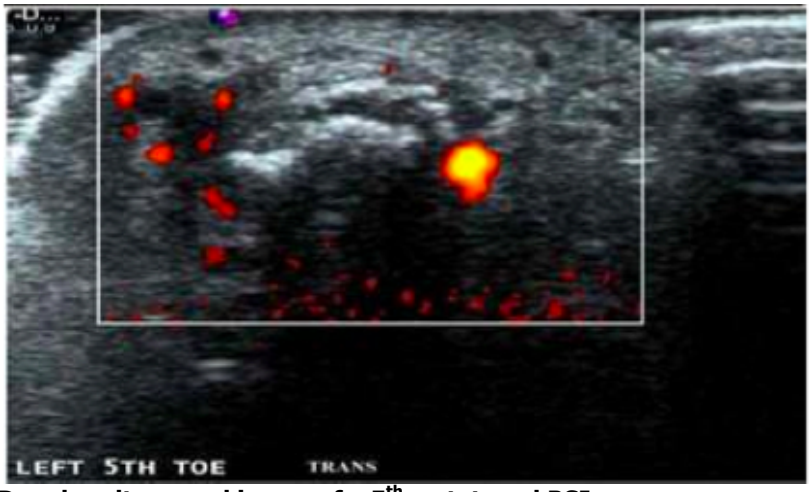


Figure 28: A power Doppler ultrasound image of a 5th metatarsal BSI.
The associated positive power Doppler image to accompany 35 demonstrating neoangiogenesis which accompanies osteoblast proliferation (Jones & Philips, 2010, p. 4).

Colour Doppler US has been used in association with imaging traumatic fractures and can demonstrate neoangiogenesis (Figure 28) to confirm healing (Caruso, Lagalla, Derchi, Lovane, & Sanfilippo, 2000) and is a useful adjunct to traditional grey scale US in a diagnosing BSI (Jones & Philips, 2010). A study by Caruso et al. (2000) on trauma fractures suggested that angiogenesis accompanying osteoblast proliferation can be visualised one-week post fracture whilst grey-scale US takes approximately three weeks and whilst not as quick as other modalities, is still faster than radiography at 30-40 days.

If the injury progresses focal buckling, cortical discontinuity, callus formation and increased blood flow at fracture site have also been noted under US using colour Doppler, (Figure 28).

Despite this, diagnostic US has been found to have a limited sensitivity when diagnosing BSI in a comparison study with bone scintigraphy (Boam et al., 1996). Furthermore a comparison study of therapeutic ultrasound (TUS) and MRI found TUS had a sensitivity of 81.8% and specificity of 66.6% (Papalada et al., 2012), suggesting that MRI is still the preferred modality for diagnosing BSI, but TUS is a reproducible procedure that is reliable, quick, cheap and easy to perform.

Summary of Imaging

It is clear from the large evidence base that MRI is the gold standard in imaging BSI. However each modality has its place and can be a useful adjunct in difficult cases. Bone scintigraphy has proven useful in highlighting multi focal BSI which would otherwise not be identified but as radiation is now more closely monitored both MRI and US offer safer alternatives. US is widely available and can be used in small centres by a range of health professionals, but both cost and availability have been driven down making MRI a more accessible tool to most, particularly in sport and the military, which appear to be the most prevalent populations for BSI.

Diagnosis

A thorough history is paramount in order to gain the correct diagnosis for patients suffering with a potential BSI. Key questions to ascertain this diagnosis include:

>Is there a presence of pain?
>What is the mechanism of pain, for example does it get worse on impact?
>Where is the pain?
>Is the pain focal or diffuse?
>Has the patient commenced a new training schedule or had a sudden increase in training volume?
>What type of surface is the patient training on?

(Bradshaw et al., 2006 p. 559).

When taking a patient's history a more involved line of questioning is undertaken to rule out the differential diagnosis such as: tumour, compartment syndrome, medial tibia stress syndrome, periostitis, muscle strains etc., a more complete copy of these questions taken from (Bradshaw et al., 2006) can be seen in Appendix One.

The importance of having a high index of suspicion in new military recruits was reiterated in a study where it was noted that 69% of cases presented within the first seven weeks of military training of Nepalese recruits (Joshi, Shah, Chand, Thapa, & Kayastha, 2009), possibly due to the high initial training intensity. In contrast another study reported that most of the BSI were recorded towards the end of the training in British Marines, proposing that they were due to the increasing intensity towards the end of the training programme (Stoneham, Chir, & Morgan, 1991). In both reports the increase in training intensity was found to coincide with increase BSI rates, implying that clinicians and trainers should have a high index of suspicion with any increase in training intensity (Brukner, 2000).

A high index of suspicion should be accompanied by good health promotion regarding BSI. This must be targeted at both recruits/athletes and trainers to aid in the early detection of BSI and improve patient treatment and management thus reduce the morbidity associated with BSI (Joshi et al., 2009).

The location and the grade of injury can determine the degree of pain the patient may present with (Fredericson et al., 1995). The onset of pain can be gradual and tends to develop over 1-3 weeks, with pain present only during exercise (Armstrong et al., 2004; Greaney et al., 1983). If pain is reported at this initial stage when it first becomes noticeable and training (the stressor) is reduced or stopped the individual should recover (Geslien et al., 1976). However if the pain is ignored and training continues, the BSI will continue to advance, causing pain at rest and ultimately can lead to a displaced fracture (Blickenstaff & Morris, 1966). Essentially the phase of pathogenesis determines the symptoms (Figure 20) (Anderson & Greenspan, 1996). But there have been cases where some very early BSI have no symptoms. In severe cases clinicians have been known to palpate callus formation (Hallel et al., 1976; Wilson & Katz, 1969) however with better education amongst athletes and military alike and a high index of suspicion in clinicians, should result that BSIs are detected before higher grade injuries occur (Joshi et al., 2009).

Clinical decision trees are a useful tool, allowing clinicians to apply evidence based medicine to clinical symptoms, resulting in objective clinical discussions on: imaging, management and treatment (Figure 29) (Lappe et al., 2001).

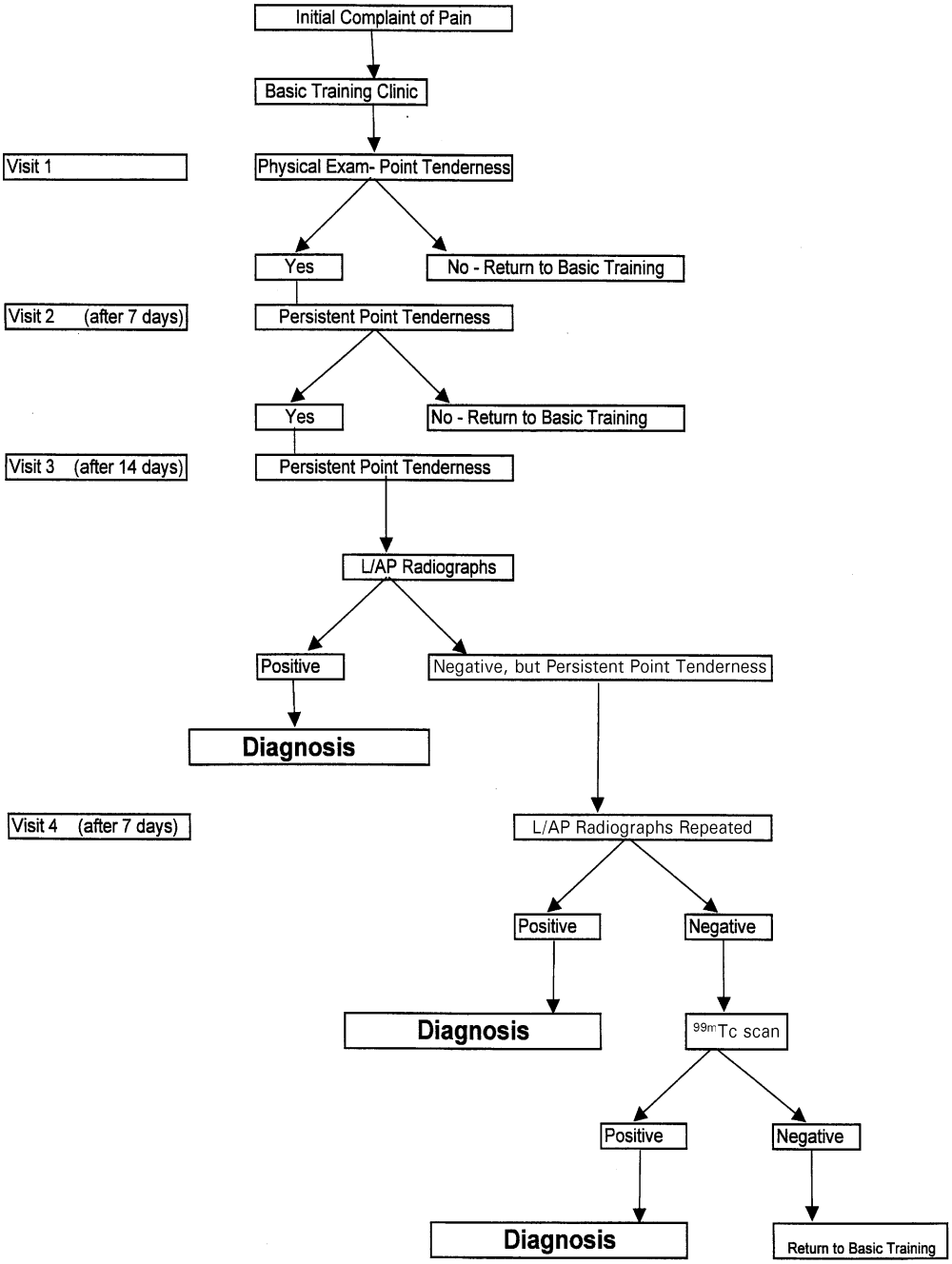


Figure 29: A clinical decision tree for BSI (Lappe et al., 2001, p. 37).

It is important to note that BSI can be misleading (Hodler et al., 1998), particularly when there is failure to report symptoms promptly. It is unclear if this is intentional, with personnel hiding symptoms in order to continue training due to high levels of motivation

and/or a high pain threshold (Hallel et al., 1976; Stoneham et al., 1991). However Greaney et al. (1983) found that some military recruits were diagnosed with multiple BSIs and suggest that more advanced injuries may mask symptoms at other sites.

During clinical examination individuals may present without any symptoms, as pain only occurs during training (Bradshaw et al., 2006). Therefore a number of tests has been devised to initiate the pain in certain areas, for example the fulcrum test for BSI of the femur (Johnson et al., 1994), the hop test for the lower extremities (Ishibashi et al., 2002) and the percussion test for the tibia (Lesho, 1997).

Other clinical symptoms include: warmth and swelling over the area of pain, occasionally discolouration may be seen (Figure 30) and in more advanced stages a palpable lump may be found from a periosteal reaction (Wilson & Katz, 1969). The location of the BSI can both affect the clinical detection and the prognostic importance (Reeder et al., 1996) and can be divided into high and low risk (Pegrum et al., 2012). But ultimately the earlier a diagnosis is made, the more favourable the outcome and diagnostic imaging plays an essential role in this (Bennell et al., 1996a; Matheson et al., 1987b).

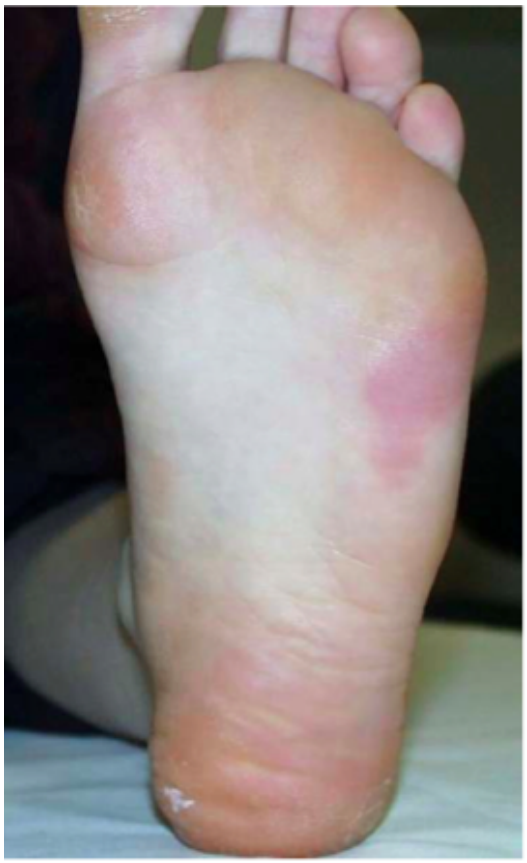


Figure 30: A photograph depicting the clinical presentation of a BSI to the foot.
Note the area of redness over the lateral aspect of the foot. Ultrasound confirmed a BSI of 5th metatarsal head (Jones & Philips, 2010, p. 4).

Lab tests can be performed to aid diagnosis and can be requested as part of the medical work up in cases of suspected BSI and the possible differential diagnoses (Weiss Kelly & Hame, 2010). Although Blickenstaff and Morris (1966) report that the complete blood cell count, serum calcium and alkaline phosphatase levels have all been within the normal range in patients with BSI in the femur, whilst the erythrocyte sedimentation rate was only slightly raised in a few instances. This possibly suggests the tests are of limited value in providing a definitive diagnosis of BSI, but maybe more useful in picking up other differential diagnoses, such as a tumour for example.

There have been reports of mismatching between clinical examinations and imaging reports. This is particular prevalent with bone scintigraphy, with its larger field of view compared to plain radiography, CT, MRI and US, making it better able to pick up symptomatic site(s) but also additional asymptomatic 'hot spots' which may be related to BSI (Matheson et al., 1987a). Further mismatching occurred in many of the early research papers, where symptomatic patients were reported to have negative radiographs

(due to the low sensitivity) only to have follow-up images depicting BSI (Bernstein & Stone, 1944; Devas & Sweetnam, 1956; Hallel et al., 1976).

Classification Systems

Discrepancies in clinical definitions of BSI have been examined and the implications for the USA army (Smith, 2011). Whilst it was a review, it was interesting to note that 45% (22 studies) failed to define the presentation of the BSI and healing. Instead they simply reported the existence without using any classification or grading system. This overall lack of standardisation within the army negatively affects patient disposition regarding training and ultimately long-term health. This will place a financial burden on the army and possibly have long-term health implications for the recruits, such as unwarranted discharge. Smith (2011) also conducted a limited review outside the army and suggested that this lack of standardisation mirrors that of the wider medical community. Recommendations included standardising: the definition, the diagnosis (grading systems) and the management of BSI to uphold high patient care standards.

…any grading system is only useful if it relates to increasing accuracy in defining the clinical picture, which in turn directly relates to clinical management of an individual case
(Arendt & Griffiths, 1997 p. 291-292).

Every BSI can be graded or classified, which significantly assists in the diagnosis of the injury (Carmont et al., 2009; Philipson & Parker, 2009). There appear to be two approaches to classification: a clinical approach used by orthopaedics and sports medicine clinicians and an approach using one of the many imaging modalities. The first method is concerned with the position, location and then degree of risk of non-union (Fredericson et al., 2006). The risk relates to the bone(s) involved and the associated anatomic preconditions such as blood supply. This information enables clinicians to design an individualised treatment plan for each patient determined by their injury (Dobrindt et al., 2012).

The second method uses imaging, for example MRI or bone scintigraphy, to classify the extent of the lesion using one of the many different imaging classifications systems proposed throughout the literature.

Both Arendt and Griffiths (1997) and Zwas et al. (1987) produced generalised grading systems that can be applied to any bone. Blickenstaff and Morris (1966) and Devas (1965) designed grading systems exclusively for the femoral neck, whilst Fredericson et al. (1995) published a grading system purely for the tibia. Further differences between these classification systems involve the imaging modalities used, for example the Zwas et al., (1987) system only used bone scintigraphy whilst both Blickenstaff and Morris (1966) and Devas (1965) used radiographs. Fredericson et al. (1995) utilised both MRI and bone scintigraphy (Table 1) whilst Arendt and Griffiths (1997) employed radiographs, bone scintigraphy and MRI (Table 1) and appears to be the most cited and utilised system throughout the literature (Miller, Kaeding, & Flanigan, 2011).

However the Arendt and Griffiths (1997) system does not appear to be published - the report states they had produced a grading system five years previous – therefore it is difficult to assess the grading system. Arendt and Griffiths (1997) explained the importance of MRI in assessing BSI in high performance athletes and made sensitivity and specificity comparisons against plain radiographs and scintigraphy. Whilst the Arendt and Griffiths (1997) classification system has been widely utilised within the literature, it also does not appear to have been validated, as they failed to report results of statistical analysis or inter-observer reliability and therefore the quality of the system remains unclear and therefore the validity of the evaluation maybe disputed (Miller et al., 2011). A systematic review of the classification systems for BSI suggested that the lack of statistical analysis was most likely because of the time in which it was produced (Miller et al., 2011), before evidence based medicine became commonplace (Sur & Dahm, 2011) and consequently may not have been a major concern for the authors at that time. However Fredericson et al. (1995) did supply this data at a similar time, potentially making it a more credible piece of research.

Imaging modality	**X-Ray**	**Bone Scintigraphy**		**MRI**		**Treatment**
Authors	**(Arendt & Griffiths, 1997)**	**(Arendt & Griffiths, 1997)**	**Fredericson et al., (1995)**	**(Arendt & Griffiths, 1997)**	**Fredericson et al., (1995)**	**(Arendt & Griffiths, 1997)**
Normal	**Normal**	**Normal**	**-**	**Normal**	**-**	**None**
1	Normal	Poorly defined area of increased activity	Small, ill-defined cortical areas of mildly increased activity	Positive STIR	Periosteal oedema: mild to moderate on T2-weighted images; Marrow: normal on T1 and T2 weighted images	3 weeks rest
2	Normal	More intense but still poorly defined	Better-defined cortical areas of moderately increased activity	Positive STIR plus positive T2	Periosteal oedema: moderate to severe on T2 weighted images; Marrow oedema on T1 and T2 weighted images	3-6 weeks rest
3	Discrete line (?); discrete periosteal reaction (?)	Sharply marginated area of increased activity focal or fusiform	Wide to fusiform, cortical-medullary area of high increased activity	Positive T1 and T2, but without definite cortical break	Periosteal oedema: moderate to severe on T2-weighted images; Marrow: oedema T1 and T2 weighted images	12 - 16 weeks rest
4	Fracture or periosteal reaction	More intense transcortical localized uptake	Transcortical area of intensely	Positive T1 and T2 fracture line	Periosteal oedema: moderate to	16 + weeks rest

			increased activity		severe on T2 weighted images; Marrow oedema on T1 and T2 weighted images; fracture line clearly visible	

Table 1: A radiological BSI classification table.

This table compares Arendt and Griffiths, (1997) and Fredericson et al., (1995).

The Fredericson et al. (1995) classification system, used a small sample of only 14 patients in their prospective case series and compared bone scintigraphy to MRI. The study hypothesis stated that MRI would give additional information that would assist clinicians in the treatment and rehabilitation of BSI. Their data supported this hypothesis and allowed them to produce a grading system and correlate it with recovery, defined as the time from diagnosis to return to pain-free running. However the study's selection criteria looked at runners with only tibial stress pain, but researchers have modified this for BSI at other locations (Kiuru et al., 2001). The Fredericson et al. (1995) grading system was validated by Kijowski et al. (2012) on 142 tibial stress injuries and concluded that grades 2, 3 and 4a had similar degrees of periosteal and BME and similar return to sport times recommending all three grades be combined into a single grade in an truncated system.

In spite of these popular grading systems, some BSI studies did not refer to one at all, potentially suggesting a general lack of agreement in the literature. This overall lack of consistency within the literature makes it difficult to draw valid conclusions and compare like with like.

In summary no single grading system has been proven to be more accurate or useful than another. The research has suggested that by combining both imaging classification with more clinical risk factors, such as the lesion site, the 'return to play' can be more accurately assessed, than from just risk factors or BSI severity alone (Dobrindt et al., 2012). Therefore there is a definite need for a system that classifies BSI lesions into

degrees of severity that can be utilised throughout the entire skeletal system and across imaging modalities. Miller et al. (2011) are making further investigations into developing a more clinically relevant classification system that is reproducible, validated and more widely applicable and whilst this will not aid the current review, it will be useful for future BSI research.

However, for this study an important aspect of current and future classification systems is where asymptomatic BSI fit in, if at all. This review will explore the presence of asymptomatic BSI in military personnel and athletes and perhaps bring this seldom explored topic into the fore again.

Differential Diagnosis

There are a variety of conditions that can mimic the BSI in the lower limb: inflammatory problems including- tendinitis, periostitis, strain, sprain, MTSS, shin splint, compartment syndrome; neoplastic including- sarcomas and metastasis; infectious- osteomyelitis; vascular- intermittent claudication and neurological. For example infection, inflammation, bone tumour and bone bruising all posses similar imaging patterns to BME on MRI (Lazzarini, Troiano, & Smith, 1997; Schweitzer & White, 1996). Likewise on radiographs increased bone formation occurs in both BSI and tumours, however delayed films (2-3 weeks later) that demonstrate progressive maturation of the repair process are indicative of BSI, whilst tumours will not change in this time (Daffner & Pavlov, 1992). It is therefore important to gain both a good clinical history from the patient and combine this with suitable imaging, to authenticate the diagnosis (Kiuru, Pihlajamaki, & Ahovuo, 2004).

Treatment and Management

There is consistent evidence in the literature that early detection of BSI improves outcome to both athletes and military personnel (Geslien et al., 1976; Joshi et al., 2009).

In the main, BSIs are considered benign injuries that can be managed through either modification or cessation of training or stressful activity with no long-term effects or disabilities, although some need more aggressive management (Boden et al., 2001). This can be determined by the grade of the BSI and its non-union risk. BSI tends to be classified using one of several published systems. The risk of non-union is determined by

the lesions location (Table 2), the direction of loading through the lesion during stress and the natural course of healing, which is further dependent on the tension zones and blood supply (Kaeding, Yu, Wright, Amendola, & Spindler, 2005). An example of a simplified management algorithm can be seen in Figure 31 (Pegrum et al., 2012).

Fractures with a low risk of non-union	Fractures with a high risk of non-union
femoral neck (medial cortex)	femoral neck (superior cortex)
tibial shaft (posteriomedial cortex)	tibial shaft (anterior cortex)
2nd, 3rd, 4th, 5th distal metatarsal	fifth metatarsal (diaphyseal-metaphyseal junction)
calcaneus	navicular
fibula	proximal 2nd metatarsal
pubic rami	talus
cuboid	medial malleolus
cuneiform	sesamoids

Table 2: Fractures with a high and low risk of non-union
adapted from (Pegrum et al., 2012, p. 4)

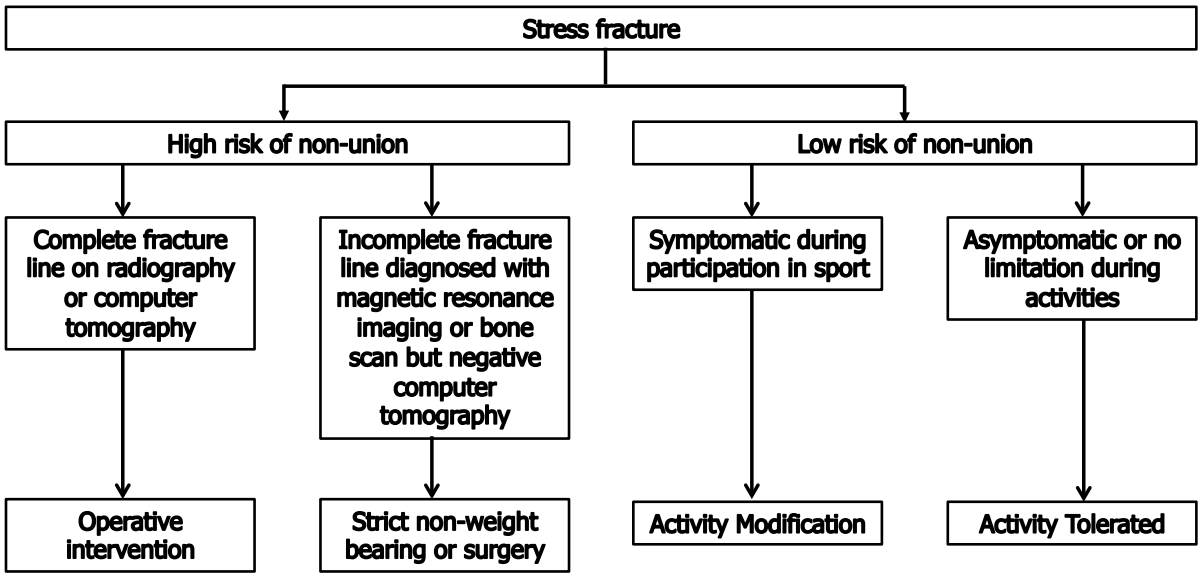


Figure 31: A simplified BSI management algorithm
This algorithm can be used to help doctors decide between activity modification, non-weight bearing, and surgery taken from (Pegrum et al., 2012, p. 7).

Low grade BSI, in bones that have a good blood supply, in the low risk of non-union category can normally be managed with a period of short rest from aggravating activity,

typically 4-8 weeks (Brukner, Bradshaw, & Bennell, 1998). Splints, casts and crutches are used in some cases to aid immobilisation and protect the bone from weight-bearing as clinicians would do in a 'normal' trauma fracture (Bradshaw et al., 2006). The length of treatment once again is totally dependent on the extent of the injury and then a modified training regime allows bone healing whilst preserving cardiovascular fitness (Boden et al., 2001).

High grade BSIs, including those that have subsequently displaced and/or have a high risk of non-union BSI often require more aggressive surgical treatment in the form of pinning or internal fixation and on occasion allografts (Figure 32). Surgical intervention provides a more stable environment for the bone to reunite and results in a quicker recovery and consequently quicker return to activity or training.

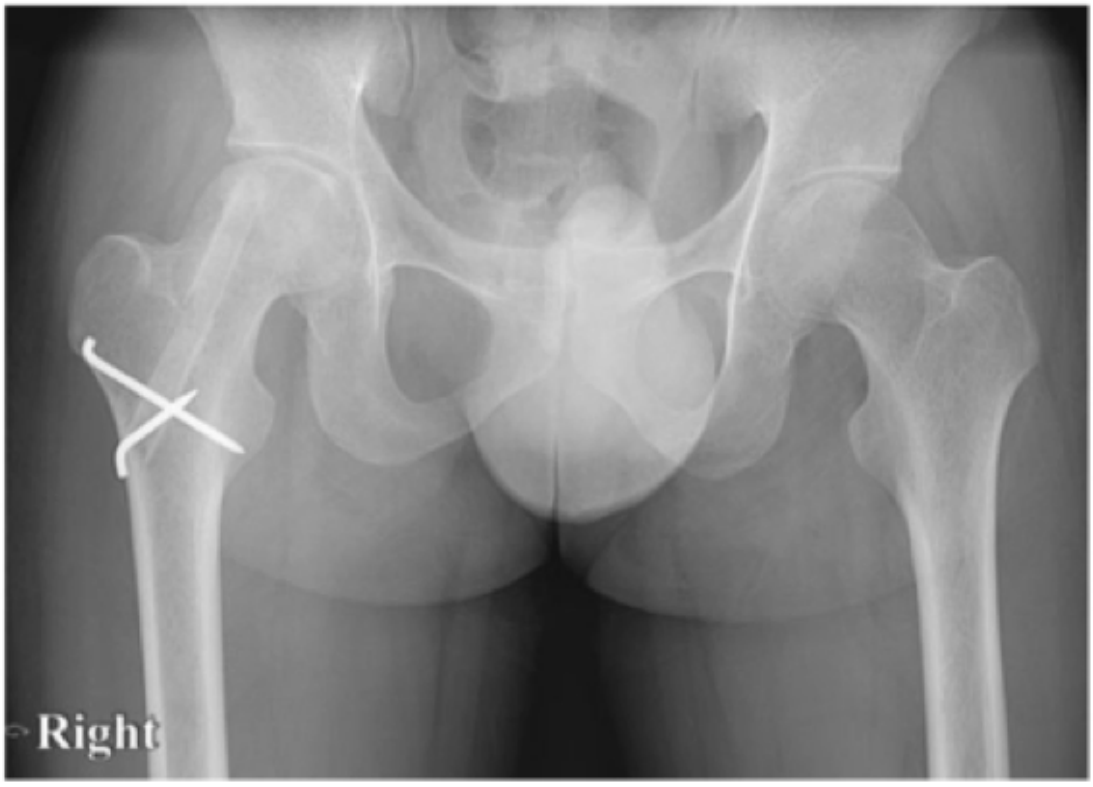


Figure 32: A post-operative radiograph demonstrating a restored femoral head and a fibular allograft. The allograft is secured within the core by two Steinmann pins that cross both cortices of the femur and the lateral femoral cortex (Yoon et al., 2012, p. 947).

Individualised patient rehabilitation should include a phased return to play with assessment and elimination of any possible risk factors (Murray, Reeder, Udermann, & Pettitt, 2006). It is important to emphasise that delayed or under treated high risk non-union BSI can lead to catastrophic results, potentially including: failure of bone union,

prolonged loss of training, avascular necrosis or even permanent disability. Conversely over treatment of low risk non-union BSI can also have negative effects including: loss of fitness, training and experience, possibly resulting in the patient losing sports contracts or military service (Kaeding et al., 2005).

Risk Factors

There is a large body of evidence identifying risk factors for BSI, highlighting how complex the pathophysiological process is, with many inter-relating factors, suggesting it is more likely that a combination of risk factors result in stress related bone failure (Figure 17) (Bennell et al., 1999).

The etiology of stress fractures continues to be a multifactorial conundrum (Armstrong et al., 2004, p. 814).

The process of identifying these factors aids diagnosis and helps prevent future BSI (Koenig, Toth, & Bosco, 2008). Specific to the lower limbs (femur to foot) risk factors can be divided into: intrinsic, extrinsic, physiologic, nutritional, hormonal, physical, psychological and more recently, genetic factors (Brukner et al., 1999). In an effort to reduce the incidence of BSI within the physical performance domains, identifying risk factors and preventing BSI appears to have become a heavily researched area in the last twenty years throughout BSI literature. When conducting research one of the most challenging areas is limiting the significant range of risk factors to the one or two factors of interest and subsequently matching the subjects in order to provide a homogenous sample. As a result of these issues there remains insufficient evidence in the peer reviewed literature to state confidently that particular factors are more responsible for the occurrence of BSI than others (Brukner et al., 1999). A summary of the main factors is provided below, but note these are neither exhortative nor causative.

Extrinsic factors

- External loading: Ground-reaction force (GRF) is the force exerted by the ground on a body in contact with it and there have been studies to examine if this is a risk factor (Bennell et al., 2004). However there is little evidence proving this to be true, for example Bennell et al., (2004) concluded that GFR did not have any effect on BSI. Furthermore,

Zadpoor and Nikooyan (2011) conducted a systematic review on this risk factor and again found no significant evidence to support this hypothesis.

- Footwear: Footwear appears to contribute to the prevalence of BSI, with shock absorbing inserts (orthotics) offering some protection from the stresses of weight-bearing exercise. A Cochrane Review by Rome, Handoll, and Ashford (2005) reported that modifications to footwear probably reduce the incidence of BSI in military personnel, although more evidence is needed to determine the best design but suggest that shock absorbing qualities probably afford some protection. Importantly one piece of literature notes that orthotics need to be professionally made and medically prescribed and if this is not the case may actually be the cause of BSI (Major, 2006).

- Surface: Harder training surfaces have been linked to increased BSI incidence (Devas & Sweetnam, 1956; Iwamoto & Takeda, 2003) and support the use of orthotics in mitigation of the training load. The theory suggests that the harder the surface the quicker muscles fatigue reducing their protectiveness to GRF on the bone (Steele & Milburn, 1988).

Intrinsic Contributing Factors

- Bone mineral density (BMD): Osteoporosis is characterised by low BMD and degradation of the bone micro-architectural and low BMD has been linked to insufficiency fractures (Iba, Wada, Takada, & Yamashita, 2003). However, the evidence is less conclusive about the impact of BMD on BSI risks (Bennell et al., 1995). One study conducted on female athletes found the BMD of the BSI group was lower than the non BSI group, but the difference was not statistically significant, potentially a direct result of the difficulty in subject matching (Bennell et al., 1995). Interestingly, Brukner et al. (1999) suggested that BMD in non-athlete participants (not physically active) was equal or less than the BMD in BSI athletes. A further report concluded that bone density was not linked to BSI incidence (Bennell et al., 2004). Whilst Armstrong et al. (2004) demonstrated that 'total body' BMD was lower in male subjects with BSI, the BMD readings taken from the tibia and femur were not significantly different between the groups. Pouilles, Bernard, Tremollieres, Louvet, and Ribot (1989) concluded that a lower BMD (ranging from 10% to

2% in their study) may be a risk factor but only at specific sites, for example the femur and calcaneus.

- Bone geometry: Bone geometry appears to be a predictor of BSI, with smaller tibial cross sectional areas and section modulus linked to athletes with BSI and sedentary males, with higher bone geometry values found in uninjured athletes (Crossley et al., 1999; Franklyn, Oakes, Field, Wells, & Morgan, 2008) reported that bone geometry is a risk factor for male runners with small bones in relation to their body size being at increased risk of BSI. However in contrast a similar study, found no link with GRF or bone geometry in female athletes (Bennell et al., 2004).

- Skeletal alignment: Whilst pes cavus (high arch) and pes planus (flat feet) are anatomically different, both may be predisposed to BSI. The former providing less shock absorbance and the latter possibly too flexible. These anatomical differences results in BSI affecting different bones, pes cavus allows stress to propagate up through the tibia and femur, whilst pes planus absorbs stress and may also cause hyper-pronate, resulting in additional torsion of the tibia and associated muscle fatigue (Bennell & Brunker, 2005). Leg length inequality is another biomechanical factor found to increase BSI incidence, with 83% of BSI cases having an inequality of at least 1mm and BSIs being more prevalent in the shorter leg (49%) than the longer leg (38%) (Korpelainen, Orava, Karpakka, Siira, & Hulkko, 2001). Moreover 60% were in the dominant side, which may be due to this leg having more use (Korpelainen et al., 2001). This also concurred with Friberg (1982) who also found leg length discrepancies may have a predisposing role in BSI, but they found that 73% of BSI in the lower limb occurred in the longer leg, and 16% in the shorter leg (11% were equal) in military personnel, and they suggest the longer leg may undergo greater stress due to its length.

- Body size and composition: BSI has been reported to be more prevalent in recruits with a lower adult weight (Givon et al., 2000) and males with a waist circumference of less than 75 cm (Moran, Finestone, Arbel, Shabshin, & Laor, 2012). Bennell et al. (1999) suggest this may be due to individuals who have a leaner fat mass and lower body weight being linked to a lower BMD. Furthermore Beck et al. (1996) reported that smaller military recruits had greater incidence of BSI and they suggested that this may be due to

the heavy training equipment they carry affecting smaller recruits more than those with a higher body mass (Beck et al., 1996).

- Gender: There are a number of physical differences between males and females including: build (narrower bone width), BMD, menstrual irregularities, and maladapted training loads for females. However there is no clear evidence to suggest that one gender is more at risk than the other. One military study has demonstrated that females have a higher incidence of BSI than their male counterparts (Itskoviz, Marom, & Ostfeld, 2011). Although another study failed to note a difference in BSI incidence in female subjects in their study (Bennell et al., 1996a). This difference maybe due to training load, with Itskoviz et al., (2011) noting that the females in their study had to undergo similar training to their male comrades whereas Bennell et al. (1996a) examined athletes who would have individualised training plans reducing this factor.

- Age: This may be a risk factor as it is understood that bone density reduces with older age, which is thought to impinge on the likelihood of a BSI (Bennell et al., 1999). Furthermore the immature skeleton of the child and young teen is also thought to be at risk as bone mass has yet to peak (Lu et al., 1994). However most of the studies performed are within quite a tight age bracket: military recruits generally appear to be between 17-29 years of age, which makes drawing conclusions regarding this difficult. One male military study demonstrated that above the age of 17, each increasing year reduced the risk of a BSI by 28% (Milgrom et al., 1994). However, Lappe et al. (2001) demonstrated that older females appear to have a higher BSI incidence compared to younger females and similarly Reis et al. (2007) concurred with this in males.

- Race: It is well accepted that black skinned individuals have a higher bone mass than others and is one suggested explanation as to why white and Asian women appear to have a higher incidence of BSI compared to women of African origin (Lappe et al., 2001). Furthermore, Ethiopian males appeared to be afforded some protection from BSI when compared to their fellow white recruits in a military study (Milgrom et al., 1994).

Physical training

- Training schedules: These are developed to improve fitness and physical condition, however without adequate recovery they can have negative effects on the physiological

process of bone remodelling (Fredericson et al., 1995). Supporting this notion, military studies note a reduction in marching accompanied a drop in BSI incidence (Shaffer, Brodine, Almeida, Williams, & Ronagh, 1999) and importantly these soldiers were still as physically 'trained' as before, suggesting that changes can be made to training schedules at no detriment to overall fitness but still offer significant protection from BSI (Shaffer et al., 1999). Another study found that training modifications resulted a reduction in BSI incidence from 4.8% (non modification) to 1.6% (modification) (Scully & Besterman, 1982), supporting the argument that training schedules are a risk factor for BSI. Bennell et al. (2004) further demonstrated that training schedules could affect the risk of BSI. Reducing the weight of military equipment, pack, rifle and clothing, has also been demonstrated to lower the incidence from 18.3% to 8.0% (Constantini et al., 2010).

- Physical fitness: Unsurprisingly there is evidence to suggest that some previous exercise (or level of fitness) before commencing military service offers some protection against BSI where the longer the period of pre training is relative to the reduction in their relative risk (Leabhart, 1959). Recruits have been reported to cut their risk of BSI by half if they had a history of exercising for at least three times a week and as such (Lappe et al., 2001), it has been recommended that fitness screening and where applicable a preconditioning program be implemented (Jones & Knapik, 1999). It should be noted that some studies used self reported levels of fitness rather than a taking a fitness test where all participants are measured at the commencement of the study, which can lead to bias and make it difficult to distinguish if there is a relationship between the two.

- Previous injury: Milgrom, Giladi, Chisin, and Dizian (1985c) followed 295 male military recruits and found that those whose sustained a BSI during basic training were at a 10.6% increased risk of further BSI during the rest of their training. Rauh, Macera, Trone, Shaffer, and Brodine (2006) followed 891 female recruits and found that the rate of subsequent BSI was 3.5 times than those injured for the first time. This supports previous and more generally with work by Macera (1992) and Beck (1998) who both performed reviews in sports injuries and both recognised that past injury is associated with future injury. However it is still unclear if this is due to insufficient healing of old injuries or other factors such as training errors, biomechanical anomalies and as such needs more research.

Physiologic Factors

- Bone turnover: Whilst it is understood that bone turnover affects BSI, there is a lack of evidence to suggest that this can be measured using bio chemical markers. One study measured and analysed blood and urine samples to determine bone turnover but failed to find a link using either single or multiple measurements of bone turnover, possibly illustrating its failure to predict BSI (Bennell et al., 1998).

- Muscle mass and strength: Muscle fatigue is thought to increase the risk of BSI, therefore stronger muscles are suggested to offer protection (Fyhrie et al., 1998; Hoffman, Chapnik, Shamis, Givon, & Davidson, 1999). In support of these findings it has been suggested that as muscle fatigues it fails to provide shock-absorbing benefits and therefore weaker muscles increase the risk of BSI (Milgrom, 1989).

Psychological Factors

- Motivation: There is evidence to suggest that runners who have a greater motivation are at a increased risk of developing a BSI, indicating that high motivation may enable participants to train though pain and to hide symptoms for fear of losing training time, resulting in the case of military recruits being discharged or athletes being over looked for selection (Ekenman, Hassmen, Koivula, Rolf, & Fellander-Tsai, 2001). Conversely another study's results contradict this, with BSI associated with lower scores in motivation, self-efficacy, and satisfaction (Hadid, Evans, Yanovich, Luria, & Moran, 2008). Low motivation has been linked to less or no pre-training, which has been proven to affect BSI risk (Gilbert & Johnson, 1966), which may explain this difference.

Nutritional Factors

- Calorie intake and eating disorders: The female triad is a syndrome characterised by three interrelated conditions: eating disorders, osteopenia and amenorrhea (Otis, Drinkwater, Johnson, Loucks, & Wilmore, 1997). It has been noted that female athletes with low weight, are at increased risk of developing the female triad which in turn places them at further risk of a BSI (Warren & Shantha, 2000) although work by Kang, Belcher, and Hulstyn (2005) supports the theory that not all three elements are required to increase the risk of BSI. Combinations of dieting and restrictive eating were also found to be more common in women with BSI (Bennell et al., 1995). Furthermore they also found

that there was no statistical difference between the incidence of BSI and both BMD and body composition. Weight loss has also been linked to BSI in both males and females (Armstrong et al., 2004). They theorized that a 'negative energy balance' achieved by restrictive eating may affect bone synthesis, muscle strength and fatigue all of which are linked to BSI (Armstrong et al., 2004).

- Nutrient deficient: Disordered eating can have a negative affect on bone health by reducing the intake of nutrients essential to promote it (Kiuru et al., 2003; Markey, 1987). A study examining nutrition in navy recruits found that both calcium and vitamin D supplementation prevent BSI (Lappe et al., 2008). A further study also found a link between lower levels of vitamin D and BSI in military recruits (Givon et al., 2000). Interestingly an earlier study Schwellnus and Jordaan (1992) found that calcium supplementation did not prevent BSI. This result could be in part be due to the short time span of the study (9 weeks), the poor specificity of the imaging modality (X-ray) or that the there were BSIs but only sub clinical that failed to present symptoms (Schwellnus & Jordaan, 1992).

- Smoking: A link between smoking levels and BSI in recruits has been noted in Israeli soldiers, with higher smoking levels linked to lower BSI rates (Givon et al., 2000). Whilst they were far from suggesting that smoking offered some protective value from BSI it is noteworthy. Explanations involve smokers being less fit therefore placing less stress on their bodies and that nicotine may have an effect on bone synthesis, but the most probable cause of this correlation is the methodology and the sample selection (Givon et al., 2000). Furthermore a meta-analysis of cigarette smoking on BMD and hip fracture suggests that whilst cigarette smoking effected BMD and fracture risk in post menopausal women, it was similar at age 50 (Law & Hackshaw, 1997).

Hormonal Factors

- Menarche disturbances: It has been demonstrated that female distances runners who have had menarche disturbances and never used oral contraceptives were at increased risk of BSI (Barrow & Saha, 1988). Furthermore amenorrhea (one of the conditions in the female triad) and menarche disturbances were also linked to BSI (Bennell et al., 1995)

Genetic Factors

- Genetics: Most recently there is evidence to suggest that genetic factors may contribute to BSI pathogenesis (Yanovich et al., 2012). The study conducted a candidate gene analysis in Israeli soldiers with stress fractures and found genetic factors may predispose the carrier of particular genes to BSI. But like most research this needs to be replicated on a larger group in order to be validated. They conclude that it is probably the combination of environmental factors in genetically susceptible individuals that contribute to the increased risk of BSI.

Prevention

A study by Scott et al., (2012) used evidence based prevention strategies including: education, modifications to training and nutrient supplements to reduce neck of femur (NOF) BSI in military personnel. Results demonstrated a saving of $5.3 million (USD) in the form of 75 fewer NOF BSIs (Scott et al., 2012). If this were to be widened to include all lower limb bones it would undoubtedly demonstrate that research in this field to date has been successful.

Training errors are a frequent cause of BSI, but educating and supporting staff these can be corrected (Brukner, 2000). Training equipment should be regularly maintained and/or replaced, particularly footwear, which has a life span of approximately 500km and training schedules should be individualised (Bradshaw et al., 2006) with adequate rest periods allowing the body to repair itself (Kiuru et al., 2003; Markey, 1987).

To conclude, education is the key preventative measure, in the athletes, military recruits and the trainers, coaches and support staff who are monitoring them.

Summary

The peer-reviewed literature is vague about whether asymptomatic BSIs are a pathological process or a part of a normal physiological response. More research is needed to more closely examine the presence and development of asymptomatic BSIs in athletes and military personnel in order to more fully understand this process.

This investigation will systematically review all available and relevant data in order to calculate the prevalence of asymptomatic BSIs in military personnel, athletes and in the

total population including civilians however it is beyond the scope of this study to reach firm conclusions on the clinical relevance of asymptomatic BSIs. Instead the results will be critically discussed, offering a further perspective on this contentious topic.

This thesis will systematically examine the asymptomatic BSI phenomenon throughout the peer reviewed research in military personnel, athletes and in the total population including civilians and establish if it is an important incidental finding that should be studied in more detail, potentially assisting in the prevention of BSI or is simply a false positive and a normal physiological action and as such may be disregarded.

Methods

Introduction

There appears to be limited research examining the prevalence and impact of asymptomatic BSI on athletes and military personnel. In order to add to the literature a number of research paradigms were considered, but after much deliberation a systematic review of the current literature was conducted in order to gain a more complete understanding of what is presently known in this area. In undertaking a thorough appraisal of all available research within the area, it may highlight areas that have been exhausted and others that still require further investigation either from recommendations from other researchers or apparent gaps within the literature.

A systematic review provides

explicitly formulated, reproducible, and up to date summaries of the effects of health care interventions
(Egger, Smith, & O'Rourke, 2001, p. 4).

Although systematic reviews have traditionally evaluated intervention studies, they are increasingly being used to evaluate prevalence and outcome studies. This is achieved using a structured approach to reviewing literature, which follows five stages:

- Determine review question or objective
- The literature search process
- Literature selection criteria (inclusion and exclusion)
- Pool studies
- Place the findings in context (Biggam, 2011).

If these steps are followed correctly the resultant systematic review will be a credible and trustworthy addition to the research community and policy decision-makers and is recognised as the highest level according to Evans (2003) (Table 3). The strength of this methodology is in the systematic approach to searching and selecting high quality multi-centred studies (Evans, 2003). These studies often incorporate a wide range of populations, circumstances and settings, all of which provide the most reliable and valid

evidence (Evans, 2003). To reiterate, its superiority and strength in part lies in the weight of evidence from a number of studies in contrast to a single one (Evans, 2003).

	Effectiveness	Appropriateness	Feasibility
Excellent	• Systematic review • Multi-centre studies	• Systematic review • Multi-centre studies	• Systematic review • Multi-centre studies
Good	• RCT • Observational studies	• RCT • Observational studies • Interpretive studies	• RCT • Observational studies • Interpretive studies
Fair	• Uncontrolled trials with dramatic results • Before and after studies • Non-randomized controlled trials	• Descriptive studies • Focus groups	• Descriptive studies • Action research • Before and after studies • Focus groups
Poor	• Descriptive studies • Case studies • Expert opinion • Studies of poor methodological quality	• Expert opinion • Case studies • Studies of poor methodological quality	• Expert opinion • Case studies • Studies of poor methodological quality

Table 3: Hierarchy of evidence

This table provides the ranking of research evidence evaluating health care interventions (Evans, 2003, p. 79).

The Cochrane collaboration is the benchmark in this field, internationally recognised for its high quality library of systematic reviews on healthcare and associated policy. They have helped and continue to assist healthcare workers and policy makers to make well informed empirically sound decisions (Cochrane-Collaboration, 2013). Conducting systematic reviews based on the results of trials, which meet their stringent pre-set high quality criteria, does this. Furthermore the reviews are regularly updated as new evidence is found, reducing the time between new discoveries and their use clinically (Cochrane-Collaboration, 2013).

The Review Question

The first step in this systematic review was to identify an area and refine this into a clear research question. After a mind-mapping session and discussion with a number of health clinicians the topic of asymptomatic BSI was chosen. Initial searching established that the prevalence of asymptomatic BSI in the physical performance domain was unclear. This gap in the literature means that there is no clear empirically based guidance on how medical professionals should best manage asymptomatic BSI within these elite physical

performance communities. In order to expand the knowledge pool it was decided to perform a systematic review, to identify the *"prevalence of lower limb asymptomatic BSI in athletes and military personnel"*. It was hoped this would contribute to a more complete understanding of BSI and thus support the medical professionals responsible for their treatment and management. The objective of this study was to review and determine an overall estimate of the prevalence of lower limb asymptomatic BSI and also the prevalence rates specifically in athletic and military populations and identify any differences between the two groups and specifically distinguish anatomical risk sites including an analysis of the distribution of asymptomatic BSI in the lower limb.

The Literature Search

Following on from the establishment of the research question, the next issue was how and where to complete the initial search as the main processes that set a systematic review apart from a narrative literature review is the process of searching. In a narrative review, there is no set method of searching, critiquing or synthesizing and these often only use a small number of articles from a vast area of literature and as a result do not produce reliable evidence, rather one sided reviews (Aveyard, 2007). The researcher can pick and choose appropriate quotes that support their own theory from an array of books and journals, rather than collecting all the data in that area, whether it supports or opposes it (Greenhalgh, 1997). Moreover, a systematic review clearly and transparently lays out the search strategy: how the data will be collected, involving specific search terms, whether they were truncated or exploded, specifying search engines and databases used, all of which should allow replicable results in order that the reader could recreate the search.

Even the most thorough searches, using such databases as Medline and PubMed, can fail to identify all the literature (Greenhalgh, 1997). Missing reports can lead to bias, therefore it is advisable to look up references in a bid to gain a more complete search, that may not have been possible from the initial search (Greenhalgh, 1997). This may be due to the search terms used and this systematic review was no exception, as 12 of 36 studies were found this way, possibly suggesting that the search terms were not broad enough. This process was not repeated which is a potential limitation of the study. However an extensive review of references was undertaken, possibly reducing this to

some extent. But the author appreciates that this is turn reduces the reproducibility of the study.

Moreover it is recommended that a broad spectrum of data from a number of sources be obtained, rather than just rely on published peer reviewed articles alone. Grey literature such as government reports, conference proceedings, work in progress, personal communications in the field and other unpublished work are all examples. If these are excluded the researcher is adding potential bias to their search. This publication bias occurs when only the results that are published in peer review journals are used in systematic reviews. It is a problem because positive results are more likely to be published than non-significant or negative results, meaning there is often an over-representation of positive results in use according to the Cochrane-Collaboration (2013).

Furthermore when statistical synthesis (meta-analysis) is undertaken it is prudent to request the raw data from the studies (Greenhalgh, 1997). Unfortunately in this systematic review most studies included were not recent (ranging from 1979-2007) and in most cases contact details were thus out of date, making it difficult to contact the authors. Several attempts to correspond resulted in the email being bounced back because of an invalid email address or no response was received. The 'linkedin' database and other search engines were also used to gain up to date information, but either this was not available or again no response was received all of which were frustrating.

As previously discussed, BSI has many pseudonyms which add a potential bias as articles may have been missed because of an obscure title or keyword. However in order to minimise this bias every effort was made to read through the references of the searched papers.

The Literature Selection Criteria

The next part of the process was to provide criteria to judge the searched literature objectively, thus limiting personal bias (Greenhalgh, 1997). Each study was evaluated in terms of its: relevance to the study (Biggam, 2011), methodological quality, precision and external validity (Greenhalgh, 1997). Any results that did not match or help answer the primary question were excluded immediately, no matter how interesting or well conducted the research. In this thesis endnote was used to search and store all the results from

Medline and PubMed and categories were created for the exclusion criteria. This meant the rationale for exclusion could be logged to remind the author why it was excluded and is evidence to counteract any suggestion that bias may have occurred during this selection process (Biggam, 2011).

The next criteria examined the methodology - did the studies clearly present the methods used to collect and analyse the data? It should be possible to reproduce the study adequately from the detail in the methodology. If this is not so, it was excluded. Additionally the hierarchy of the evidence (Table 3) used was considered (Evans, 2003). Evans (2003) explained that studies from the 'poor' section are the most likely to contain bias or error and Biggam (2011) concurred, recommending that studies in the 'poor' section of the hierarchy be excluded, such as case studies due to the small sample size (Biggam, 2011). Whilst the studies in the 'fair' category such as uncontrolled studies can be used, they should be interpreted with caution as they may also contain fluctuating degrees of error, therefore should not be used as a base for clinical practice but can offer ideas that may warrant further investigation according to Evans (2003).

In the case of this type of systematic review the preferred choice of study is observation studies with large cohorts and case studies were excluded due to their small sample sizes.

Pooled Studies

After all of the studies have been through the exclusion criteria a key number of high quality studies should remain. These then need to be pooled together to form a final outcome or answer to the research question called synthesising or 'evidence-synthesis' (Biggam, 2011). However pooling all of the results together can be difficult, particularly when the studies have been conducted using different methods: for example randomized controlled trials provide quantitative data whilst focus groups may give qualitative results and Biggam (2011) recommends avoiding collaborating data from both as it can make it difficult to pool the different types of data together.

The next step was therefore to decide what type of data was being collected as this decision affected how the data is collated. In this thesis quantitative data was collated, i.e. the number of asymptomatic BSIs and this could either have been collated by a meta-analysis or a narrative summary. Meta-analysis are used in homogenous samples where the methodology, sample etc., are all the same and narrative summaries are usually conducted if the sample is non-homogeneous (Figure 33) (Biggam, 2011).

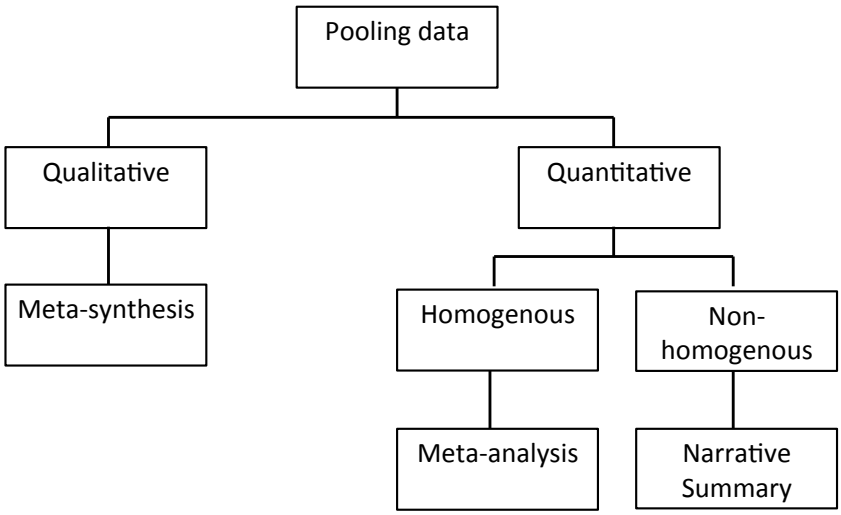


Figure 33: A flow diagram illustrating the process of pooling the data: synthesizing the evidence (Biggam, 2011, p. 109).

In this study the data is quantitative and statistical techniques were performed to analyse these data. Moreover a narrative summary was also included, where relevant, critically discussing the strengths and weaknesses of the evidence.

In Context

Finally the synthesized results were interpreted to answer the thesis questions: what are the "overall prevalence of asymptomatic BSI in the lower limb" and "prevalence of lower limb asymptomatic BSI in athletes and military personnel", then the limitations and any further uses.

Rationale

A systematic review has the advantage of being an efficient technique and is usually quicker and cheaper than starting a new study (Mulrow, 1994) and this was a significant

influence on the author's decision to choose the systematic review method to answer the thesis question.

Furthermore lessons can be learnt from experts who have previously studied in the chosen field. In this way errors and pitfalls are highlighted (Mulrow, 1994), helping to shape and refine future studies in this area. The transparent and explicit methods used reduce bias in the selection criteria, allowing more reliable and accurate conclusions to be drawn. By performing a systematic review all available literature on one topic can be compared and findings generalised. This is particularly useful when a new field or topic is being studied as in this case, where the researcher knew very little about this area. Once this information had been gained suitable search terms were then developed.

In quantitative systematic reviews meta-analyses can be used to find any over arching results with some precision (Mulrow, 1994). Systematic reviews lend themselves to the assimilation of a large amount of data to researchers, healthcare professionals and policy makers, reducing the delay between new findings and the implementation of more effective diagnostic and therapeutic strategies (Cochrane-Collaboration, 2013; Greenhalgh, 1997).

Pooling evidence together increases the overall sample size and thus the power of the study, as well as improving the precision when calculating the risk or effect size which is particularly pertinent in this study (Mulrow, 1994). The reporting rate of asymptomatic BSI appears to be relatively low compared to symptomatic BSI, which provides relatively little power, thus making it difficult to examine any trends or come to any strong conclusions. However collating the studies together increases both the sample size and the power of these smaller asymptomatic findings. This provides a more accurate picture of the prevalence of asymptomatic BSI for a future study to see and examine whether there is any clinical relevance of asymptomatic BSI. In addition, as new studies are completed they can be added, supplying new results to a constantly evolving piece of research, in a similar manner to the Cochrane reviews, continually building the power and relevance of any conclusions.

Furthermore a systematic review enables the authors to significantly develop their expertise in the area and it provides them with a vast knowledge base including: well

published authors and journals in the area, the problems that are encountered and the various research designs that are used (Lang, 2004). All these are of a huge benefit to someone starting out in a new field.

Despite the benefit of valuable time being saved as ethical approval or participant consent is not required, time is lost through the arduous, time consuming process of performing the search and data collection process (Mulrow, 1994). Additionally, the process can be prone to publication bias (Cochrane-Collaboration, 2013). It is a significant advantage to the reviewer to have good access to a wide range of literature and supportive academic libraries. This was highlighted in this study, as many of the search results were papers that were over twenty years old and whilst online databases are improving a large number of the papers still had to be requested in their original form.

In this study a number of search results were published in foreign languages but due to financial constraints only English language papers were included, potentially adding to publication bias and restricting the knowledge pool and any conclusions. Lastly whilst a systematic review is at the top of Evan's hierarchy of evidence and is very worthwhile, it is not clinical research and therefore the researcher does not have any contact with patients nor do they collect their own data and learn about the many problems that clinical research entails. However some may view this as an advantage as applying for ethical approval, funding or informed consent can be a long and tedious process (Lang, 2004).

Identification of Studies

Medline is a biomedical searchable index, which can be accessed through three interfaces: PubMed, Ovid Medline, and EBSCO Medline. Whilst all three search interfaces have access to the same studies, due to the differences in the search features it can result in slightly different results being yielded, whilst using the same terms. In this study, published articles were identified through PubMed and EBSCO Medline, both of which are supported by endnote, which was used to store the searches and the data.

The final choice of search terms were:

- Bone stress injur*
- Bone stress reaction*

- Stress fractur*
- Fatigue fractur*
- Magnetic Resonance Imag*
- MRI
- Scintigraphy

The terms were truncated to reduce exclusion, for example stress fracture(s)(ing)(ed).

The initial search terms relating to 'military', and 'athlete' were not included to widen the search to find as many reports on asymptomatic BSI as possible.

Papers published from inception until December 2012 were searched.

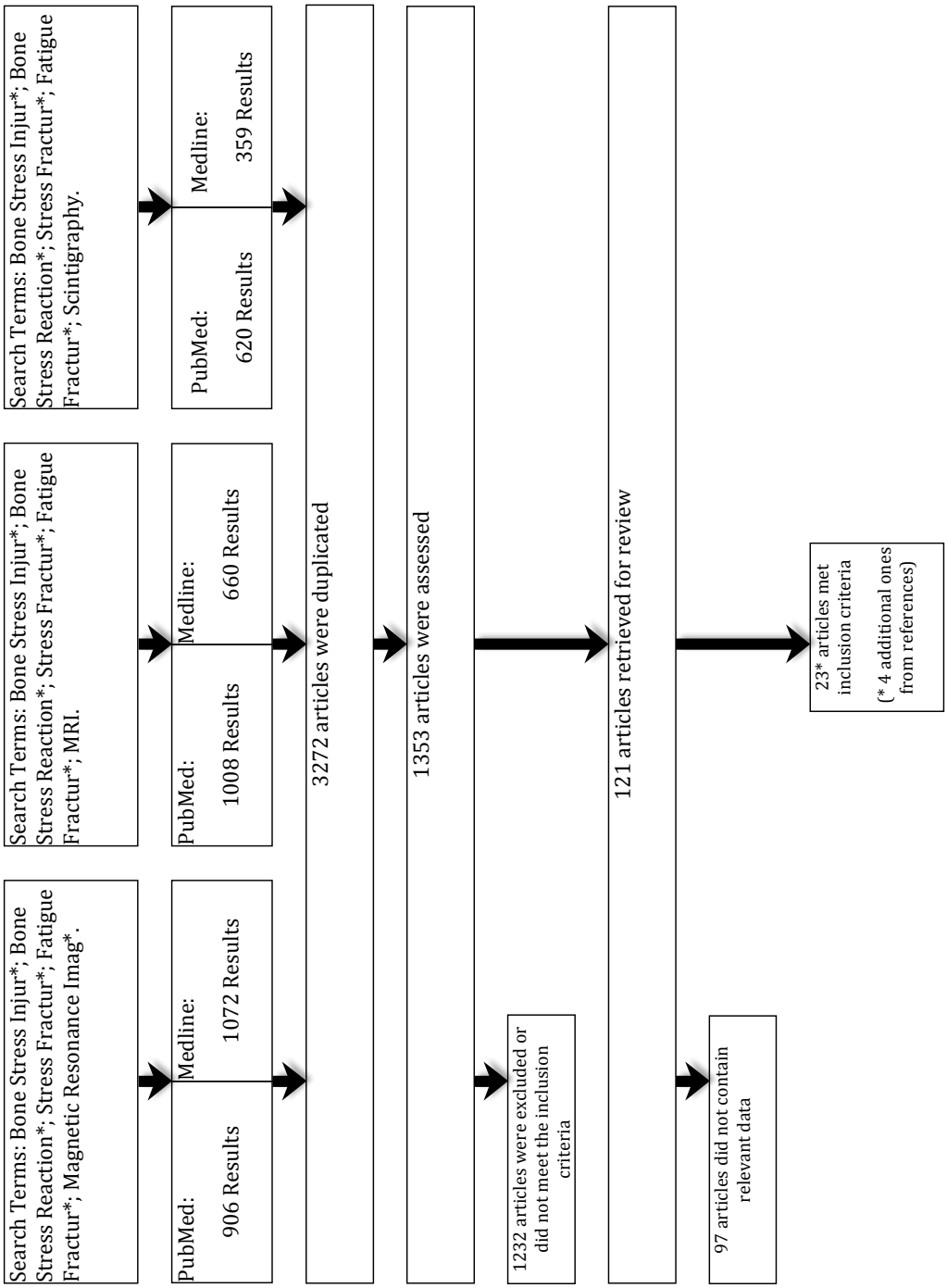


Figure 34: A flow chart outlining the process of the literature search using Medline and PubMed databases.

The search produced 4625 studies. Of these, 3272 were duplicated among the databases and subsequently removed.

Two reviewers (myself and my supervisor GW) reviewed all the papers and they extracted and confirmed the data. Any differences were discussed until a position was reached. Figure 34 lays out the search process.

Study Criteria

The resultant 1232 studies were screened using the following process:

Exclusions Criteria

A list of exclusion criteria were set out (Table 4) and the papers were assessed against these and automatically removed if they answered positively to any of them. In most cases the abstracts gave adequate information on whether they met any of the exclusion critera, but if this could not be ascertained the full article was reviewed before making a decision. This removed any irrelevant studies in order to obtain as homogenous sample group as possible.

Exclusion Criteria	**Rationale**
Insufficiency fractures	These papers were excluded as insufficiency fractures occur when pre-weakened bone (from old age, drugs or other medical conditions) fail under normal or physiological stress, whereas BSI occurs when a repeated amount of normal and or excessive stress is applied to normal bone (Kiuru et al., 2003) and was the focus of this study.
Subjects less than 18 years of age at point of selection.	These papers were also excluded because of the immature skeletal system. Histological results indicate that the immature adolescent skeleton has a number of differences when compared to the mature adult. For example internal remodelling occurs in the femur in maturing human bones, from circumferential lamellar bone to adult osteonal bone. It has been demonstrated that the greater the percentage of osteonal bone, the less likely BSIs are to occur during repetitive stress. Furthermore the transition time when osteons increase in number and activity means more bone resorption is occurring resulting in higher incidence of BSI (Evans & Riolo, 1970). In adolescents the macroscopic anatomy is different as the physis is not fused resulting in a weak point in their immature skeleton (Van der Wall et al., 2010). Also the appearance of BSIs can be different on radiographs. Devas (1963) commented that a child's callus may extend up and down the shaft of a long

	bone and may be situated entirely under the periosteum, raising it but remaining intact. They also explain that the periosteal stripping may elicit pain but there is no relationship between the amount of callus and severity of pain, which is a further variable when compared to a mature skeleton. Furthermore it has been demonstrated that the epiphyseal plate on an immature (adolescent) skeleton can present as a hotspot (increased intensity) on bone scintigraphy, which could be confused as a BSI. Therefore due to the delicate nature of this study - examining asymptomatic BSI, it seemed appropriate to exclude all under 18 participants in order to eliminate this bias (Geslien et al., 1976).
Subjects knowingly pregnant at point of selection.	Pregnant participants have been excluded as pregnancy is a contraindication for radiographs, bone scintigraphy and CT, and only used in risk verses benefit cases in MRI which would make imaging potential BSI difficult and restrict follow up. Furthermore pregnancy has been known to affect BMD and whilst this has been linked insufficiency fractures rather than a true BSI from repetitive stress it still may bias the results. (Aynaci, Kerimoglu, Ozturk, & Saracoglu, 2008; Schmid, Pfirrmann, Hess, & Schlumpf, 1999).
Subjects with other pathological disease	Arthritis and osteoporosis for example may affected bone health, increasing the risk of insufficiency fractures (Lingg, Soltesz, Kessler, & Dreher, 1997) and furthermore many drugs are known to affect bone physiology (Kwek, Goh, Koh, Png, & Howe, 2008).
Small sample size, case studies, descriptive studies and expert opinion.	Studies and case studies with a sample size less than 7 were eliminated in the main data capture because of their low statistical value, however they were included in the discussion if they offered a unique insight into BSI.
Examination of BSI other than lower limb	Studies were also disregarded if the article looked at the upper limb, spine or pelvis in isolation as this review is examining the lower limbs: femur to toes.
Ambiguously connected terminology: Shin splint, MTSS, traction periostitis	These injuries are a different entity to BSI but have been loosely associated with BSI (Bradshaw et al., 2006; Brukner, 2000; Zwas et al., 1987). In this study it is important that only BSIs are included and other injuries do not confuse the picture.
Animal models	Animal studies were excluded because of the differences in their bone geometry (Markey, 1987; Pearce, Richards, Milz, Schneider, & Pearce, 2007)
Non-English language papers.	Only English language articles were included due the cost implications to the author, which inhibited official translation of foreign language papers. Although there has been a proliferation of translation services such as Google Translate™, making it increasingly available/easy to translate foreign language papers, it was decided not to use them because of the potential inaccuracies in medical terminology and possible subtleties, which may be missed in translation. Therefore the approach was taken not to use these translation sites and thus to

	maintain the quality of the study potentially at the expense of its breadth.
Qualitative studies	Qualitative research that did not provide primary research data were excluded to preserve the quality and accuracy of the data and reduce any bias, which review articles may place on their report (Aveyard, 2007).
Subjects solely self reporting BSI	Several studies utilised self-reporting in the form of questionnaires to examine participants' BSI rates. These were excluded, as they were unable to provide any irrefutable evidence e.g. medical imaging of any BSI. Furthermore asymptomatic BSI would never be reported if researchers were to rely solely on self-reporting.

Table 4: Exclusion criteria

Final Selection

Following the initial filtering process 121 articles remained and were retrieved for detailed review. Each of these papers were either primarily examining asymptomatic BSI or were more focused on symptomatic BSIs but happened to note and comment on asymptomatic BSIs that occurred.

Inclusion Criteria

Studies were only included if they were asymptomatic studies that included one of the following criteria:

1. RCT or
2. observational studies or
3. uncontrolled trails or
4. before and after studies or
5. non-randomized controlled trials
6. case studies with more than 7 participants

During the course of this review 97 BSI studies had to be excluded due to little or no data pertaining to asymptomatic BSI. These exclusions fell into two categories: firstly genuinely no asymptomatic BSI were found and secondly that asymptomatic BSIs did occur but inadequate data was available for analysis.

The majority of studies reported asymptomatic data as an afterthought or by product of an examination of symptomatic participants. In some studies the authors often mentioned asymptomatic sites in the discussion but did not provide the data in the results section to support this. Thus it appears that there are significantly more reports of asymptomatic BSIs than studies that provided data for. This is especially true of the many papers published prior to the 1990s, where reporting tended to be brief affair for example Dowey and Moore (1984) compared to current standards today, where a more detailed account is required to pass peer review.

After this closer evaluation a total of 23 studies were used for analysis and a further 4 were discovered within the references of other papers. The studies were categorised by their subject population and there were 16 military, 8 athlete and 3 civilian studies (Table 5). The civilian studies were part of the overall prevalence rate and BSI distribution but were excluded for the detailed comparison of the athlete and military BSI rates and were not subsequently compared with these specific populations for two reasons: firstly, there is little evidence of BSI being important or prevalent in the general population and secondly only three studies used civilians making any direct comparison using only this population very weak statistically. No direct comparisons were made between athlete and military populations for the distribution of BSI.

Author & Year	Participant Type	Sample Size	Imaging methods	Search or Reference
Bergman et al. (2004)	Endurance Athlete	21	MRI	Search
Butler, Brown, and McConnell (1982)	Track & Field Athletes	7	Bone scintigraphy & X-ray	Search
Giladi et al. (1985)	Military	86	Bone scintigraphy & X-ray	Search
Gofrit and Livneh (1994)	Military	1118	Bone scintigraphy	Search
Groshar et al. (1985)	Military	64	Bone scintigraphy	Search
Hadid et al. (2008)	Military	201	Bone scintigraphy & MRI	Search
Harolds (1981)	Military	No data	Bone scintigraphy & X-ray	Search
Hod et al. (2006)	Military	146	Bone scintigraphy & X-ray	Search
Kiuru et al. (2003)	Military	340	MRI & X-ray	Search
Kiuru et al. (2005)	Military	21	MRI	
Lohman et al. (2001)	Marathon Runners	38	MRI	Reference
Major and Helms (2002)	Basketball Players	17	MRI	Reference
Major (2006)	Basketball Players	26	MRI	Search
Matheson et al. (1987a)	Athlete	320	Bone scintigraphy & X-ray	Search
Meurman and Elfving (1980a)	Military	42	Bone scintigraphy & X-ray	Search
Milgrom et al. (1985a)	Military	295	Bone scintigraphy & X-ray	Reference
Niva, Kiuru, Haataja, and Pihlajamaki (2005)	Military	170	MRI	Search
Niva, Mattila, Kiuru, and Pihlajamaki (2009)	Military	28	MRI	Search
Nielsen et al. (1991)	Military	22	Bone scintigraphy & X-ray	Search

Roub et al. (1979)	Athlete	48	Bone scintigraphy & X-ray	Search
Schweitzer and White (1996)	Civilians	15	MRI	Search
Shin et al. (1996)	Military	19	Bone scintigraphy, MRI & X-ray	Search
Sopov, Liberson, and Groshar (2000)	Military	100	Bone scintigraphy & X-ray	Search
Tappeniers et al. (2003)	Civilians	10	MRI	Reference
Yildirim, Gursoy, Varoglu, Oztasyonar, and Cogalgil (2004)	Athlete	42	Bone scintigraphy	Search
Zubler et al. (2007)	Civilians	78	MRI	Search
Zwas et al. (1987)	Military	310 sample	Bone scintigraphy	Search

Table 5: Final research papers selected

27 were selected for final systematic review: 23 were found during the systematic search and 4 additional papers were found in the reference section of other reports.

Data Extraction

Once the 27 studies were selected, the data was extracted from them and then compiled into a spreadsheet. A full table of the data extracted can be viewed in Appendix Two. Table 6 lists the data that collected from the 27 papers and the rationale for each. Please note that none of the papers presented all of required data and therefore there were incomplete sections within the spreadsheet. To make it even more challenging to extract the data, some studies simply expressed the case and or participant rates as percentages; either as the total percentage of BSI or the number of BSIs per 100 participants. In some cases it was clear which method was used, but in others it was not.

More of the studies used the incidence rates of BSI but reported the data in a variety of different ways. Some studies presented their data as participant rates, where the total number of participants with BSI are divided by the total number of participants (Brukner et al., 1999). This is particularly problematic in this review as many studies presented multiple BSI sites within the populations. Alternatively a number of studies calculated the case rate, where the total number of BSIs were reported during the study, making the

extraction and separation of symptomatic and asymptomatic data difficult. In a number of studies it was not possible to determine the numbers of participants with asymptomatic verses symptomatic BSI and in these cases were not included.

Year	This was collected to look for any possible trends appearing over time.
Age	This was collected to ensure all samples were in the selected age and examine any correlation between age and (asymptomatic?) BSI prevalence.
Country	This was collected to examine any differences between countries, for example the contrasting incidence rates of American and Israeli military recruits BSIs.
Imaging modality	This was collected to examine which modality, if any, had a higher specificity and or sensitivity to asymptomatic BSI.
Sample size (number of subjects)	This was collected to enable prevalence rate to be calculated.
Control group	In several studies that used control groups, asymptomatic BSIs were present in these groups.
Sex	This was collected to look for any correlation between sex and BSI.
Physical performance domain	One of the main aims in this thesis is to determine if there is a difference in prevalence of asymptomatic BSI between military and athletic samples.
Location of BSI	This was collected to establish the distribution rates of symptomatic and asymptomatic BSI.
Total asymptomatic and symptomatic BSI	Both the number of asymptomatic and symptomatic BSIs were recorded to examine the prevalence rates. These will be counted per bone and also as a total number.
Grading system	This was originally collected in order to utilise the grades of BSI. Unfortunately so few of the results used a classification system that it was not used in analysis.
Study type	This was collected to demonstrate what type of study was conducted and to establish its quality.
Prevalence rate, BSI per 100 people.	This was calculated by extracting the number of subjects in each study and the number of BSI reported and was not calculated using a prevalence rate from the individual studies.

Table 6: Data extraction table.

Data Analysis

A mixed model analysis (SAS Institute Inc, v9.2 Cary NC) was used to estimate confidence intervals (CIs) and P values and included a random effect (the paper identifier) and a repeated term (for studies 18, 21, 24), so the CI was not inappropriately reduced by counting the same participants more than once. Study 11 and 20 were comprised of two treatment arms of different people and were therefore counted as different studies, hence the total number of studies exceeded the 27 from which the analysis was taken. The analysis was also weighted for sample size. The rates were calculated using www.openepi.com. The length for follow up was not consistent for all studies, but was treated as such to simplify the calculations, however it must be noted that this could result in a bias.

Results

Initial literature searches identified 1353 papers for evaluation. Of these, 1232 have been excluded on the basis of meeting one or more of the exclusion criteria. Of the remaining 121 articles have been selected for review, a further 97 failed meet the inclusion criteria; or did not report any asymptomatic BSI; or presented a data set that was ambiguous and these studies were thus excluded from the data capture and analysis.

At the conclusion of this process 23 studies met the predefined inclusion criteria and an additional four papers where found from examining the reference lists, resulting in a total of 27 papers being selected for data capture and analysis. The studies were categorised according to their subject population:

- 16 military studies
- 8 athlete studies
- 3 civilian studies

The raw data can be found in Appendix Two, where each study is listed by different experimental cohorts. These different cohorts were treated separately during the analysis and hence the number of actual studies does not necessarily equate to the number of cohorts or groups included, e.g. eight athlete studies may present with more than eight groups.

Prevalence Rates

Overall

The total data set utilising all 27 selected studies resulted in an overall prevalence rate of asymptomatic BSI of 27/100 people (SD=4.56) (see Table 7). The overall prevalence rate of symptomatic BSI was 34/100 (SD=4.81). There was no significant difference between symptomatic and asymptomatic BSI rates per 100 people (p=0.51).

Within specific populations

The data from the athlete studies presented a different picture. The rate of asymptomatic BSI in athletes was 75/100 people (SD=2.78). Whereas the symptomatic rate in this population was only 10/100 people (SD=2.61). The difference between the rate of asymptomatic BSI and symptomatic BSI within the athlete population was highly

significant (p=0.001) (Table 7). The results of this analysis suggest that athletes have a much higher rate of asymptomatic than symptomatic BSI.

The analysis of the military studies provided a stark contrast to the athlete population. The military rate of asymptomatic BSI was only 28/100 people (SD=4.6) but the symptomatic rate was much higher at 77/100 people (SD=3.99). The different rates of BSI within the military population were again significant, although not to the same high level as the athlete results (p=0.048) (Table 7). These data suggest that the military population have a much lower rate of asymptomatic than symptomatic BSI.

The civilian studies were deemed insufficient in number to complete an analysis of the differences between asymptomatic and symptomatic rates of BSI on their own and thus there are inadequate data to examine whether the asymptomatic rate in the civilian population is different to the symptomatic rate.

BSI per 100 people	Number of cohorts/groups		Mean (SD)		95% CI		Asymptomatic versus Symptomatic p- value
	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic	
Total	31	28	27 (4.56)	34 (4.81)	11, 43	17, 52	0.51
Athletes	10	9	75 (2.78)	10 (2.61)	47, 100	0, 36	0.00112
Military	16	15	28 (4.6)	77 (3.99)	3.7, 52	52, 100	0.048

Table 7: Prevalence rates of BSI in military, athlete and all studies and the comparison between the rates of symptomatic and asymptomatic BSI in these studies.

Between populations

The total rate of BSI in the military and athlete populations was then calculated. These data included both asymptomatic and symptomatic BSI and assessed the differences between these populations rather than the above data (Table 7) that looked within those populations.

The total rate of BSI in the military studies was 70/100 people (SD=9.1). The total rate of BSI in the athlete studies was slightly higher at 76/100 people (SD=2.54) (Table 8). The analysis found no significant difference between these two populations' total BSI rates (p=0.48).

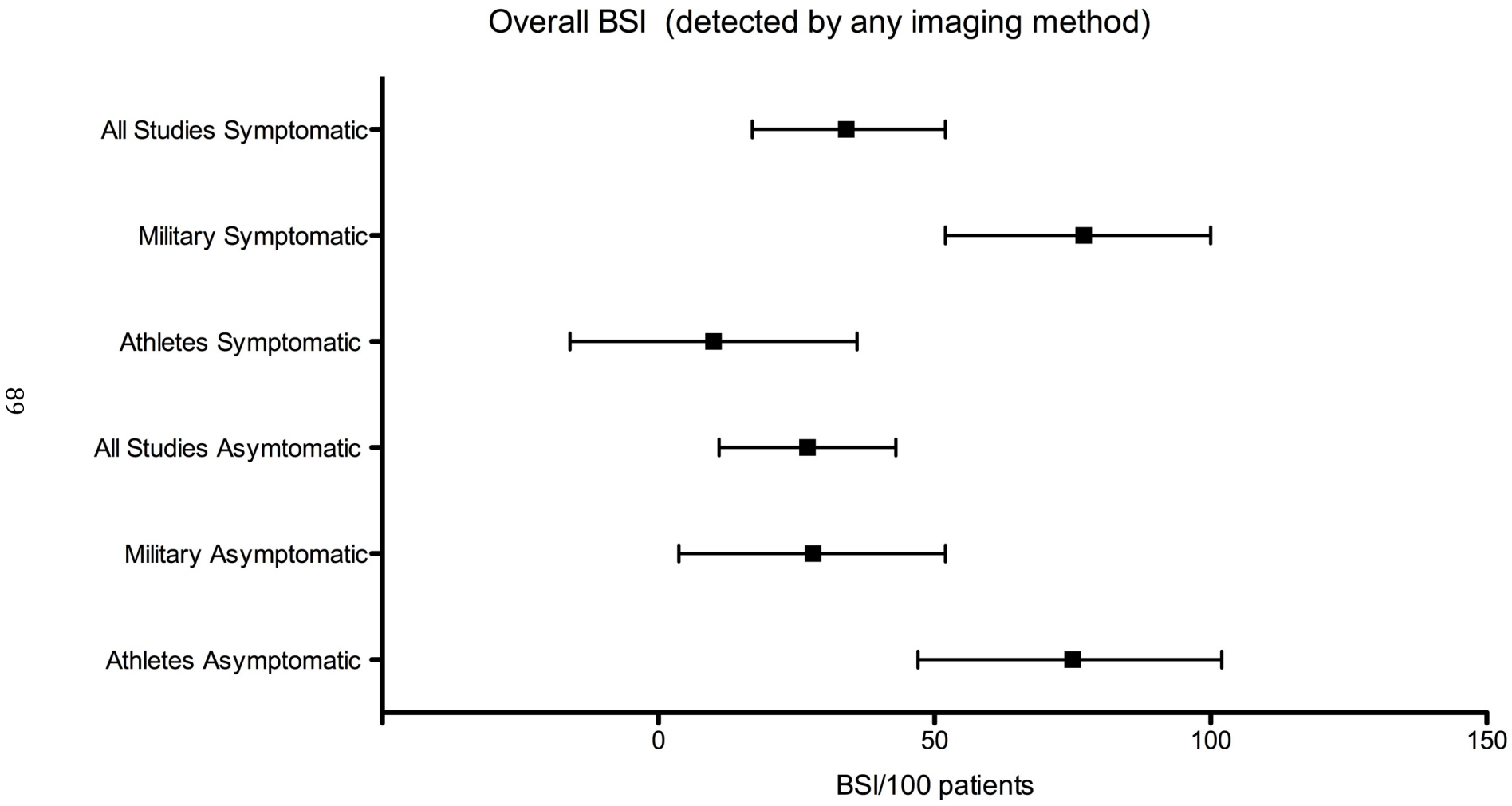
The total rate of BSI was not calculated for the civilian studies due to the lack of data and therefore they were not compared against either the military or the athlete studies.

The similar rates of total BSI in the athlete and military populations is made up of very different rates of symptomatic and asymptomatic BSI. The 75/100 rate (SD=2.78) of asymptomatic BSI in the athletes was much greater than the 28/100 rate (SD=4.6) found in the military studies. This difference is highly significant (p=0.0065). In contrast the 77/100 rate (SD=3.99) of symptomatic BSI in the military studies is considerably greater than the lowly 10/100 rate (SD=2.61) found in the athlete studies. This difference was again highly significant (p=0.0036).

Thus whilst the overall rates between these populations are comparable, the differences in the composition of the BSI rates within them are important and of great interest. Figure 35 clearly shows the stark contrast that these data report, clearly demonstrating the differences between and within the populations for symptomatic and asymptomatic BSI rates detected using any imaging modality.

BSI/per 100 people	Number studies		Mean (SD)		95% CI		Athletes versus military p-value
	Military	Athletes	Military	Athletes	Military	Athletes	
Total	16	9	70 (9.1)	76 (2.54)	34, 100	35, 100	0.48
Symptomatic	13	10	77 (3.99)	10 (2.61)	52, 100	0, 36	0.0036
Asymptomatic	15	10	28 (4.6)	75 (2.78)	3.7, 52	47, 100	0.0065

Table 8: General prevalence of asymptomatic BSI.


Overall BSI (detected by any imaging method)
All Studies Symptomatic
Military Symptomatic
Athletes Symptomatic
All Studies Asymtomatic
Military Asymptomatic
Athletes Asymptomatic
0
50
100
150
BSI/100 patients

Distribution of BSI

Asymptomatic

The highest rate of asymptomatic BSI across all studies that reported distribution was 30/100 people (SD=2.88) in the tibia; this was closely followed by the tarsal bones at 28/100 people (SD=1.72). The lowest rate of asymptomatic BSI reported was the fibula at 6.8/100 people (SD=0.068). There were no recorded asymptomatic BSI in the patella and sesamoid bones, although it is possible that they were simply not recorded specifically. For example within the study data collected 26/100 asymptomatic BSI were 'not stated' and 8.2/100 were labelled 'other' (Table 9).

There were no significant differences between the distribution of asymptomatic BSI in these studies. See Table 12.

Symptomatic

The highest rate of symptomatic BSI across all studies that reported the distribution was again found in the tibia at 58.8/100 people (SD=2.85). The next highest was the femur with 37/100 people (SD=3.55). Interestingly the lowest rate of symptomatic BSI was reported in the tarsal bones with 0.30/100 people (SD=0.21). Again there was a large rate of 51/100 people with unstated symptomatic BSI and 47/100 people with other symptomatic BSI (Table 9).

There were significant differences in the distribution of symptomatic BSI across the lower limb. The tibia (58.8/100 people) had significantly higher rates of symptomatic BSI than either the fibula (2.4/100 people, p=0.026) or the metatarsal (7.8/100 people, p=0.039). The tibia was also trending towards a higher rate of symptomatic BSI than the tarsal (0.30/100 people, p=0.061), although not significantly (Table 11).

Total

Unsurprisingly the total rate of BSI was highest in the tibia, 41/100 people (SD=3), followed by both the femur (SD=3.13) and the tarsal (SD=1.49) both with 21/100 people. The lowest total rate was recorded in the fibula (5.1/100 people, SD=0.25). The rates for the not stated and other lower limb total BSI were 35/100 (SD=4.62) and 8.2 (SD=0.83) respectively (Table 9).

Interestingly the distribution of all the BSI was slightly different to the symptomatic rates, with a significantly higher rate of BSI in the tibia (41/100 people) than in the femur (21/100 people, p=0.034) as well as the fibula (5.1/100 people, p=0.011) and the metatarsal (9.4/100 people, p=0.015). The other slight difference was the lack of a trend of higher BSI in the tibia than in the tarsal (p=0.17) (Table 10).

Figure 37 illustrates the different rates for asymptomatic, symptomatic and total BSI across all the studies that reported the distribution of BSI in the bones of the lower limb. The patterns of distribution of the different types of BSI are distinct, as is the fact that the highest rates for all three (asymptomatic, symptomatic and total) BSI categories are found in the tibia. The comparable rate, with the tibia, for asymptomatic BSI in the tarsal are also clear as is the fact that the greatest rates of BSI appear to be symptomatic (58.8/100) in the tibia and (37/100) in the femur.

Symptomatic versus Asymptomatic

Figure 36 shows the different distributions of the symptomatic and asymptomatic BSI. The overlap of the confidence intervals for the means BSI rates is apparent, although the analysis does highlight some significant distributions of symptomatic and asymptomatic BSI. The fibula has significantly higher rates of asymptomatic BSI (6.8/100 people) than the symptomatic (2.4/100 people, p=0.024). The tarsal bones also have a significantly higher rate of asymptomatic BSI (28/100 people) than symptomatic BSI (0.30/100 people, p=0.049).

There were no bones with significantly higher rates of symptomatic than asymptomatic BSI, although the tibia rates of 58.8/100 people with symptomatic BSI was suggestive of a higher trend than the asymptomatic rate of 30/100 people (p=0.081) (Table 9). The femur also recorded higher rates of symptomatic (37/100) than asymptomatic (13/100) although not significantly so (p=0.12).

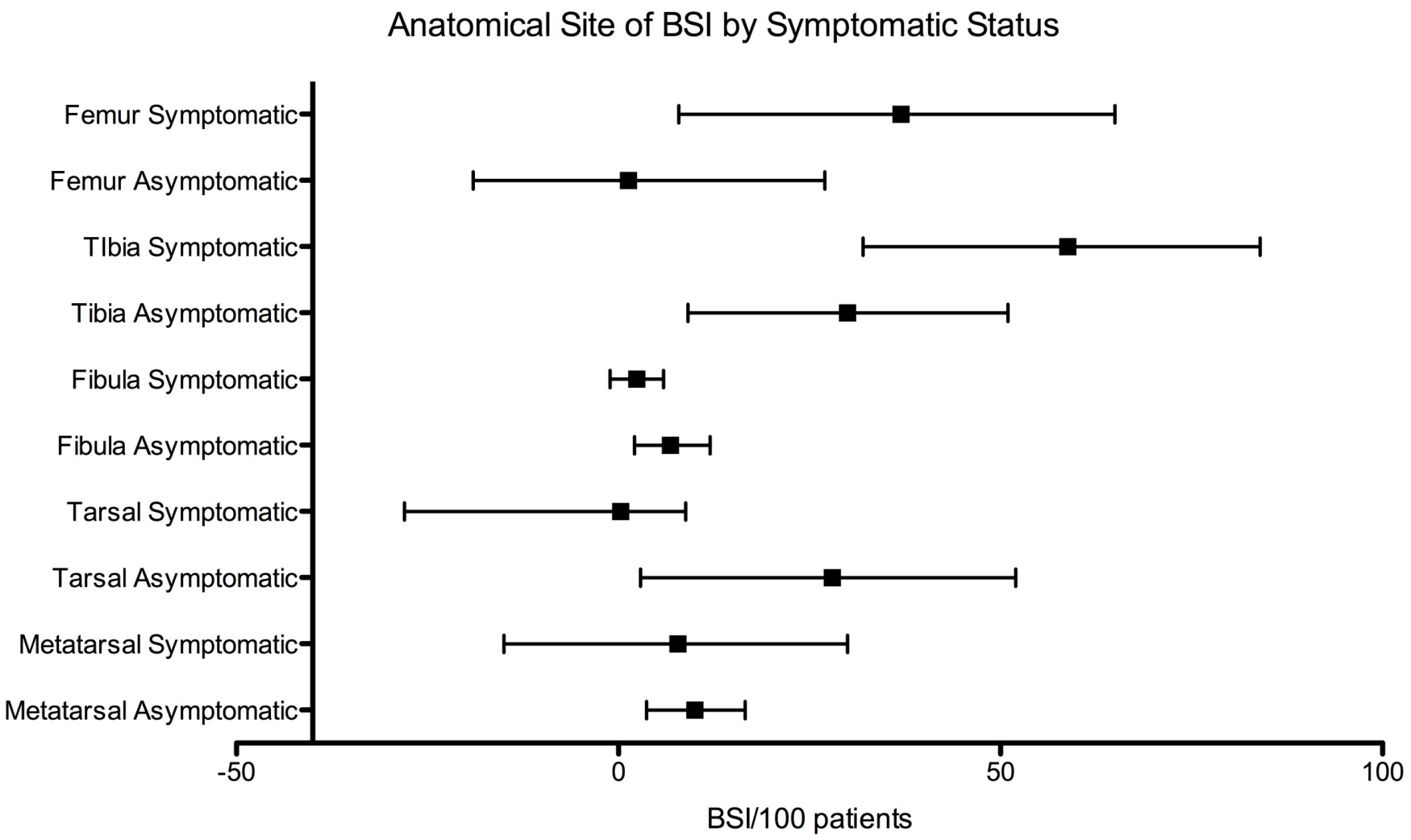


Figure 36: A forest chart presenting the anatomical site of BSI by symptomatic status.

BSI/100 people	Number studies			Mean (SD)			95% CI			Difference Asymptomatic versus Symptomatic p Value
	Asymptomatic	Symptomatic	Total	Asymptomatic	Symptomatic	Total	Asymptomatic	Symptomatic	Total	
Femur	13	12	25	13 (2.42)	37 (3.55)	21 (3.13)	0, 27	7.9, 65	6.8, 35	0.12
Patella	-	-	2	-	-		-	-		-
Tibia	13	12	25	30 (2.88)	58.8 (2.85)	41 (3.0)	9.1, 51	32, 84	24, 57	0.081
Fibula	2	5	7	6.8 (0.068)	2.4 (0.18)	5.1 (0.25)	2.1, 12	0, 5.9	2.5, 7.8	0.024
Sesamoid	-	-	2	-	-		-	-		-
Tarsal	5	4	9	28 (1.72)	0.30 (0.21)	21 (1.49)	2.9, 52	0, 9	5.8, 36	0.049
Metatarsal	9	5	14	10 (0.61)	7.8 (1.20)	9.4 0.82)	3.7, 17	0, 30	2.6, 16	0.74
Not Stated	7	5	12	26 (3.29)	51 (0.76)	35 (4.62)	0, 53	0, 100	9.3, 60	0.45
Other	4	6	10	8.2 (1.37)	47 (6.18)	8.2 (0.83)	0, 28	0, 100	0, 15	0.97

Table 9: Distribution of BSI by anatomical site.

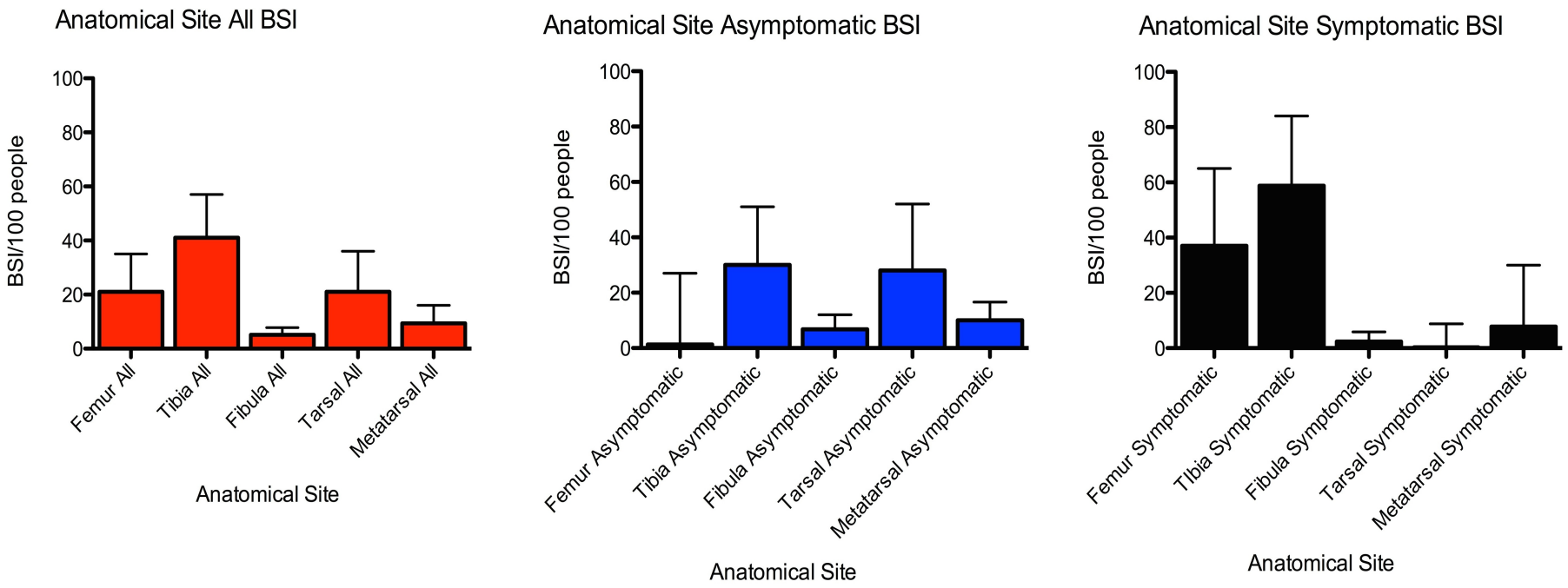


Figure37: Three graphs demonstrating the anatomic sites of all BSI (red), asymptomatic BSI (blue) and symptomatic BSI (black).

	Femur	Patella	Tibia	Fibula	Sesamoid	Tarsal	Metatarsal	Not Stated	Other
Femur	-								
Patella	0.6	-							
Tibia	0.034	0.32	-						
Fibula	0.23	0.9	0.011	-					
Sesamoid	0.6	0.99	0.31	0.9	-				
Tarsal	0.98	0.61	0.17	0.34	0.61	-			
Metatarsal	0.34	0.82	0.015	0.78	0.82	0.46	-		
Not Stated	0.13	0.39	0.56	0.031	0.39	0.33	0.044	-	
Other	0.3	0.84	0.013	0.85	0.84	0.42	0.93	0.038	-

Table 10: Total BSI distribution- p values.

	Femur	Patella	Tibia	Fibula	Sesamoid	Tarsal	Metatarsal	Not Stated	Other
Femur	-								
Patella	0.41	-							
Tibia	0.21	0.2	-						
Fibula	0.15	0.96	0.026	-					
Sesamoid	0.41	0.99	0.2	0.96	-				
Tarsal	0.24	0.95	0.061	0.99	0.95	-			
Metatarsal	0.21	0.87	0.039	0.85	0.87	0.88	-		
Not Stated	0.53	0.3	0.51	0.066	0.3	0.13	0.098	-	
Other	0.24	0.87	0.052	0.85	0.87	0.88	0.99	0.12	-

Table 11: Symptomatic BSI distribution- p values.

	Femur	Patella	Tibia	Fibula	Sesamoid	Tarsal	Metatarsal	Not Stated	Other
Femur	-								
Patella	ND	-							
Tibia	0.0901	ND	-						
Fibula	0.6901	ND	0.1307	-					
Sesamoid	ND	ND	ND	ND	-				
Tarsal	0.2774	ND	0.8795	0.245	ND	-			
Metatarsal	0.8514	ND	0.1468	0.842	ND	0.2902	-		
Not Stated	0.1969	ND	0.7101	0.2143	ND	0.8952	0.2513	-	
Other	0.7356	ND	0.1124	0.931	ND	0.2415	0.9018	0.1987	-

Table 12: Asymptomatic BSI distribution- p values.

Imaging modalities

Scintigraphy

The highest prevalence rate of asymptomatic BSI was identified in the athlete population that were imaged using scintigraphy, 70/100 (SD=3.43). By contrast, the lowest prevalence rate using scintigraphy was also in the athlete population but this time imaging symptomatic people, BSI 11/100 (SD=2.77).

Scintigraphy reported a lower rate of asymptomatic BSI in military studies, only 15/100 people (SD=2.82) but a higher rate in symptomatic people than in the athlete population, BSI 31/100 (SD=5.6). The prevalence rate for asymptomatic BSI reported using scintigraphy was significantly higher for athletes (70/100) than for the military studies (15/100), (p=0.0023). This was the only significant difference between the athlete and military studies compared using the differing imaging modalities (Table 13).

MRI

The highest prevalence rate reported using MRI was from the military studies symptomatic BSI, 10/100 people (SD=4.28), in contrast there were no symptomatic BSI imaged using MRI (0/100 people) and also no significant difference between the symptomatic military and athlete BSI rates (p=0.18).

The rate for asymptomatic BSI imaged using MRI was 7.9/100 (SD=1.5) athletes and the asymptomatic military rate was a comparable 5/100 people (SD=4.26) and thus there was no significant difference between the two populations (p=0.96) (Table 13).

X-Ray

X-ray did not identify any asymptomatic athletes (0/100) and had a low prevalence rate of 1/100 (SD= 0.57) people in the military studies with no significant differences between the two groups of studies (p=0.66).

This imaging modality had a slightly higher prevalence rate when imaging symptomatic subjects, with military studies having a 3/100 people rate (SD=2.19) and the athlete studies 4/100 people (SD=1.14). Not surprising there were no significant differences between these two prevalence rates for symptomatic BSI imaged using X-ray (p=0.84). See Table 13.

Overall

Three different imaging modalities were used to image BSI, and in the main they did not detect different rates of BSI between athlete and military populations, with the exception of asymptomatic BSI imaged using bone scintigraphy. The overall trend was for higher rates of BSI, both symptomatic and asymptomatic, being reported using scintigraphy than either MRI or x-ray, although there was not statistical analysis of the differences between the modalities in the current study. See Table 13.

BSI/100 people	Number studies		Mean (SD)		95% CI		Difference athletes versus military P value
	Military	Athletes	Military	Athletes	Military	Athletes	
Bone scintigraphy total	14	8	42 (9.03)	62 (3.28)	5, 79	4, 100	0.66
Bone scintigraphy symptomatic	12	9	31 (5.62)	11 (2.77)	0, 63	0, 39	0.41
Bone scintigraphy asymptomatic	13	9	15 (2.82)	70 (3.43)	0, 30	34, 100	0.0023
MRI total	16	9	19 (7.16)	8 (1.59)	9, 48	0, 24	0.19
MRI symptomatic	15	10	10 (4.28)	0 (0)	0, 29	,	0.18
MRI asymptomatic	16	10	5 (4.26)	7.9 (1.5)	0. 22	7, 23	0.96
X-Ray total	16	10	5 (2.57)	6.7 (1.1)	0, 16	4, 18	0.76
X-Ray symptomatic	13	10	3 (2.19)	4 (1.14)	0, 13	7, 15	0.84
X-Ray asymptomatic	13	10	1 (0.57)	0 (0)	0, 3	,	0.66
BSI total	16	9	70 (9.1)	76 (2.54)	34, 100	35, 100	0.48

Table 13 : Imaging modalities and BSI rates.

Discussion

BSI, defined as a partial or complete fracture as a result of repetitive stress (Martin & McCulloch, 1987), appears to result from an unsuccessful adaptation of bone to a change in its environment, although the exact initiation process remains unclear (Bennell et al., 1996b). BSI can be divided into two distinct groups: symptomatic, characterised by their symptoms for example: exercised induced pain and swelling (Clement et al., 1993) and asymptomatic which are detected incidentally through medical imaging without clinical symptoms (Groshar et al., 1985). Due to the inconspicuous nature of asymptomatic BSI much less attention has been placed on the entity within the literature in comparison to symptomatic BSI. The literature review highlighted the existence of asymptomatic BSI but the prevalence in the lower limb was not easy to establish without the results of this systematic review.

Asymptomatic BSIs have been noted in a number of papers as incidental findings and researchers have questioned their clinical significance. However a number of other papers have interpreted these data differently suggesting that the relevance of asymptomatic BSI is unclear and that further investigations are required to present a more complete picture. The results of the analysis in this study indicate that the overall prevalence of asymptomatic BSI is 27 fractures per 100 people and the overall prevalence rate of symptomatic BSI was only slightly higher at 34 fractures per 100 people.

Contextualizing these data with published papers is difficult as there are limited numbers of articles either examining asymptomatic BSI or presenting data that can be interpreted as a prevalence of asymptomatic BSI in the general population. The papers included in this study either examined asymptomatic BSI in specific populations or reported asymptomatic BSI as part of a symptomatic study and thus there are very few studies that a general prevalence rate can be interpreted from. In one paper Ruohola et al. (2006) reported an asymptomatic prevalence of 24/85 (28%) from their military study of the lower leg, which is consistent with the results of the current study.

Several other papers reported femoral prevalence rates that were higher than the overall rate of this study, Milgrom et al. (1985a) reported 69% and Kiuru et al. (2005) reported

60%. Whilst the Kiuru et al. (2005) study was relatively small including just 21 recruits, the Milgrom et al. (1985a) study included 295 recruits, potentially a statistically more powerful study and thus a more accurate result.

One of the strongest study designs that fits to assist in determining if asymptomatic BSI are clinically relevant is by selecting a large cohort at increased risk, then screening them using an imaging modality before, during and on completion of training with appropriate follow up at specified intervals (Morrow, 2010). These data highlight patterns of BSI, both symptomatic and asymptomatic and they could be examined in further detail to present a clearer picture of the prevalence and clinical relevance of BSI in the specific population. This study design is of course protracted, expensive, potentially radiologically invasive and ethically challenging. For these reasons this type of study has not been undertaken and thus the smaller studies, whilst contributing to the research base, frequently present either too narrow a perspective or add additional uncertainties to the picture. Thus, there are few comparisons for the prevalence rate of asymptomatic BSI and hence this systematic review.

Whilst there seems to be a general consensus amongst the BSI expert community that clinical symptoms are the most important consideration and this should guide clinicians, this is where agreement ends. Some authors have presented very compelling evidence that suggests asymptomatic BSI are just an incidental finding that are clinically irrelevant requiring no monitoring or treatment (Bergman et al., 2004; Freund, Weber, Billich, & Schuetz, 2012; Kiuru et al., 2005; Matheson et al., 1987a; Nielsen et al., 1991; Niva et al., 2005; Roub et al., 1979). However there is also evidence that asymptomatic BSI should be viewed as clinically relevant (Matheson et al., 1987a) and subsequently they need managing to prevent them progressing to symptomatic BSI and in turn to complete fractures. Matheson et al. (1987a) describes previous clinical experience of asymptomatic BSI becoming symptomatic over subsequent months and increasing in severity. They suggested that asymptomatic BSI possibly have clinical and physiological relevance and this was the rationale for their retrospective review of 320 athletes.

Kiuru et al. (2005) conducted a study to determine if asymptomatic BSI can progress to 'stress fractures'. They reported a total of 75 BSI (30 symptomatic and 45 asymptomatic). Unfortunately the results were not discussed in sufficient detail, the majority of the paper

focused on 25 asymptomatic grade 1 BSI and there was no discussion of the further 20 higher-grade asymptomatic BSI. They report that 24 of the 25 grade 1 BSI either persisted at the same level or spontaneously healed with only one maintaining the grade 1 but became symptomatic. They then concluded that asymptomatic grade 1 BSI are a common occurrence during high levels of training and are a physiological response to stress rather than a pathological process and are of "no clinical significance" and do not require screening. However in their closing sentence they recommend that training can continue under clinical follow up, which appears to contradict their previous statement. If they consider asymptomatic BSI to be of no clinical significance it is unclear why they recommend clinical follow up. Furthermore, there was no discussion or write up on these lesions and whilst the tables show the prevalence in the sites, it is difficult to ascertain which if any have progressed or regressed/healed, this is particularly important with the asymptomatic grade 4 BSI in the femur as these have been reported to subsequently displace (Dugowson, Drinkwater, & Clark, 1991; Luchini et al., 1980; Provost & Morris, 1969). So whilst these authors conclude that only individuals whom present with pain should be investigated using imaging, the data they present does not adequately support this position. It appears that they are potentially ignoring the important role that motivation appears to play as elite recruits are likely to 'hide' or ignore bone scintigraphy (Elias et al., 2008). The question remains whether clinicians should be concerned with a symptomatic grade 1 BSI more than an asymptomatic grade 4 BSI? It could be argued that the grade should take priority over the symptoms, especially given that highly motivated individuals may be less inclined to report symptom and the onset of pain. Therefore it is important when trying to contextualize the 27/100 prevalence rate reported in this study to understand how many of these are likely to progress further and develop symptoms or other complications. Whilst this study was unable to examine this question, future studies should seek to and by doing so, a clearer picture of the impact of the asymptomatic BSI will emerge. Aiding understanding as to whether the focus should be on the grade of BSI or the presence of symptoms.

Whilst large studies are able to provide more statistical weight to theories they can fail to give good detail and follow up which case studies can demonstrate. Of particular interest is a case study concerning a professional football league player reported by Brahms,

Fumich, and Ippolito (1980). The player was found to have a palpable deformity in their tibia but denied symptoms of pain or trauma. A radiograph demonstrated a well-healed and stable BSI of the anterior cortex, which carries a high risk of non-union. The player continued to train and play and a year later the X-ray was repeated and the BSI had remained silent and well healed. The following year pain was present in the left ankle and the player underwent bone scintigraphy, which demonstrated increased uptake in the same right tibia, radiographs remained unchanged. A year later the football player was running during a game when they fell and suffered a comminuted fracture through the mid right tibia – where the original deformity was observed. The player denied being tackled during the game and is supported by video coverage. This case study demonstrates that pain is not always indicative of an active BSI, and secondly a BSI that may appear to be 'healed' on radiograph may not be and could in fact be at increase risk of re-fracture. This case study gives a unique insight into the evolution of BSI in a professional athlete, additional larger sample in-depth studies are required confirm this (Brahms et al., 1980). Whilst the current investigation did not include this case study as it did not meet the entry criteria (it was below the sample size threshold) it does support very strongly the need to understand the impact and prevalence of asymptomatic BSI.

Nielsen et al. (1991) suggested a possible explanation for the asymptomatic lesions (N=5 from 29 in total) noted in their study of 22 recruits, was that remodelling does not necessarily have to be painful. However their results also found that one of the grade 2 lesions demonstrated periosteal reaction on follow up X-ray and is therefore questioning whether the remodelling resulting in BSI are a normal physiological response or possibly evidence of a pathophysiological process. Thus it could be argued that clinical symptoms are not necessarily effective and should not be relied on solely.

In another study 12 civilian volunteers were given an orthotic in one shoe and asked to continue their normal physical routine for two weeks. The subjects were scanned once before as a baseline, once after 2 weeks and 3 randomly selected two weeks after orthotic removal, the authors noted that bone marrow oedema (BME) changes were evident on MRI in 11 out of 12. It is proposed from the results of this study, that under certain conditions a certain stress (such as the orthotic induces in this study) maybe adequate to cause an asymptomatic increase bone signal intensity or BME on MRI, with four volunteers

demonstrating this in multiple bones (Schweitzer & White, 1996). Furthermore in two volunteers, the changes were said to resemble stress fractures and the authors believed that they successfully simulated a bone stress response but stopped the stressor early and therefore unable to determine if the asymptomatic lesions are the beginning of an evolution of a potentially problematic BSI or clinically irrelevant physiological response.

Symptoms may or may not be a reliable indicator. For example, Luchini et al. (1980) reported two runners, neither of which complained of symptoms before they displaced their asymptomatic femoral BSI, although symptoms may have been present but not reported. Fredericson et al. (1995) reported that pain did not develop in 81% of patients until the BSI was a grade 3-4 on their grading system, implying that for the majority of patients lower grade BSI are asymptomatic. Finally Stoneham et al. (1991) p. 147 were concerned that:

A relatively asymptomatic patient may develop a complete fracture at a site of a previous stress fracture.

They recommended that clinicians should have a heightened awareness of BSI and use this knowledge to offer improved and earlier investigation using diagnostic imaging.

Early diagnosis and appropriate rest and or training modification may result in patients with asymptomatic BSI recovering and not progressing further along the continuum (Lee, 2011). This potentially suggests that understanding and diagnosing the asymptomatic period within BSI, the focus of this paper, may be critical in promoting rapid recovery and return to training. Khan, Fuller, Brukner, Kearney, and Burry (1992) conducted a study on navicular BSI using CT. The study included four patients who had previously had bone scintigraphy for tibial pain. These four patients all had incidental findings of asymptomatic navicular uptake. At the time of the bone scintigraphy one patient underwent CT, which did not diagnose BSI and with no symptoms the four continued full training. This appears unusual given they were diagnosed with symptomatic tibial stress. Interestingly a few months later (2-5) all four developed clinical symptoms and CT confirmed navicular BSI. Although this is a small study - 4 subjects, with an age range outside the scope of this current investigation - it highlights the role of smaller studies in better understanding the detail of asymptomatic BSI and additionally supports the theory that asymptomatic BSI could be a precursor to symptomatic BSI (Khan et al., 1992).

There are reports suggesting symptomatic BSI may have gone through an asymptomatic stage, but due to study design it is difficult to know how their symptomatic BSI developed and thus the role of asymptomatic BSI. It may be that the 27/100 rate from this current investigation is extremely important, if even 50% go on to become symptomatic, half the rate of the Khan et al. (1992) study, this will be significant. It is unclear whether 27/100 is a general prevalence or more a combination of athlete and or military populations as only three civilian studies were included in the overall analysis and deemed insufficient to examine statistically.

Bergman et al. (2004) followed 21 elite runners through an eight-week intensive training program. None of the runners had a history of lower leg pain before the training. MRI demonstrated that 12 (57%) had normal tibia bilaterally and the remaining 9 (43%) had evidence of bone stress injuries graded 1-3. Follow up in the form of interviews were performed over the following 48 months and found that 7/9 continued training and remained asymptomatic, and 2/9 ceased running after 1 year, but neither had developed symptoms. They concluded that the positive appearance of BSI with MRI on an asymptomatic runner was not a predictor for further stress reactions.

Another small prospective study followed 10 female recruits over the length of their training course, collecting three data points: before, during and on completion of their training, over a period of three months. The ten recruits all had between 2-5 BSI (30 in total) on commencement of the training course, two thirds of which were low grade and asymptomatic, most commonly in the tibia and femur. Despite the continuation of heavy training at six weeks, five BSI had disappeared on MRI and one new grade 4 appeared. On completion of the course 16 new BSI were found on MRI (12 asymptomatic). Of the remaining BSI seen on the six-week scan none had progressed in severity. The authors concluded that despite heavy training low grade asymptomatic BSI did not progress along the bone stress continuum to higher grade and/or symptomatic injuries recommending that routine screening should not be undertaken (Niva et al., 2009). Although these are small studies and it is thus difficult to generalize, this would suggest that the 27/100 prevalence rate is of little note to both military and athletes' support staff and thus could be ignored.

In support of this Matheson et al. (1987a), concluded that the asymptomatic uptake in areas of bone probably represents bone remodelling below the pain threshold and labelled this 'bone strain' to reflect the dynamic process, however they did not appear to publish any evidence to support this theory, potentially because of the retrospective nature of the study, where it can be difficult to track athletes for follow up imaging.

In addition Harolds (1981) concurred with the Sweet and Allman (1971) rationale, that false positives are due to accelerated bone remodelling, causing increased blood flow. On closer examination it appears they drew this conclusion from physiotherapy reports a year later, an unusual methodology not used in many studies and this making it difficult to compare to other imaging studies. This is a common flaw in most of the asymptomatic papers, where the authors find idiosyncrasies and postulate that BSI are of limited clinical significance but fail to 'prove' this by simple imaging at follow up. Harolds (1981) concluded that follow up X-rays are recommended to make a definitive diagnosis and that bone scintigraphy will occasionally reveal unsuspected and potentially more serious BSI elsewhere.

Interestingly Roub et al. (1979) concluded that asymptomatic BSI are false positives, they do note that the sites of accelerated bone remodelling may become 'gross' fractures if the stress continues at high level and so despite their assuredness that asymptomatic BSI are not relevant, they also question whether they are the result of a physiological response to exercise stress. Thus it may be that the prevalence rate in this study is very important if stress levels continue at their current rate and as such would be very important for any future studies to combine stress levels in any assessment of the impact of asymptomatic BSI.

Lazzarini et al. (1997) conducted a small study with a population of 32 examining the effects of running in the form of BME. They found that whilst there was a statistical significance between BME in runners verses non-runners, they hypothesised that given the lack of symptoms the clinical relevance of these foci was 'likely to be minimal'. Unfortunately the study failed to follow the sample population, to provide evidence to support this claim.

Furthermore the increased uptake of radionuclides in bone scintigraphy, indicative of asymptomatic BSI is caused by accelerated bone remodelling, from repetitive stress and does not necessarily result in symptomatic BSI (Sweet & Allman, 1971). Therefore whilst asymptomatic BSI do not always become symptomatic, it is useful to more fully understand which of the 27/100 patients in this study are most likely to progress. Ultimately, if a strategy to predict progression could be developed, it would transform both the role of imaging in monitoring athlete and military recruits as well as the management of BSI.

But, both Niva et al. (2009) and Kiuru et al. (2005) express very clear opinions about the role of asymptomatic BSI, noting that BSI were only relevant when they were symptomatic, and thus it can be concluded that the prevalence rate of asymptomatic BSI is of little interest in their opinion to medical practitioners or personnel, even those working in physical domains - with 'heavy' or normal training programmes.

In summary, it appears that there is considerably more work to be done in order to fully understand the role of asymptomatic BSI and the importance and potential impact of asymptomatic BSI in different populations. This makes it extremely challenging to contextualise and explain the relevance of the results of the current study regarding the prevalence of asymptomatic BSI, other than to say that it is unlikely that all the 27/100 patients are likely to progress to symptomatic BSI, but that the role of pain in assessing which ones are most likely to progress is questionable.

The results of this study suggest that athletes have a significantly higher rate of lower limb asymptomatic BSI than military recruits. On first examination of the data, the significant difference between the two populations would appear straight forward and relatively simple to explain: athletes have potentially greater training history, coaching and medical support that minimises the progression of asymptomatic BSI to symptomatic fracture, whereas their military counterparts do not have such support and thus their asymptomatic BSI rapidly develop symptoms.

However, a closer exploration of these data may herald another and potentially more important cause of the difference and before examining the more potentially

straightforward causes, it is worth understanding the other issue, namely the question of symptoms.

Asymptomatic injuries by their very definition are ones that are difficult to see or feel and thus are hard to detect let alone self-report. Even symptomatic BSI can have vague symptoms, leading to BSI being potentially reported as other abnormalities, for example muscle strain (Clement et al., 1993). Further complications arise from the fact that the subjects (athletes and military) frequently have multiple BSI and other more advanced injuries, and may have higher pain thresholds than 'normal' and as a consequence may fail to identify injury. Moreover Kiuru et al. (2005) suggested that there maybe a relationship between a high incidence of asymptomatic BSI and higher motivation, suggesting that their participants were more highly motivated and may have trained through the pain. This finding is further supported by Elias et al. (2008) who found ballet dancers maybe potentially hide symptoms in order to avoid being rested. Major and Helms (2002) suggest that it is impossible to determine if an athlete has symptoms given the huge incentive to deny symptoms at a high level of sport. It does appear logical that highly motivated and determined athletes and military personnel would push through the pain thus potentially risking their health (bone integrity) for an increase in physical fitness (Ekenman et al., 2001).

Frequently, papers discuss the stoic athlete/recruit (Major & Helms, 2002; Milgrom et al., 1985b) or describe subjects that are highly ambitious and highly motivated (Dowey & Moore, 1984; Gaeta et al., 2005; Hallel et al., 1976). These appear to increase the pain threshold or allow individuals to ignore pain for many reasons, including the fear of losing training time, exposure in competition, military posting and sports and military contracts (Major & Helms, 2002; Milgrom et al., 1985b), particularly for professionals whose income is dependent on good results (Gaeta et al., 2005). One of the greatest predictors of future injury is past injury (Jacques, 2012; Rauh et al., 2006) potentially with BSI rates 3.5 times higher in those who had sustained a previous BSI according to Rauh et al. (2006). Milgrom et al.'s (1985c) results concur with this, with a 10.6% increased risk of recurrence in military recruits who have already sustained a BSI. These results are well known within athlete populations (Jacques, 2012) suggesting that if athletes can hide potential injuries they will choose to do so. These studies highlight the importance of understanding the

potentially moderating role that motivation plays in the reporting of symptoms and therefore it is reasonable to propose that the rates of asymptomatic BSI are potentially enlarged by an unwillingness to report symptoms.

However other studies suggest that higher levels of motivation may lead to higher BSI rates (Hallel et al., 1976) and that type A personalities, characterised by behaviour traits including high motivation and competitiveness (Ekenman et al., 2001; Hadid et al., 2008) may make up a greater percentage of athletes with both BSI (Ekenman et al., 2001) and other sporting injuries (Fields, Delaney, & Hinkle, 1990) than non-injured subjects. These findings appear to challenge the suggestion that high levels of motivation may inhibit the reporting of symptoms and thus the higher levels of asymptomatic BSI amongst the highly motivated athlete population in this study. However the majority of these studies (Geslien et al., 1976; Gofrit & Livneh, 1994; Greaney et al., 1983; Milgrom et al., 1985a) did not examine asymptomatic patients merely reporting symptomatic BSI and therefore may not accurately capture the levels of asymptomatic BSI in these populations. Again it is necessary to prospectively follow an asymptomatic cohort through a long-term training programme with regular screening in order to fully understand this picture. A number of studies did perform multiple data points including: Bergman et al. (2004); Kiuru et al. (2005); Major (2006); Nielsen et al. (1991); Niva et al. (2009); Roub et al. (1979); Schweitzer and White (1996); Shin et al. (1996); Tappeniers et al. (2003). However none of these prospective studies incorporated both a large sample size and long-term follow up using imaging.

Interestingly type-A behaviour, especially motivation has also been examined in military recruits where overall BSI rates were linked with lower motivation (Gilbert & Johnson, 1966; Hadid et al., 2008). Military recruits with lower motivation may have less or no previous physical exercise than more motivated recruits, for example Gilbert and Johnson (1966) found that of the 265 recruits with BSI, only two had previous athletic training experience, furthermore Leabhart (1959) found that whilst over 50% of total cohort had a history of fitness prior to military training only 13 of 134 who developed BSI had a history of being physically active. These data suggest that having a history of previous exercise before commencing military training offers some protection from BSI, with longer histories and more regular training providing more protection although they do not provide a

relationship with motivation. Gilbert and Johnson (1966) note that military recruits with lower motivation were more likely to have a lower history of training (Lappe et al., 2001; Moran et al., 2012; Provost & Morris, 1969; Reis et al., 2007; Shaffer et al., 1999).

The motivation to train in military recruits might thus have the opposite effect to athletes, with conscripted recruits having lower motivation and less training history having a higher rate of BSI than their more motivated voluntarily recruited colleagues. Again the lower rate of asymptomatic BSI in military may be partly explained by the number of studies that used conscripts as the subjects: eight in total (Giladi et al., 1985; Gofrit & Livneh, 1994; Groshar et al., 1985; Hadid et al., 2008; Kiuru et al., 2005; Kiuru et al., 2003; Meurman & Elfving, 1980a; Milgrom et al., 1985a; Zwas et al., 1987), with an additional two using a combination volunteers and conscripts (Hadid et al., 2008; Niva et al., 2005), as the subjects in these studies may have been less likely to ignore symptoms and thus be reported as symptomatic, although no comparison was made between them.

These studies are interesting evidence of the role of a long training history in minimising BSI, however they all sought to image symptomatic BSI rather than asymptomatic subjects and therefore it would be more accurate to draw the conclusion that a longer training history may reduce the risk of symptomatic BSI.

However, it is possible that some or all of the subjects both athletes and military are genuinely either asymptomatic or symptomatic. Matheson et al. (1987b, p. 74) state that:

Asymptomatic 99mTc uptake probably represents active bone remodelling in response to on-going physical stress.
Suggesting that it is possible this is a normal physiological response of bone, rather than a pathophysiological one below the pain threshold.

A number of studies (Jones et al., 1993; Kowal, 1980; Rauh et al., 2006; Shaffer et al., 1999) have consistently found a link between the fitness of military recruits and BSI, where a higher level of fitness appears to reduce the prevalence of BSI. Shaffer et al. (1999) found recruits who could run 1.5 miles in under 12 minutes were less likely to develop a BSI than those who could not. Furthermore, Jones et al. (1993) suggest that recruits with slower 1 mile run times had increased BSI incidence and Rauh et al. (2006) found that female recruits had a lower risk of BSI when they had greater levels of aerobic

fitness and lower limb strength. Similarly, Cowan, Bedno, Urban, Lee, and Niebuhr (2012) found that female recruits who failed a step test prior to training had a 76% higher BSI incidence. Finally, Hoffman et al. (1999) concluded that aerobic fitness and muscle strength can reduce the risk of BSI by up to five times.

Contrastingly, neither Swissa et al. (1989) or Giladi, Milgrom, Simkin, and Danon (1991) found that aerobic fitness was a predictor of BSI in their studies of military recruits. However the lack of consistency of these studies with those above may be the result of different testing methods, with these studies completing their assessments of aerobic fitness using a non-weight bearing cycle test or indirectly from the Astrand nomogram of heart rate, rather than the previous studies that utilised a running assessment. Non-weight bearing cycle ergometer tests are known to require lower levels of aerobic fitness (as measured by VO2) than running tests (McKay & Banister, 1976) potentially suggesting that the lack of support for the impact of aerobic fitness from these studies may be due in part to the testing protocols. It is also possible that subject bias was a factor in the lack of support for aerobic fitness levels predicting BSI in these studies. Furthermore, Swissa et al. (1989) used a different definition of BSI, including asymptomatic BSI in their study, adding another variable to this picture and potentially suggesting that total BSI (symptomatic and asymptomatic) rates are similar irrespective of aerobic fitness levels between fit and less fit populations a finding collaborated in this study and discussed later. In the current study the asymptomatic BSI rate in athletes was significantly higher than in military potentially because the athletes have a longer training history, although this was not measured in the current study, thus their training does not result in them developing symptomatic BSI as their bodies have 'normalised' the increased training load and therefore BSI predominantly remain asymptomatic. Military recruits may not have the training history to have reached this higher level of normalisation of the increased training stress and thus their asymptomatic BSI more rapidly progress to symptomatic and therefore result in the lower levels of asymptomatic BSI reported here. This is consistent with Wolff's Law, which states that bone adapts to its environment, strengthening more with higher stress rates than with lower ones. This is supported by Matheson et al. (1987b) who commented that military and athletic communities often have different musculoskeletal fitness levels upon commencement of a new training regime or cycle

(Matheson et al., 1987b) and they further explained that unlike athletes, military recruits commence their intense training over a number of weeks, often having insufficient time to accommodate the new intensity/stress placed on the body. Whereas athletes tend to have built their fitness up over a longer period often over many years, allowing the body adequate time to respond. This may go some way to explain why military BSI, especially conscripts, are more likely symptomatic than the possibly better adapted athletes.

More recently Milgrom, Simkin, Eldad, Nyska, and Finestone (2000) reported two studies: firstly they examined data from three separate military cohorts, totalling 1118 recruits, suggesting that recruits who played ball sports specifically basketball, two years prior to induction to military training had a significantly lower incidence of BSI than those played for less than two years or who did not participate in basketball even if they had done other sports including running. They further note that recruits who participated in swimming as their principle exercise prior to military induction had a higher BSI rate than those who did not participate in any regular exercise. From these data it could be suggested that it is not necessarily the aerobic fitness that offers protection, but the type of weight bearing training involved, whilst recruits with a high aerobic capacity developed in swimming, maybe able to train harder than their less fit counterparts, they lack the capacity for bones to be able to cope with the increased training stress. Milgrom et al. (2000) examined compression, tension and strain rates of bone and hypothesized that the significantly higher bone strain rates observed in their basketball rebounding study, might elicit maximal bone remodelling, which if repeated over a two-year period prior to induction to military training, could potentially remodel bone to a sufficient standard and strength to offer protection from developing a BSI.

The results of the current study suggest that athlete and military populations have the same overall BSI rates. However asymptomatic rates are significantly higher in athlete populations but symptomatic BSI rates are significantly higher in military populations, these combine to produce a comparable total rate. This may be the result of longer relevant weight-bearing training history in the athletes (at the time of the studies) in comparison to the military counterparts, and thus the athletes may be able to adapt to stress levels more effectively, only producing asymptomatic BSI, rather than the military recruits failing to adapt or recover and develop symptomatic BSI.

A further explanation of these results maybe the age limitation as most performance athletes will have a amassed a significant history of training in a variety of sports by the time they are 18 years, and this may well be less likely amongst military recruits. This would be especially true for conscripted military and several of the studies included are form countries where military service is compulsory (Ahovuo, Kiuru, & Visuri, 2004; Kaltsas, 1981; Kiuru, Pihlajamaki, Hietanen, & Ahovuo, 2002; Pihlajamäki, Ruohola, Weckström, Kiuru, & Visuri, 2006b).

In addition, there appears to be a relationship between the type and the level of training intensity and the BSI rates; where training programmes of high intensity were more likely to have BSI than training programmes of lower intensity (Brunet, Cook, Brinker, & Dickinson, 1990; Kuusela, 1984). Kuusela (1984) reported an incidence of BSI in parachutists; 63%, normal infantry were 35% and light infantry were 15%. Whilst the paper did not detail the training involved, the authors stated that the level of training performed aimed to increase the level of endurance so the recruits could cope with the service requirements. The training was carried out over a period of ten weeks, a very linear approach to training, possibly not allowing sufficient time for recovery and adaption (Kuusela, 1984). Finestone et al. (2008) also studied recruits who followed a 16-week cumulative linear training model training which resulted in a 12% BSI rate in female recruits, although male recruits and the control group reported zero BSI. The use of a non-adaptive linear model for training recruits is in stark contrast to athletes, who would undertake periodised annual plans, where training volume and intensity change and build towards annual high performance objectives (Stone et al., 1999) and in this process each athlete is monitored for their response to the stress during this time and training load and frequency is varied accordingly. This method of training takes into account the impact of biological complexity, which proposes that no two people will respond to the same stimulus in the same way (Kiely, 2011). Recruits however are all exposed to the same training stimulus at the same frequency and load, in a non-adaptive manner and are therefore either going to survive and adapt or not, and if they have not adapted sufficiently symptomatic BSI are a very real result (Moran et al., 2013). This may be another possible difference between athlete and military populations and may help to

further explain why military are more likely to present with symptomatic BSI while athletes remain asymptomatic.

Many military studies have clearly demonstrated a lack of recovery in military training using progressive, continuous training models as apposed to cyclical (Hill, Chatterji, Chambers, & Keeling, 1996; Kaltsas, 1981; Stoneham et al., 1991) which reduce and or eliminate the time that bone has to remodel. This is a further difference from athletes. Recovery has been identified as an important part of training and improving and some military studies have tested modification in training regimes in particular incorporating additional recovery, that have demonstrated a reduction in BSI (Pester & Smith, 1992; Popovich, Gardner, Potter, Knapik, & Jones, 2000; Scully & Besterman, 1982). However there are no recent studies making direct comparisons between the training programmes in military and athletes and the resultant injury rates. In general this is worthy of further investigation to assist in developing a greater understanding of the role of asymptomatic BSI.

High performance athletes are frequently supported by highly specialized support staff and are regularly monitored and assessed for their adaptation to training, injury prevention and a high array of other monitoring, not least of which is provided by a coach, who generally works with a very small number of elite athletes. The presence of this support may explain the lower rates of symptomatic BSI amongst athlete populations, although there is little published research investigating any relationship. Furthermore it appears that military recruits do not experience the same optimisation of their training environment, support and monitoring and this is suggestive of their higher rates of symptomatic BSI.

Nutritional support and supplementation has been linked with BSI rates in military recruits with evidence suggesting a positive reduction in BSI rates (symptomatic) with certain supplements (such as vitamin D, iron and calcium) (Givon et al., 2000; Lappe et al., 2008). In contrast to military recruits, nutritional support is readily available to increasing number of elite athletes with frequent monitoring of specific blood markers and BMD and again may contribute to the decreased risk of symptomatic BSI in athletes.

In summary the literature appears sparse in the prevalence rate comparing military and athletic groups, but also vague as to why both symptomatic and more importantly for this study, asymptomatic BSI rates are statistically different in military and athletic groups. Therefore further research is required to determine if the results of this study are a true representation of the athletic and military populations and it would be a useful addition to understand why the rates maybe different, which may identify risk factors for BSI and maybe even confirm the role of imaging modalities in both the collection of this data and potentially evaluate the use of screening for at risk populations.

It is difficult to position the results of the current study into the literature as this review has examined a number of papers from different eras, from 1979 to 2008. Results in the current study report that the tibia has the highest rate of both symptomatic and asymptomatic BSI. The tibia is statistically different to the fibula in symptomatic BSI. The distribution of BSI reported in the literature appears to have shifted over time. This can be attributed to a number of changes to: equipment, training and the development of medical imaging (Markey, 1987). Initially, studies of symptomatic BSI before and during World War II described this injury being 'reserved to the foot' of soldiers, in particular the metatarsal bones and as such was usually coined ‘March fracture’ (Bernstein & Stone, 1944; Hartley, 1943). It was speculated that the injury and its particular location (metatarsals) was due to long marches carrying a heavy military pack (Carlson & Wertz, 1944) and early studies reported that 94% -100% of BSI where found in the metatarsal (Carlson & Wertz, 1944; Sirbu & Palmer, 1942). There were some case reports noting BSI in other bones for example the fibula in athletes (McPhee & Montanye Franklin, 1946; Weaver & Franciso, 1940) and even housewives (Burrows, 1948) but these are uncommon.

By the 1960s both recreational and professional sport were becoming more popular and an increasing number of papers had highlighted symptomatic BSI in athletes (Darby, 1967; Devas & Sweetnam, 1956; Morris, 1968), demonstrating that BSI was not just an injury confined to military personnel. It was suggested that BSI was probably more common in the civilian population with various occupations and athletic pursuits that require similar physical exertion to that of a military recruit (Darby, 1967). This under reporting is probably multifactorial, with a combination of vague patient history resulting

in few radiographs undertaken, the poor sensitivity of X-rays and the lack of clinical suspicion amongst the medical profession (Carlson & Wertz, 1944; Darby, 1967). Interestingly a number of papers published at this time highlighted a changing trend in the distribution of BSI, with a decrease of metatarsal BSI across military and civilian populations. In one military study of 300 BSI, 38.7% were located in the metatarsal, which is a particularly large drop in prevalence whilst tibial BSI prevalence increased to 13.3%, but interestingly the calcaneum in this report has the highest incidence at 43% (Darby, 1967).

By the 1970s, BSI in military personnel continued this trend of a reduction in the prevalence of BSI in the metatarsal and increasingly prevalent in other areas for example: Geslien et al. (1976) later reported 39% tibial plateau, 35% calcaeum, 7.5% metatarsal and 19% in the femur. In other athlete studies the prevalence of BSI in the lower leg mirrored the change found in the military: Orava, Puranen, and Ala-Ketola (1978) found that the tibia was the most prevalent site of BSI in the athlete accounting for 53.5%, with metatarsal at 18.3% and fibula at 14.1%.

Later studies further support these shifts and by the 1980s the increase in tibial and femoral BSI was reported more consistently across the literature with tibial rates ranging from 38% to 72% (Giladi et al., 1985; Hulkko & Orava, 1987; Johnson et al., 1994; Matheson et al., 1987b;Zwas et al., 1987) and the femur 6.2% to 25% (Giladi et al., 1985; Hulkko & Orava, 1987; Johnson et al., 1994; Matheson et al., 1987b; Zwas et al., 1987) with an accompanying reduction in BSI in the metatarsal ranging from 2% to 20% (Giladi et al., 1985; Hulkko & Orava, 1987; Johnson et al., 1994; Matheson et al., 1987b; Zwas et al., 1987).

More recent studies suggest that there has been an increase in prevalence in the feet: Bennell et al. (1995) athlete study reported in the tibia, 40% in the feet (20% tarsal navicular, 20% metatarsal); Hod et al. (2006) found 39% in the feet (27.7% tarsal & 16.2% metatarsal) of military recruits; Papalada et al. (2012) reported 40% in feet of elite male and female mixed sex track and field athletes; and most recently (Cosman et al., 2013) report found 58% in the metatarsal. These recent studies carry extra significance as they included large numbers of mixed gender and are similar across athletes and military recruits.

The results of this review found that the predominant area of BSI in both symptomatic and asymptomatic individuals was the leg, in particular the tibia (58.8/100 and 30/100) followed closely by the femur (37/100 and 13/100) (Table 9). This seems to be consistent throughout individual studies, suggesting that BSI are now more prevalent in the leg bones rather than the bones in the foot/ankle. These results would suggest that despite the range of papers examined in this investigation that the general trend amongst these populations is for a greater prevalence in the tibia in both types of BSI. Although this study was unable to examine any differences between athletic and military populations it would be useful to note whether they experienced different distribution rates.

Due to the small number of studies and lack of detailed data, it is difficult to differentiate the BSI in any further detail. Additionally the differences in the methods of data collection, definition of BSI, number of cases and the type of activity studied may all affect the reported distribution of BSI and thus whilst this investigation appears consistent with the evolving trend in the literature it is by no means conclusive.

It is likely that the change in distribution of BSI is multifactorial and includes changes to the nature and intensity of training, the equipment used, recruitment criteria, general fitness levels and range of psychological factors e.g. motivation (Geslien et al., 1976; Giladi et al., 1985). The shift of military training to more running has led to military BSI prevalence more closely mirroring that found in the athletic community (Markey, 1987). In particular, Giladi et al. (1985) noted that training based on running and marching, with less drill and parades, resembles athletic training and other military reports suggest that training regimes have moved from predominantly drill and parades on paved surfaces, linked to tarsal and metatarsal BSI, to running, which is linked to BSI in the leg (Giladi et al., 1985; Markey, 1987).

It has also been suggested the change in distribution of BSI from the metatarsal to the calcaneum was due to a reduction in marching with heavy packs (Darby, 1967). The elimination of the heal snap from the marching and training in tennis shoes on grass, led to a dramatic reduction in calcaneal BSI from 20.5% to 7% (Greaney et al., 1983). Gilbert and Johnson (1966) hypothesised that marines underwent more strenuous training with a difference cadence during drilling which caused an increased rate of calcaneal BSI when

compared with navel recruits, where metatarsal BSI were more common. This suggests a direct link between training intensity and type and BSI location.

Equipment changes, principally to footwear, have enabled soldiers to sustain a greater level of training than was previously possible and appears to affect the prevalence and distribution of BSI (Greaney et al., 1983). The footwear worn by athletes is generally designed or adapted to individual sports however military recruits all traditionally wore similar standard issue combat boots for training. It's likely that differences in the distribution of BSI between athletes and military has probably become less pronounced in recent years as a direct result of injury research leading to equipment and training changes.

As previously suggested the type of physical training undertaken can have quite significant effects on it and where BSI may occur. Devas and Sweetnam (1956) proposed a correlation between the strong muscle contraction and development of BSI at particular sites. Athletes who partake in sprinting, hurdles, jumping and multi events have a higher rate of foot BSI (tarsal and metatarsal) whilst middle and long distance runners had a greater rate of long bone (tibia, fibular and femoral) and pelvic BSI (Bennell et al., 1996a). However Orava and Hulkko (1988) found that in all the sports studied the distribution was highest in the lower leg (tibia and fibula), with jumping and ball sports the distribution was in the tarsal and metatarsal and running had more BSI in the longs bones tibia, fibula and femur.

Finally the development of new imaging modalities is another probable cause for this change in distribution and thus could be considered a change in sensitivity and specificity rather than purely distribution changes. For example the introduction and subsequent high use of bone scintigraphy in the detection of BSI (Milgrom et al., 1985a) improved sensitivity in the 1970s and 1980s and resulted in an increased uptake of all BSI particularly, those which have a late presentation on plain radiographs (Geslien et al., 1976; Meurman & Elfving, 1980a; Wilcox, Moniot, & Green, 1977). Greaney et al. (1983) explain that in a large number of cases, metatarsal BSI can be diagnosed using radiographs earlier than the same injury in the femur or tibia and thus the timing of the scans may skew the data in favour of metatarsal BSI. When bone scintigraphy was used the rate of tibial and femoral BSI increased as bone scintigraphy can image these BSI

earlier and more sensitively and specifically than plain radiographs could previously. Furthermore the introduction of bone scintigraphy allowed asymptomatic BSI to be more widely imaged. Giladi et al. (1985) and Milgrom et al. (1985a) reported significant asymptomatic BSI in the femur that would never have been diagnosed using radiographs. In this study, bone scintigraphy had particularly high rates of asymptomatic BSI in the athletic populations.

Kiuru et al. (2005) noted a relationship between the site or distribution of BSI and the presence of symptoms, with both the tibia and metatarsal more likely to be symptomatic, whilst the femoral shaft BSI were more likely to be asymptomatic. However it was also noted that symptoms were related to the grade of BSI, which suggests a multitude of factors are involved.

The current study supports the tibial trend towards symptoms, but reports a consistent level of BSI in the metatarsals of 10/100 asymptomatic and 8/100 symptomatic. In addition, significant differences between symptomatic (3/100) and asymptomatic (28/100) BSI in the tarsal bone were noted. It is unclear why the distribution of asymptomatic and symptomatic would differ from the Kiuru et al. (2005) study, although they noted that symptoms were related to the grade of BSI, which was not examined in this study.

The result of the current study suggests asymptomatic BSI within the feet and ankle have a higher rate than symptomatic and this is significant in the tarsal but not metatarsal bones.

One possible reason for this difference is that tarsal fractures are particularly difficult to diagnose (Hunter, 1981) in comparison to the long bones in the leg. Unlike other BSI symptoms, this area can be difficult to assess, often with a vague history of diffuse pain and little or no swelling accompanied by negative radiographs (Hunter, 1981; Moran, Fairclough, & Evans, 1987). In addition Matheson et al. (1987b) found it took a longer time to diagnose tarsal BSI than other lower extremity bones although not statistically significant. Apart from the insidious onset of symptoms, the imaging modality utilised appears to be the biggest factor involved in the speed of diagnosis. For example navicular BSIs generally appear to propagate in the sagittal plane in the central third or the central and lateral thirds of the bone, which reduces possible visualization on radiographs (Fitch,

Blackwell, & Gilmour, 1989). Furthermore as the navicular lies in an oblique position if specialised 'inverted foot views' are not undertaken diagnosis can be even harder (Torg et al., 1982).

The results of this review, appear to correlate with the historical reports that prevalence of tarsal BSI are low (Hunter, 1981; Moran et al., 1987) with only 0.1 per 100 patients being diagnosed with a symptomatic tarsal BSI in this study. However 2.9 per 100/patients were found to have a asymptomatic tarsal BSI and this is potentially an important finding because of the potential complications if these were to progress along the BSI continuum with or without symptoms.

Hulkko and Orava (1987) investigated athletes at a variety of performance standards, the reports suggest that athletes at the highest standard (i.e. international level) had a significantly higher proportion of delayed or non-union BSI particularly in the tarsal navicular (related to the onset of symptoms). Thus the high rates of asymptomatic BSI in the tarsal area are a cause for concern as they maybe more prone to non-union issues and thus a lack of symptoms combined with the high-risk site may be sufficient to require a monitoring service.

BSIs in the talus have a variable outcome, frequently the injured individuals fail to return to their pre-injury condition (Bradshaw, Khan, & Brukner, 1996) and ultimately this can be career ending for both military recruits and athletes. Sormaala, Niva, Kiuru, Mattila, and Pihlajamaki (2006) found in their study that whilst there were no complications with talus BSI healing, mid term follow-up showed minor to moderate symptoms and radiological degradation had occurred in half of all patients. Whilst this was not related to their return to play, it does suggest that effects from these injuries can continue long after the injury has healed. Furthermore Orava and Hulkko (1988) reported osteoarthritis from a non-union navicular BSI which stopped the athlete from continuing to train.

Limits of data interpretation

This review is subject to a number of biases, the most important of which is the method of data collection and objectives of the primary studies. This review analysed 16 military studies, 14 of which sought to examine symptomatic recruits and reported asymptomatic BSI as an incidental finding. It would be prudent therefore to suggest that more

symptomatic BSI are more likely to be found than asymptomatic. Unsurprisingly, this was the case in recruits, with the symptomatic BSI rate at 40/100 and the asymptomatic BSI rate at 17/100. The retrospective design of most of these studies examined military recruits after symptoms presented and their data sample only included symptomatic recruits. Thus they are possibly less likely to be in a position to provide comprehensive data on the prevalence of asymptomatic rates in the general military population let alone the population as a whole. However the evidence of bilateral BSI in subjects may suggest that by examining symptomatic BSI the investigators are possibly enabling a clearer picture of asymptomatic prevalence rates than simply examining a true random sample of the population. Yoon et al. (2012) presented such an example (Figure 43 & 44) where by pain began in the left knee of a military recruit. Radiographs were subsequently taken, reported as normal and training was continued. One week later right knee pain developed followed by right hip pain and left hip pain over a period of five days. MRI was then requested and clearly demonstrated the symmetrical BSI findings, with one side occurring slightly ahead of the other in terms of both symptoms and imaging findings.

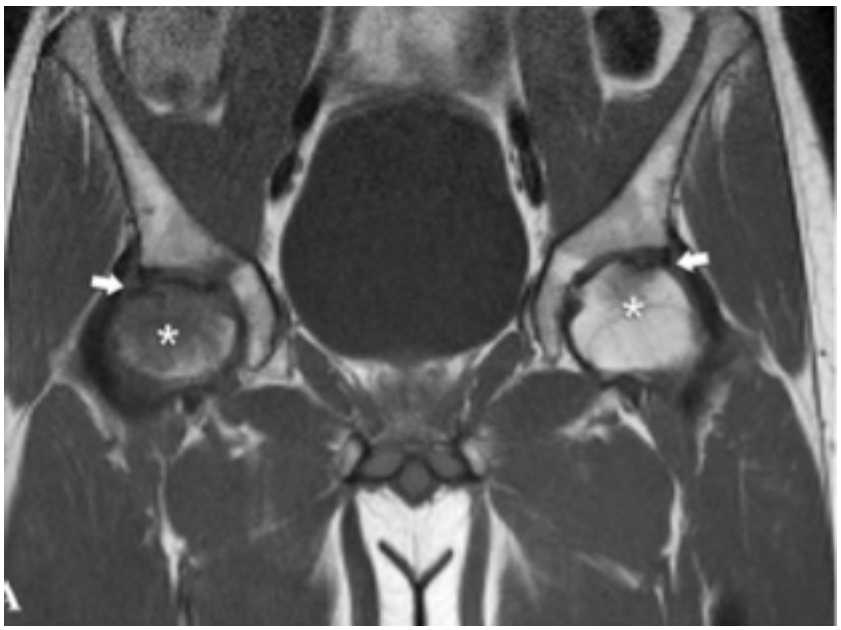


Figure 38: A T1 weighted MRI sequence of a pelvis with bilateral BSI.
The 27-year-old male military recruit was diagnosed with subchondral fractures (arrows) and the bone marrow edema pattern (asterisks) extending to the subchondral area without additional abnormal signal intensity band, representing the reactive margin of the necrotic area (Yoon et al., 2012, p. 947).

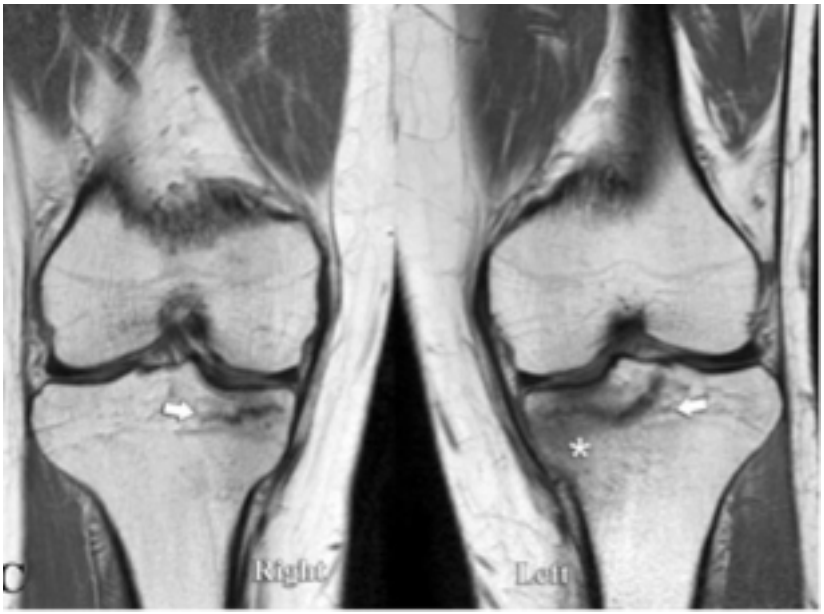


Figure 39: A T1-weighted MRI image of bilateral BSI to the tibial plateau.
These are the corresponding images to the recruit discussed in Figure 38 (Yoon et al., 2012, p. 947).

Other studies have also reported bilateral BSI (Blatz, 1981; Fredericson, Jang, Bergman, & Gold, 2004; Giladi et al., 1985; Nielsen et al., 1991; Ruohola et al., 2006; Shin et al., 1996; Sopov et al., 2000).

Conversely, half of the eight athlete studies used in this investigation examined symptomatic subjects, thus having a more equal probability of the two types of BSI but at an increased probability of asymptomatic BSI being reported compared to military. This again appeared to be the case in athletes with the asymptomatic BSI rate being (75/100) whilst the symptomatic BSI rate was (10/100).

Moreover all 8 studies that specifically studied asymptomatic BSI were prospective studies, allowing more detailed information to be extracted at the time of the event, compared to retrospective studies, which may have reported asymptomatic BSI, during a study on symptomatic BSI, (although it must be noted that several of these have excluded symptomatic subjects adding potential bias).

Whilst retrospective studies can be a very useful way of gaining large amounts of data, this type of data capture often relies on medical records and/or self-reporting potentially leading to bias and resulting in skewed data. This is particularly pertinent in examining an asymptomatic injury, as patients will not be able to report these injuries. However a

number of retrospective studies have included data on asymptomatic BSI, but is difficult to know the extent of reporting.

A total of 27 studies were included in this review, but most of these included small sample (mean= 108, range 7-1118) populations, making the results of this study prone to data skew. For example Matheson et al. (1987b) conducted a study of 320 athletes using bone scintigraphy, which was the largest study in an athlete population, but more importantly all the other athlete studies together only totalled 167, possibly impacting the final results, as any result found by Matheson would be likely to greatly affect the overall result. For example, bone scintigraphy proved to be significantly greater at diagnosing asymptomatic BSI in athletes than military recruits and this was the modality used in Matheson et al. One of the strengths of a systematic review is the ability to combine studies and extract a more powerful trend or difference, however in this case the weighting of the Matheson study might have skewed the data and highlighted a trend or difference that might not exist if these data were excluded.

At this point it is important to explain that it was not possible to get a comprehensive view of the overall prevalence of symptomatic and total BSI using all published data, as this study only collected data from studies that reported evidence of both asymptomatic and symptomatic BSI. Undoubtedly this will lead to potential bias in both symptomatic and total BSI prevalence rates, for example the actual symptomatic rate may be significantly higher and affect the total BSI rate in a similar manner.

The imaging modalities themselves have also been reported to affect the prevalence rates of asymptomatic BSI (Greaney et al., 1983; Milgrom et al., 1985a).

The evolution of medical imaging has allowed medical professionals to visualize BSI with increasing accuracy and speed. In 1895, when X-rays were introduced as an imaging tool, it allowed clinicians to visualize the process for the first time and gain a wider understanding the pathogenesis of BSI (Morris, 1968). However it soon became apparent that it was not a wholly accurate tool, particularly in the early stages of symptoms as although they are specific they have relatively low sensitivity (Roub et al., 1979; Zwas et al., 1987). Typically radiographs would be negative until a periosteal reaction had begun and the subjects were symptomatic (Matheson et al., 1987b). This is difficult to quantify

exactly but typically ranges from 2 weeks to 3 months and is partly conditional on the location of the BSI (Engber, 1977; Prather et al., 1977; Sullivan, Warren, Pavlov, & Kelman, 1984).

Therefore relatively few studies have been found to describe asymptomatic BSI on radiographs (Kuusela, 1984; Luchini et al., 1980). Brahms et al. (1980) presented a case where an asymptomatic deformity was noted and subsequently X-rayed denoted a callus from a suspected BSI. Luchini et al. (1980) reported stated that the BSI did not present until the bone completely failed, with no symptoms being reported prior to the event, on closer examination however callus formation can be seen near the displaced fracture sight on initial radiographs (Figure 40).

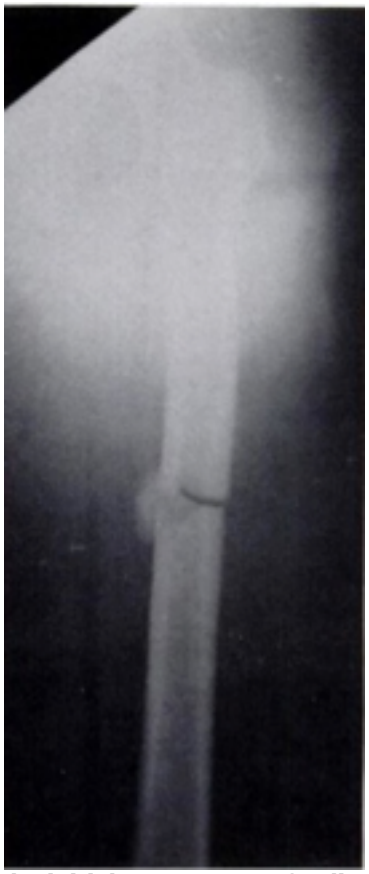


Figure 40: A radiograph demonstrating the initial appearance of a displaced transverse fracture in the mid portion of the femur.
(Luchini et al., 1980, p. 690).

The introduction of bone scintigraphy in 1971, utilising the process of bone metabolism, meant medical professionals could mage symptomatic BSI earlier and interestingly gave the hard first evidence of asymptomatic bone remodelling, whether this is a pathological

process or a normal physiological response was and remains unclear (Subramanian & McAfee, 1971). Suddenly there were growing numbers asymptomatic BSI being reported within the literature using bone scintigraphy (Milgrom et al., 1985a).

Kuusela (1984) studied 45 recruits and increased uptake on bone scintigraphy with a total of 72 separate foci. The authors noted in their report that recruits with radiographic findings in the upper legs usually denied having symptoms during their examinations and illustrated an example of this in their study, however due to copyright issues cannot be visualised here. The publised demonstrates an asymptomatic BSI visible on both bone scintigraphy and radiograph, one of very few examples. This radiographic evidence is proof that asymptomatic BSI imaged on bone scintigraphy can evolve significantly to be visible on radiographs and subsequently be labelled as a BSI. This paper was one of the earliest to suggest that asymptomatic BSI maybe of clinical significance. As Luchini et al. (1980) and Kuusela (1984) appear to prove the only two single cases of reported asymptomatic BSI on radiographs they carry little weight in the larger picture, but it is note worthy. However it is possible that both these lesions may have been symptomatic but not reported or screened as such. Although the low sensitivity and specificity play a role in the general lack of evidence of asymptomatic BSI on radiographs it must be noted that particularly in the early days of BSI researchers and clinicians did not X-ray asymptomatic individuals. This was part due to it being unethical to X-ray asymptomatic individuals but also not a cost effective method of research. It was not until bone scintigraphy emerged on the clinical scene did asymptomatic BSI become reported, due to the modality offering a large FOV, which located asymptomatic BSI.

Once bone scintigraphy came into mainstream use, asymptomatic BSI reports began to appear in the literature (Giladi et al., 1985; Matheson et al., 1987a; Zwas et al., 1987). Over time it was noted that overall prevalence rates from military studies varied, possibly because of the imaging modalities used. Israeli military studies (Milgrom et al., 1985a) used bone scintigraphy primarily for diagnosing BSI, whereas American studies (Brudvig et al., 1983; Pester & Smith, 1992; Protzman & Griffis, 1977) primarily used plain radiographs. Possibly as a consequence the overall prevalence rates of BSI in the Israeli studies were higher than the American. Furthermore the American studies were based on

symptomatic BSI whilst the Israeli studies reported both symptomatic and asymptomatic BSI, resulting in a mixed picture of the overall prevalence.

Reporting of asymptomatic BSI continued with the invention of MRI, although it did not become widely available until the 1990's (Yao et al., 1998). It soon became the gold standard because of its high sensitivity and specificity the (Kiuru et al., 2003; Kiuru et al., 2002).

A difference in asymptomatic BSI prevalence in military continued to be reported throughout the literature, probably dependent on the imaging modality used (Brudvig et al., 1983; Fullerton & Snowdy, 1988; Kiuru et al., 2002; Wilson & Katz, 1969). The studies that used bone scintigraphy and MRI all found asymptomatic lesions, whilst older studies that used radiographs only initially imaged clinically symptomatic lesions. Without this critical assessment of the methodologies, it would potentially affect American recruits imaged with radiographs, as they have lower total BSI rate than their peers from other countries that used bone scintigraphy or MRI.

It may be possible that American training methodologies and support networks have minimized the BSI rates compared to other recruits, however the lack of a common imaging method prevents this picture from clearly emerging.

In this systematic review the highest prevalence of both symptomatic and asymptomatic BSI in the lower limb was found using bone scintigraphy. In total BSI in military studies this was 42/100 and 62/100 in athletes. The lowest prevalence rates were recorded using X-ray 5/100 and 7/100 in military and athletes respectively and then MRI was 19/100 and 8/100 in military and athletes respectively. Possible explanations for the contrasting results of bone scintigraphy over MRI include: MRI not being used for any symptomatic BSI studies, possibly skewing the data (Table 13). Another possible bias in these results is the variable FOV across the imaging modalities. Bone scintigraphy routinely images pelvis to toes in a large FOV, coupled with its high sensitivity and specificity it enables medics to detect asymptomatic BSI that would have other wise been missed if only the symptomatic site be imaged. MRI due to its inherent physical principles, cost and time restraints, tends only to image small FOVs usually only incorporating only the symptomatic areas. Therefore even MRI, with its superior sensitivity and specificity, has been suggested that it

may be less likely to pick up asymptomatic lesions (Kiuru et al., 2003). Kiuru et al. (2003) noted this potential flaw in MRI and chose to use a slightly larger FOV than normally used and found a significant number (18%) of asymptomatic BSI that would have been missed (false negative) if a smaller surface coil had been used. This 18% consisted of BME, fracture lines and callus all seen on the contralateral side, which they also refer to as the asymptomatic side, although it is possible that the subjects had radiated pain and simply did not identify it on that side. As a result they concluded the entire pelvis and both proximal femora should be imaged using MRI. Whilst their study does not advocate routine MRI screening for all asymptomatic recruits it does recommend that patients with hip pain, should have their entire pelvis and both femorae imaged simultaneously using a large FOV for a more accurate diagnosis and management. Prather et al. (1977) agrees that whole body scans should be offered for people at risk of BSI. Explaining that 4 of their patients had multiple BSI in different locations and some of these would not have been detected if only small FOV imaging was performed over the area of symptoms. Furthermore they suggest that referred pain can sometimes cause confusion and lead to lesions being missed. Sofka (2006) also suggested using a "survey image" with a large FOV STIR sequence, be performed to gain a global overview and recommended this protocol for patients with non specific hip, lower back and groin pain, where BSI was of high clinical suspicion. Then if an area of BME is seen, further specialized imaging of that lesion or area can be undertaken. This potential bias needs to be understood when measuring the incidence and prevalence rates and ideally studies should use the same imaging modality and the same FOV for all participants to reduce this bias. This bias needs to be considered in several studies, for example Hadid et al. (2008) used MRI with the standard small FOV in the asymptomatic recruits and bone scintigraphy with the standard large FOV for the symptomatic recruits. This standardization prevents a number of challenges, firstly many studies are retrospective and the imaging has already been undertaken, secondly ethical approval to irradiate all participants (asymptomatic and symptomatic) using bone scintigraphy especially those without a clinical indication would be challenging and thirdly there would be significant resources cost and time implication for a study to image all participants (asymptomatic and symptomatic) with the 'safer' big FOV MRI option.

Other Limitations

The observation period for diagnosing BSI is a variable since asymptomatic BSI (by definition) remain unknown until discovered using medical imaging. Milgrom et al. (1985a) noted that they could not determine the time of onset in 35% of BSI diagnosed. This could indicate that BSI being recorded were old injuries which have healed, but due to the delay in bone scintigraphy, may appear still active skewing the prevalence rates. To overcome this would require a baseline screen in all individuals as a baseline collection point, with any pre existing injuries being excluded from the study. In many of the military studies the data is collected and the incidence or prevalence rates are calculated after 12 weeks, or at the end of the recruits training (Kiuru et al., 2005; Milgrom et al., 1985a). Niva et al. (2009) had three sampling points in their study, at the beginning of the training, after 6 weeks and finally after 12 weeks, which provided an opportunity to follow the progression of both asymptomatic and symptomatic BSI. In this study, where repeated scans were incorporated in the analysis, a fixed period of observation was assumed.

The follow up period appears to be another limitation of the published literature, with most studies measuring a single point in time, which may provide data on asymptomatic BSI, but do not provide follow up, to determine if these asymptomatic BSI progress as seen in Major (2006) or continue to stay silent or disappear as in Niva et al. (2009).

A further problem in the literature is the attrition occurring in the prospective studies with both the Niva et al. (2009) and, to a greater extent the Major (2006), studies suffering from this. Major (2006) reported that 14 of 26 were unable to be followed up. This attrition can cause significant bias in results and is especially disappointing if the participants who drop out have BSI as this further limits the ability to understand the impact and risks of these or even if the reason for dropping out is directly due to the asymptomatic BSI.

Only lower extremity BSI have been included in this study, unfortunately this excludes a great many studies on asymptomatic BSI of the spine, pelvis, ribs and upper extremity, however the focus of this paper was on true weight bearing bones and wanted to

specifically examine the prevalence rates in both military and athletes and lower extremity appeared to be similar.

Another weakness in the literature as a whole is the lack of reported asymptomatic BSI. Many studies examining symptomatic BSI did find asymptomatic BSI, but then failed to report them (Dowey & Moore, 1984). This resulted in some studies being excluded due to a lack of clear data. As a result, asymptomatic BSI could have a higher prevalence than this systematic review of the literature suggests.

Throughout this review it has become apparent that there is a lack of standardization in regard to diagnosing and grading BSI. This may have affected the result in this review as some studies may have excluded signs of low-grade stress on MRI or bone scintigraphy, as it was not deemed a high grade enough with associated callus for example to be classified as a BSI.

Conclusion

A combination of both epidemiological and clinical research data collected spanning over four decades has slowly improved the knowledge base of BSI. Whilst symptomatic BSI appear to be widely accepted throughout the medical and sports world, there is still some contention as to the clinical significance of asymptomatic BSI. This review sought to record the prevalence of asymptomatic BSI as a preliminary step into answering this much larger question in this under reported field.

This systematic review had found that the total prevalence of asymptomatic BSI is (27/100), compared to (34/100) symptomatic BSI. It is difficult to understand the clinical significance of this finding given the lack of empirical evidence. Athletes had a higher prevalence of asymptomatic BSI (75/100) than military personnel (17/100), which is probably multifactorial involving: motivation, fitness and sampling bias.

The distribution in this review is generally consistent with the peer-reviewed literature, finding the tibia to be the most prevalent site for both symptomatic and asymptomatic BSI with 9.3 and 7.7 per 100 patients respectively.

The study also found a significant difference between symptomatic (3/100) and asymptomatic (28/100) BSI in the tarsal bones. The reason for this difference is unknown, but it has been previously reported that tarsal fractures are particularly difficult to diagnose (Hunter, 1981) in comparison to the long bones in the leg. However given the high risk of non-union this is an area that needs further investigation.

BSI is generally accepted to be on a sliding continuum (Roub et al., 1979), however the lines are more blurred regarding where pain commences along this continuum.

During the process of this review it was noted that whilst a number of studies have identified the existence of asymptomatic BSI, most failed to provide adequate follow-up in order to allow the clinical significance to be properly assessed. This has led to a clear gap in the literature for a large robust study examining asymptomatic BSI in more detail with a follow up to come to some more solid conclusions.

Future studies

This study has produced a number of questions, which are possible areas for further research. Perhaps the most important question is to determine if asymptomatic BSI are clinically relevant. A large prospective longitudinal study on an athlete or military population would enhance the knowledge base in this field and help ascertain this.

It would be useful to gain an insight into why some people possibly feel pain sooner, for example in low grade BSI while others remain asymptomatic with higher grade BSI. This may help clinicians to understand if treatment should be planned purely on symptoms. As this area may be linked to motivation qualitative data in the forms of interviewing recruits or athletes on how they perceive pain etc., may aid understanding in this area.

Finally any studies should include an analysis of subjects training history, aerobic fitness levels, status e.g. recruit or conscript, elite or non elite athlete, tracking these against all BSI rates as the subjects progress through the study.

References

Ahovuo, J. A., Kiuru, M. J., & Visuri, T. I. (2004). Fatigue stress fractures of the sacrum: diagnosis with MR imaging. *European Radiology, 14*(3), 500-505.

American Medical Association. (1966). *Committee on the medical aspects of sports, Subcommittee on classification of sports injuries. Standard Nomenclature of Athletic Injuries.* Chicago: American Medical Association.

Anderson, E. G. (1990). Fatigue fractures of the foot. *Injury, 21*(5), 275-279.

Anderson, M. W., & Greenspan, A. (1996). Stress fractures. *Radiology, 199*(1), 1-12.

Aoki, Y., Yasuda, K., Tohyama, H., Ito, H., & Minami, A. (2004). Magnetic resonance imaging in stress fractures and shin splints. *Clinical Orthopaedics & Related Research, 421*, 260–267.

Arendt, E. A., Agel, J., Heikes, C., & Griffiths, H. J. (2003). Stress injuries to bone in college athletes- a retrospective review of experience at a single institution. *The American Journal of Sports Medicine, 31*(6), 959-968.

Arendt, E. A., & Griffiths, H. J. (1997). The use of MR imaging in the assessment and clinical management of stress reactions of bone in high-performance athletes. *Clinical Sports Medicine 16*(2), 291-306.

Armstrong, D. W., Rue, J. P., Wilckens, J. H., & Frassica, F. J. (2004). Stress fracture injury in young military men and women. *Bone, 35*(8), 806-816.

Arnett, T. (2013). Osteoclast SEM. Retrieved 28 November 2013 from http://www.anatomybox.com/osteoclast-sem/

Aveyard. (2007). *Doing a literature review in health and social care - A practial guide.* Berkshire, England.: Open University Press.

Aynaci, O., Kerimoglu, S., Ozturk, C., & Saracoglu, M. (2008). Bilateral non-traumatic acetabular and femoral neck fractures due to pregnancy-associated osteoporosis. *Archives of Orthopaedic and Trauma Surgery, 128*(3), 313-316.

Barrow, G. W., & Saha, S. (1988). Menstrual irregularity and stress fractures in collegiate female distance runners. *American Journal of Sports Medicine, 16*(3), 209-216.

Beck, B. R. (1998). Tibial stress injuries. *Sports Medicine, 26*(4), 265-279.

Beck, T. J., Ruff, C. B., Mourtada, F. A., Shaffer, R. A., Maxwell-Williams, K., Kao, G. L., . . . Brodine, S. (1996). Dual-energy x-ray absorptiomety derived structural geometry for stress fracture prediction in male US marine corps recruits. *Journal of Bone and Mineral Research, 11*(5), 645-653.

Bennell, K. L., & Brunker, P. D. (2005). Preventing and managing stress fractures in athletes. *Physical Therapy in Sport, 6*(4), 171-180.

Bennell, K. L., Crossley, K., Jayarajan, J., Walton, E., Warden, S., Kiss, Z. S., & Wrigley, T. (2004). Ground reaction forces and bone parameters in females with tibial stress fracture. *Medicine & Science in Sports & Exercise, 36*(3), 397-404.

Bennell, K. L., Malcolm, S. A., Brunker, P. D., Green, R. M., Hopper, J. D., Wark, J. D., & Ebeling, P. R. (1998). A 12-month prospective study of the relationship between stress fractures and bone turnover in athletes. *Calcified Tiisue International, 63*(1), 80-85.

Bennell, K. L., Malcolm, S. A., Thomas, S. A., Ebeling, P. R., McCory, P. R., Wark, J. D., & Brukner, P. D. (1995). Risk factors for stress fractures in female track-and-field athlete: A retrospective analysis. *Clinical Journal of Sport Medicine, 5*(4), 229-235.

Bennell, K. L., Malcolm, S. A., Thomas, S. A., Wark, J. D., & Brunker, P. D. (1996a). The incidence and distribution of stess fractures in competative track and field athletes. *The American Journal for Sports Medicine, 24*(2), 211-217.

Bennell, K. L., Malcolm, S. A., Wark, J., & Brunker, P. D. (1996b). Models for the pathogenesis of stress fractures in athletes. *British Journal of Sports Medicine, 30*(3), 200-204.

Bennell, K. L., Matheson, G., Meeuwisse, W., & Brukner, P. (1999). Risk factors for stress fractures. *Sports Medicine, 28*(2), 91-122.

Bergman, A. G., Fredericson, M., Ho, C., & Matheson, G. (2004). Asymptomatic tibial stress reactions: MRI detection and clinical follow-up in distance runners. *American Journal of Roentgenology, 183*, 635-638.

Bernstein, A., & Stone, J. R. (1944). March fracture - A report of three hundred and seven cases and a new method of treatment. *The Journal of Bone and Joint Surgery, 26*(4), 743-750.

Biggam, J. (2011). *Suceeding with your master's dissertation - A step-by-step handbook* (2nd ed.). Berkshire: McGraw Hill.

Blackman, P. (2010). Shin pain in athletes, assessment & management. *Australian Family Physician 39*(1/2), 24-29.

Blatz, D. J. (1981). Bilateral femoral and tibial shaft stress fractures in a runner. *The American Journal of Sports Medicine, 9*(5), 322-325.

Blickenstaff, L. D., & Morris, J. M. (1966). Fatigue fracture of the femoral neck. *Journal of Bone and Joint Surgery, 48*(6), 1031-1047.

Boam, D., Miser, W. F., Yuill, S. C., Delaplain, C. B., Gayle, E. L., & MacDonald, D. C. (1996). Comparison of ultrasound examination with bone scintiscan in the diagnosis of stress fractures. *Journal of the American Board of Family Medicine, 9*(6), 414-417.

Boden, B. P., Osbahr, D. C., & Jimenez, C. (2001). Low-risk stress fractures. *American Journal of Epidemiology, 29*, 100-111.

Bodner, G., Stockl, B., Fierlinger, A., Schocke, M., & Bernathova, M. (2005). Sonographic findings in stress fractures of the lower limb: preliminary findings. *European Radiology, 15*, 356-359.

Bradshaw, C., Hislop, M., & Hutchinson, M. (2006). Shin pain. In P. Brukner & K. Khan (Eds.), *Clinical sports medicine* (3rd ed., Vol. 3E, p. 555-577). North Ryde, N.S.W. : McGraw-Hill Professional.

Bradshaw, C., Khan, K., & Brukner, P. (1996). Stress fracture of the body of the talus in athletes demonstrated with computer tomography. *Clinical Journal of Sport Medicine, 6*(1), 48-51.

Brahms, M. A., Fumich, R. M., & Ippolito, V. D. (1980). Atypical stress fracture of the tibia in a professional athlete. *The American Journal for Sports Medicine, 8*(2), 131-132.

Brock, G. R., Kim, G., Ingraffea, A. R., Andrews, J. C., Pianetta, P., & van der Meulen, M. C. H. (2013). Nanoscale examination of microdamage in sheep cortical bone using synchrotron radiation transmission x-ray microscopy. *PLoS ONE, 8*(3), 1-8.

Brudvig, T. J., Gudger, T. D., & Obermeyer, L. (1983). Stress fractures in 295 trainees: a one-year study of incidence as related to age, sex, and race. *Military Medicine, 148*(8), 666-667.

Brukner, P. (2000). Exercise-related lower leg pain: bone. *Medicine & Science in Sports & Exercise, 32*(2), s315-s326.

Brukner, P., Bennell, K. L., & Matheson, G. (1999). *Stress fractures* (1 ed.). Victoria: Blackwell Science.

Brukner, P., Bradshaw, C., & Bennell, K. L. (1998). Managing common stress fractures: let risk level guide treatment. *The Physician and Sportsmedicine, 26*(8), 39-48.

Brunet, M. E., Cook, S. D., Brinker, M. R., & Dickinson, J. A. (1990). A survey of running injuries in 1505 competitive and recreational runners. *The Journal of Sports Medicine and Physical Fitness, 30*(3), 307-315.

Bryant, L. R., Song, W. S., Banks, K. P., Bui-Mansfield, L. T., & Bradley, Y. C. (2008). Comparison of planar scintigraphy alone and with SPECT for the initial evaluation of femoral neck stress fracture. *American Journal of Roentgenology, 191*(4), 1010-1015.

Buckwater, J. A., Glimcher, M. J., Cooper, R. R., & Recker, R. (1995). Bone biology. *Journal of Bone and Joint Surgery 77-A*, 1256-1275.

Burrows, H. J. (1948). Fatigue fractures of the fibula. *Journal of Bone & Joint Surgery, British Volume, 30*(2), 266-279.

Butler, J. E., Brown, S. L., & McConnell, B. G. (1982). Subtrochanteric Stress Fractures in Runners. *The American Journal of Sports Medicine, 10*(4), 228-232.

Carlson, G. D., & Wertz, F. (1944). March fracture, including others than those of the foot. *Radiology, 43*(1), 48-54.

Carmont, M. R., Mei-Dan, M., & Bennell, K. (2009). Stress fracture management: Current classification and new healing modalities. *Operative Techniques in Sports Medicine, 17*(2), 81-89.

Caruso, G., Lagalla, R., Derchi, L., Lovane, A., & Sanfilippo, A. (2000). Monitoring of fracture calluses with color doppler sonography. *Journal of Clinical Ultrasound, 28*(1), 20–27.

Chisin, R., Peyser, A., & Milgrom, C. (1995). Bone scintigraphy in the assessment of the hallucal sesamoids. *Foot and ankle international, 16*(5), 291-294.

Chung, M., Dahabreh, I. J., Hadar, N., Ratichek, S. J., Gaylor, J. M., & Trikalinos, T. A. (2011). Emerging MRI technologies for imaging musculoskeletal disorders under loading stress. *Annals of Internal Medicine, 155*(9), 616-624.

Clement, D. B., Anmmann, W., Taunton, J. E., Lloyd-Smith, R., Jesperson, D., McKay, H., . . . Matheson, G. O. (1993). Exercise-induced stress injuries to the femur. *Internation Journal of Sports Medicine, 14*, 347-352.

Cochrane-Collaboration. (2013). The Cochrane Collaboration. Retrieved 13 May 2013 from http://www.cochrane.org/about-us

Constantini, N., Finestone, A. S., Hod, N., Shub, I., Heinemann, S., Foldes, A. J., & Mann, G. (2010). Equipment modification is associated with fewer stress fractures in female israel border police recruits. *Military Medicine, 175*(10), 799-804.

Cosman, F., Ruffing, J., Zion, M., Uhorchak, J., Ralston, S., Tendy, S., . . . Nieves, J. (2013). Determinants of stress fracture risk in United States military academy cadets. *Bone, 55*(2), 359-366.

Cowan, D. N., Bedno, S. A., Urban, N., Lee, D. S., & Niebuhr, D. W. (2012). Step test performance and risk of stress fractures among female army trainees. *American Journal of Preventive Medicine, 42*(6), 620-624.

Crossley, K., Bennell, K. L., Wrigley, T., & Oakes, B. W. (1999). Ground reaction forces, bone characteristics, and tibial stress fracture in male runners. *Medicine & Science in Sports & Exercise, 31*(8), 1088-1093.

Daffner, R. H., & Pavlov, H. (1992). Stress fractures: current concepts. *American Journal of Roentgenology, 159*(2), 245-152.

Darby, R. E. (1967). Stress fractures of the os calcis. *Journal of the American Medical Association, 200*(13), 131-132.

Datir, A. P., Saini, A., Connell, A., & Saifuddin, A. (2007). Stress-related bone injuires with emphasis on MRI. *Clinical Radiology, 62*(9), 828-836.

DeLacerda, F. G. (1981). A case study: application of ultrasound to determine a stress fracture of the fibula. *The Journal of Orthopaedic and Sports Physical Therapy, 2*(3), 134-136.

Devas, M. B. (1963). Stress fractures in children., 45, 528-541. *Journal of Bone & Joint Surgery, British Volume, 45B*(3), 528-541.

Devas, M. B. (1965). Stress fractures of the femoral neck. *Journal of bone and Joint Surgery, British Volume, 47*(4), 728–738.

Devas, M. B., & Sweetnam, R. (1956). Stress fractures of the fibula; a review of fifty cases in athletes. *Journal of Bone and Joint Surgery, British Volume, 38-B*(4), 818-829.

Dixon, M., & Fricker, P. (1993). Injuries to elite gymnasts over 10 years. *Medicine & Science in Sports & Exercise, 25*(12), 1322-1329.

Dobrindt, O., Hoffmeyer, B., Ruf, J., Seidensticker, M., Steffen, I. G., Zarva, A., . . . Amthauer, H. (2012). MRI verse bone scitigraphy-Evalustion for diagnosis and grading for stress fractures. *Nuklearmedizin, 51*(3), 88-94.

Dowey, K. E., & Moore, G. W. (1984). Stress fractures in athletes. *Ulster Medical Journal, 53*(2), 121-124.

Dugowson, C. E., Drinkwater, B. L., & Clark, J. M. (1991). Nontraumatic femur fracture in an oligomenorrheic athlete. *Medicine and Science in Sports and Exercise, 23*(12), 1323-1325.

Egger, M., Smith, G. D., & O'Rourke, K. (2001). *Rationale, potentials, and promise of systematice reviews.* (2nd ed.). London: BMJ Books.

Einstein, A. J., Henzlova, M. J., & Rajagopalan, S. (2007). Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. *Journal of American Medical Association, 298*(3), 317-323.

Ekenman, I., Hassmen, P., Koivula, N., Rolf, C., & Fellander-Tsai, L. (2001). Stress fractues of the tibia: can personality traits help us detect the injury-prone athlete? *Scandanavian Journal of Medicine and Science in Sports, 11(2)*, 87-95.

Elias, I., Zoga, A. C., Raikin, J. S. M., Peterson, J. R., Besser, M. P., Morrison, W. B., & Schweitzer, M. E. (2008). Bone stress injury of the ankle in professional ballet dancers seen on MRI. *BMC - Musculoskeletal Disorders, 9*(39), 1-6.

Engber, W. D. (1977). Stress fractures of the medial tibial plateau. *The Journal of Bone & Joint Surgery (American), 59*(6), 767-769.

Euclid, S. (2008). *Computer tomography: physical principles, clinical applications and quality control.* (3 ed.). Missouri: Saunders Elsevier.

Evans, D. (2003). Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. *Journal of Clinical Nursing 12*(1), 77-84.

Evans, F. G., & Riolo, M. L. (1970). Relations between the fatigue life and the histology of the adult human cortical bone. *Journal of Bone and Joint Surgery, 52A(8)*, 1579-1586.

Farkash, U., Naftal, J., Deranza, E., & Blankstein, A. (2008). Ultrasound as a diagnostic modality of tibial stress fractures. *Journal of Musculoskeletal Research, 11*(2), 55-61.

Feydy, A., Drape, E., Beret, E., Sarazin, L., Pessis, E., Minoui, A., & Chevrot, A. (1998). Longitudinal stress fractures of the tibia: comparative study of CT and MR imaging. *European Radiology, 8(4)*, 598-602.

Fields, K. B., Delaney, M., & Hinkle, J. S. (1990). A prospective study of type A behavior and running injuries. *The Journal of Family Practice, 30*(4), 425-429.

Finestone, A., Milgrom, C., Evans, R., Yanovich, R., Constantini, N., & Moran, D. S. (2008). Overuse injuries in female infantry recruits during low-intensity basic training. *Medicine & Science in Sports & Exercise, 40*(11), S630-S635.

Fitch, K. D., Blackwell, J. B., & Gilmour, W. N. (1989). Operation for non-union of stress fracture of the tarsal navicular. *Journal of Bone & Joint Surgery, British Volume, 71*(1), 105-110.

Franklyn, M., Oakes, B., Field, B., Wells, P., & Morgan, D. (2008). Section modulus is the optimum geometric predictor for stress fractures and medical tibial stress syndrome in both male and female atletes. *The American Journal for Sports Medicine, 36*(6), 1179-1189.

Fredericson, M., Bergman, A. G., Hoffman, K., & Dillingham, M. S. (1995). Tibial stress reaction in runners - correlation of clinical symptoms and scintigraphy with a new magnetic resonance imaging grading system. *The American Journal of Sports Medicine, 23*(4), 472-481.

Fredericson, M., Jang, K. U., Bergman, A. G., & Gold, G. E. (2004). Femoral diaphyseal stress fractures: results of systematic bone scan and magnetic resonance imaging evaluation in 25 runners. *Physical Therapy in Sport, 5(4)*, 188-193.

Fredericson, M., Jennings, F., Beaulieu, C., & Matheson, G. O. (2006). Stress fractures in athletes. *Topics in Magnetic Resonance Imaging, 17*(5), 309-325.

Freund, W., Weber, F., Billich, C., & Schuetz, U. H. (2012). The foot in multistage ultra-marathon runners: experience in a cohort study of 22 participants of the Trans Europe Footrace Project with mobile MRI. *BMJ Open, 2*(3), 1-8.

Friberg, O. (1982). Leg length asymmetry in stress fractures - A clinical and radiological study. *Journal of Sports Medicine and Physical Fitness, 22*(4), 485-488.

Frost, H. M. (1994). Wolff's Law and bone's structural adaptions to mechanical usage: an overview for clinicans. *The Angle Orthodontist, 64*(3), 175-188.

Fullerton, L. R., & Snowdy, H. A. (1988). Femoral neck stress fractures. *The American Journal for Sports Medicine, 16*(4), 365-377.

Fyhrie, D. P., Milgrom, C., Hoshaw, S. J., Simkin, A., Dar, S., Drumb, D., & Burr, D. B. (1998). Effect of fatiguing exercise on longitudinal bone strain as related to stress fracture in humans. *Annals of Biomedical Engineering, 26(4)*, 660-665.

Gaeta, M., Minutoli, F., Scribano, E., Ascenti, G., Vinci, S., Brushetta, D., . . . Blandino, A. (2005). CT and MR imaging findings in athletes with early tibial stress injuries: comparison with bone scintigraphy findings and emphasis on cortical abnormalities. *Radiology, 235*, 553-561.

Geslien, G. E., Thrall, J. H., & Espinosa, J. L. (1976). Early detection of stress fractures using 99m Tc-polyphosphate. *Radiology, 121(3)*, 683-687.

Giladi, M., Ahronson, Z., Stein, M., Danon, Y. L., & Milgrom, C. (1985). Unusual distribution and onset of stress fractures in soldiers. *Clinical orthopaedics and related research,* (192), 142-146.

Giladi, M., Milgrom, C., Simkin, A., & Danon, Y. (1991). Stress fractures identifiable risk factors. *The American Journal of Sports Medicine, 19*(6), 647-652.

Gilbert, R. S., & Johnson, H. A. (1966). Stress fractures in military recruits - A review of twelve years' experience. *Military Medicine, 131*(8), 716-721.

Givon, U., Friedman, E., Reiner, A., Vered, I., Finestone, A., & Shemer, J. (2000). Stress fractures in the Israeli defense forces from 1995 to 1996. *Clinical Orthopaedics & Related Research, 373*, 227-232.

Gofrit, O. N., & Livneh, A. (1994). Stress fractures of bone in conscripted infantry recruits: lack of correlation to pre-army physical fitness. *Military Medicine, 159*(4), 339-341.

Greaney, R. B., Gerber, F. H., Kmet, J. P., Metz, C. D., Kilcheski, T. S., Rama Rao, B., & Silverman, E. D. (1983). Distribution and natural history of stress fractures in U.S. marine recruits. *Radiology, 146*(2), 339-346.

Greenhalgh, T. (1997). How to read a paper: Papers that summarise other papers (systematic reviews and meta-analyses). *BMJ 315*(672), 672-675.

Groshar, D., Lam, M., Even-Sapir, E., Israel, O., & Front, D. (1985). Stress fractures and bone pain: are they closely associated? *Injury, 16*(8), 526-528.

Hadid, A., Evans, R. K., Yanovich, R., Luria, O., & Moran, D. S. (2008). Motivation, cohesion, satisfaction and their relation to stress fracture among female military recruits. *European Journal of Applied Physiology, 104*, 329-335.

Hallel, T., Amit, S., & Segal, D. (1976). Fatigue fractures of tibial and femoral shaft in soldiers. *Clinical Orthopaedics & Related Research, 118*, 35-43.

Hamilton, H. K. (1984). Stress fracture of the diaphysis of the ulna in a body builder. *The American Journal for Sports Medicine, 12*(5), 405-406.

Harolds, J. A. (1981). Fatigue fractures of the medial tibial plateau. *Southern Medical Journal, 74*(5), 578-581.

Hartley, J. B. (1943). "Stress" or "fatigue" fractures of bone. *British Journal of Radiology 16*, 255-262.

Heymann, D., & Roussellem, A. V. (2000). gp130 Cytokine family and bone cells. *Cytokine 12*(10), 1455-1468.

Hickey, G. J., Fricker, P. A., & McDonald, W. A. (1997). Injuries to elite rowers over a 10-year period. *Medicine & Science in Sports & Exercise, 29*(12), 1567-1572.

Hill, P. F., Chatterji, S., Chambers, D., & Keeling, J. D. (1996). Stess fractures of the pubic ramus in female recruits. *The Journal of Bone & Joint Surgery, British Volume, 78B*(3), 383-386.

Hod, N., Ashkenazi, I., Levi, Y., Fire, G., Drori, M., Cohen, I., . . . Horne, T. (2006). Characteristics of skeletal stress fractures in female military recruits of the Israel defense forces on bone scintigraphy. *Clinical Nuclear Medicine, 31*(12), 742-749.

Hodler, J., Steinert, H., Zanetti, M., Frolicher, U., Rogala, J., Stumpe, K., & Von Schulthess, G. K. (1998). Radiologically negative stress-related bone injury - MR imaging versus two-phase bone scintigraphy. *ACTA Radiologica, 39*(4), 416-420.

Hofer, M. (2013). *Ultrasound Teaching Manual, 3rd Edition: The Basics of Performing and Interpreting Ultrasound Scans.* (3 ed.). Stuttgart: Thieme Publishers.

Hoffman, J. R., Chapnik, L., Shamis, A., Givon, U., & Davidson, B. (1999). The effect of leg strength on the incidence of lower extremity overuse injuries during military training. *Military Medicine, 164*(2), 153-156.

Hounsfield, G. N. (1973). Computer transverse axial scanning (tomography). *British Journal of Radiology, 46*, 1016-1022.

Hulkko, A., & Orava, S. (1987). Stress fractures in athletes. *International Journal of Sports Medicine, 8(3)*, 221-226.

Hunter, L. Y. (1981). Stress fracture of the tarsal navicular - More frequent than we realize? *American Journal of Sports Medicine, 9*(4), 217-219.

Iba, K., Wada, T., Takada, J., & Yamashita, T. (2003). Multiple insufficiency fractures with severe osteoporosis. *Journal of Orthopaedic Science, 8*(5), 717–720.

Ishibashi, Y., Okamura, Y., Otsuka, H., Nishizawa, K., Sasaki, T., & Toh, S. (2002). Comparison of scintigraphy and magetic resonance imaging for stress of bone. *Clinical Journal of Sport Medicine, 12*(2), 79-84.

Itskoviz, D., Marom, T., & Ostfeld, I. (2011). Trends of stress fracture prevalence among Israel defense forces basic trainees. *Military Medicine, 176*(1), 56-59.

Iwamoto, J., & Takeda, T. (2003). Stress fractures in athelets: review of 196 cases. *Journal of Orthopaedic Science 8*(3), 273-278.

Jacques, R. (2012). *Medical screening for the developing athlete - a guide.* Paper presented at the UK sport performance pathway masterclass, Bisham Abbey.

Johnson, W., Weiss, C. B., & Wheeler, D. L. (1994). Sress fractures of the femoral shaft in athletes - more common than expected. A new clinical test. *The American Journal for Sports Medicine, 22*(2), 228-256.

Jones, B. H., Bovee, M. W., Harris, J., & Cowan, D. N. (1993). Intrinsic risk factors for excerise-related injuries among male and female army trainees. *American Journal of Sports Medicine 21*(5), 705-710.

Jones, B. H., Harris, J., Vinh, T., & Clint, R. (1989). Exercise-induced stress fractures and stress reactions of bone: epidemiology, etiology, and classification. *Exercise & Sport Sciences Reviews, 17*(1), 379-422.

Jones, B. H., & Knapik, J. J. (1999). Physical training and exercise-related injuries. *Sports Medicine, 27*(2), 111-125.

Jones, S. L., & Philips, M. (2010). Early identification of foot and lower limb stress fractures using diagnostic ultrasonography: a review of three cases. *The Foot and Ankle Online Journal, 3*(4), 1-6.

Joshi, A., Shah, B. C., Chand, P., Thapa, B. B., & Kayastha, N. (2009). Femoral neck stress fractures in military personnel. *Journal of Nepal Medical Association, 48*(174), 99-102.

Kaeding, C. C., Yu, J. R., Wright, R., Amendola, A., & Spindler, K. P. (2005). Management and return to play of stress fractures. *Clinical Journal of Sport Medicine, 15*(6), 442-447.

Kaltsas, D.-S. (1981). Stress fractures of the femoral neck in young adults. *Journal of Bone & Joint Surgery, British Volume, 63*(1), 33-37.

Kang, L., Belcher, D., & Hulstyn, M. J. (2005). Stress fractures of the femoral shaft in women's college lacrosse: a report of seven cases and a review of the literature. *British Journal Sports Medicine, 39*(12), 902-906.

Kanstrup, I. L. (1997). Bone scintigraphy in sports medicine: a review. *Scandanavian Journal of Medicine and Science in Sports, 7*(6), 322-330.

Khan, M., Fuller, P. J., Brukner, P. D., Kearney, C., & Burry, H. C. (1992). Outcome of conservative and surgical management of navicular stress fracture in athletes - eighty-six cases proven with computerized tomography. *The American Journal for Sports Medicine, 20*(6), 657-666.

Kiely, J. (2011). Planning for physical performance: the individual perspective. In D. Collins, A. Button & H. Richards (Eds.), *Performance Psychology A Practitioner's Guide*, p. 139-160. London: Churchill Livingstone Elsevier.

Kijowski, R., Choi, J., Shinki, K., Munoz, A., Rio, D., & de Smet, A. (2012). Validation of MRI classification system for tibial stress injuries. *Musculoskeletal Imaging, 198*(4), 878 - 884.

Kini, U., & Nandeesh, B. N. (2012). Physiology of bone formation, remodeling, and metabolism. . In I. Fogelman, G. Gnanasegaran & H. Van der Wall (Eds.), *Radionuclide and Hybrid Bone Imaging* (p. 29-57). Berlin: Springer Berlin Heidelberg.

Kiuru, M. J., Niva, M., Reponen, A., & Pihlajamaki, H. K. (2005). Bone stress injuires in asymptomatic elite recruits: A clinical and magnetic resonance imaging study. *The American Orthopaedic Society for Sports Medicine 33*(2), 272-276.

Kiuru, M. J., Pihlajamaki, H. K., & Ahovuo, J. A. (2003). Fatigue stress injuries of the pelvic bones and proximal femur: evaluation with MR imaging. *European Radiology, 13*(3), 605-611.

Kiuru, M. J., Pihlajamaki, H. K., & Ahovuo, J. A. (2004). Bone stress injuires. *ACTA Radiologica, 45*(3), 317-326.

Kiuru, M. J., Pihlajamaki, H. K., Hietanen, H. J., & Ahovuo, J. A. (2002). MR imaging, bone scintigraphy and radiography in bone stress injuries of the pelvis and the lower extremity. *Acta Radiologica, 43*(2), 207–212.

Kiuru, M. J., Pihlajamaki, H. K., Perkio, J. P., & Ahovuo, J. A. (2001). Dynamic contrast-enhanced MR imaging in symtpmatic bone stress of the pelvis and the lower extremity. *ACTA Radiologica, 42*(3), 277-285.

Knapp, T. P., & Garrett, W. E. (1997). Stress fractures: general concepts. *Clinics in Sports Medicine, 16*(2), 339–356.

Koenig, S., Toth, A., & Bosco, J. A. (2008). Stress fractures and `stress reactions of the diaphyseal femur in collegiate athletes: An Analysis of 25 Case. *American Journal of Orthopdics 37*(9), 476-480.

Korpelainen, K., Orava, S., Karpakka, J., Siira, P., & Hulkko, A. (2001). Risk factors for recurrent stress fractures in athletes. *The American Journal for Sports Medicine, 29*(3), 304-310.

Kowal, D. M. (1980). Nature and causes of injuries in women resulting from an endurance training program. *The American Journal of Sports Medicine, 8*(4), 265-269.

Kuusela, T. V. (1984). Incidence of bone lesions in the lower extremities during endurance training. *Annals of Clinical Research, 40*(16), 17-19.

Kwek, E. B. K., Goh, S. K., Koh, J. S. B., Png, M. A., & Howe, T. S. (2008). An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? *Injury, 39*(2), 224-231.

Lang, T. A. (2004). The value of systematic reviews as research activities in medical education. *Academic Medicine, 79*(11), 1067–1072.

Lappe, J., Cullen, D., Haynatzki, G., Recker, R., Ahlf, R., & Thompson, K. (2008). Calcium and vitamin D supplementation decreases incidence of stress fractures in female navy recruits. *Journal of Bone and Mineral Research, 23*(5), 741-749.

Lappe, J. M., Stegman, M. R., & Recker, R. R. (2001). The impact of lifestyle factors on stress fractures in female army recruits. *Osteoporos International, 12*(1), 35-42.

Law, M. R., & Hackshaw, A. K. (1997). A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. *BMJ, 315*(7112), 841-846.

Lazzarini, K., Troiano, R. N., & Smith, R. C. (1997). Can running cause the appearance of marrow edema on MR images of the foot and ankle. *Radiology, 202*(2), 540-542.

Leabhart, J. W. (1959). Stress fractures of the calcaneus. *Journal of Bone and Joint Surgery, 41*(7), 1285-1290.

Lee, D. (2011). Stress fractures, active component, U.S. armed forces, 2004-2010. *Medical Surveillence Monthly Report - A Publication of the Armed Forces Health Surveillance Centre, 18*(5), 8-11.

Lee, J. C., Malara, F. A., Wood, T., Hoy, G., Saifuddin, A., & Connell, D. A. (2006). MRI of stress reaction of the distal humerus in elite tennis players. *American Journal of Roentgenology, 187*(4), 901-904.

Lesho, E. P. (1997). Can tuning forks replace bone scans for identification of tibial stress fractures? *Military Medicine, 162*(12), 802-803.

Lingg, G. M., Soltesz, I., Kessler, S., & Dreher, R. (1997). Insufficiency and stress fractures of the long bones occurring in patients with rheumatoid arthritis and other inflammatory diseases, with a contribution on the possibilities of computed tomography. *European Journal of Radiology 26*(1), 54–63.

Lohman, M., Kivisaari, A., Vehmas, T., Kallio, P., Malmivaara, A., & Kivisaari, L. (2001). MRI abnormalities of foot and ankle in asymptomatic, physically active individuals. *Skeletal Radiology, 30*(2), 61-66.

Lu, P. W., Briody, J. N., Ogle, G. D., Morley, K., Humphries, I. R., Allen, J., . . . Cowell, C. T. (1994). Bone mineral density of total body, spine, and femoral neck in children and young adults: a cross-sectional and longitudinal study. *Journal of Bone and Mineral Research 9*(9), 1451-1458.

Luchini, M. A., Sarokhan, A. J., & Micheli, L. J. (1980). Acute displaced femoral-shaft fractures in long-distance runners - Two Case Reports. *The Journal of Bone and Joint Surgery, 65*(5), 689-691.

Macera, C. A. (1992). Lower extremity injuries in runners: advances in prediction. *Sports Medicine, 13*(1), 50-57.

Major, N. (2006). Role of MRI in prevention of metatarsal stres fractures in collegiate basketball players. *American Journal of Roentgenology 186*(1), 255-258.

Major, N. M., & Helms, C. A. (2002). MR imaging of the knee: findings in asymptomatic collegiate basketball players. *American Journal of Roentgenology*, *179*(3), 641-644.

Markey, K. L. (1987). Stress fractures. *Clinical Sports Medicine, 6*(2), 405-425.

Martin, A. D., & McCulloch, R. G. (1987). Bone dynamic stress, strain and fracture. *Journal of Sports Science, 5*(2), 155-163.

Matheson, G. O., Clement, D. B., McKenzie, D. C., Taunton, J. E., Lloyd-Smith, D. R., & Macintyre, J. G. (1987b). Stress fractures in athletes - a study if 320 cases. *The American Journal for Sports Medicine, 15*(1), 46-58.

Matheson, G. O., Clement, D. B., McKenzie, J. E., Taunton, D. R., Lloyd-Smith, D. R., & Macintyre, J. G. (1987a). Scinigraphic uptake of 99m tc at non-painful sites in athletes with stress fractures - the concept of bone strain. *Sports Medicine, 4*(1), 65-75.

McBryde, A. M. (1976). Stress fractures in athletes. *American Journal of Sports Medicine, 3*(5), 212-217.

McKay, G. A., & Banister, E. W. (1976). A comparison of maximum oxygen uptake determination by bicycle ergometry at various pedaling frequencies and by treadmill running at various speeds. *European Journal of Applied Physiology and Occupational Physiology, 35*(3), 191-200.

McPhee, H. R., & Montanye Franklin, C. (1946). March fracture of the fibula in athletes. *Journal of the American Medical Association, 131* (7), 574-576.

McRobbie, D. W., Moore, E. A., Graves, M. J., & Prince, M. P. (2007). *MRI From Picture to Proton* (2nd ed.). Cambridge: Cambridge University Press.

Meurman, K. O. A., & Elfving, S. (1980a). Stress fracture in soliders: A multifocal bone disorder- a comparative radiological and scintigraphy study. *Radiology, 134*, 483-487.

Meurman, K. O., & Elfving, S. (1980b). Stress fracture of the cuneiform bones. *The British Journal Of Radiology, 53*(626), 157-160.

Milgrom, C. (1989). The Israeli elite infantry recruit: a model for understanding the biomechanics of stress fractures. *Journal of the Royal College of Surgeons of Edinburgh 34*(6), 18-22.

Milgrom, C., Finestone, A., Shlamkovitch, N., Rand, N., Lev, B., Simkin, A., & Wiener, M. (1994). Youth is a risk factor for stress fracture. A study of 783 infantry recruits. *Journal of Bone and Joint Surgery, 76*(1), 20-22.

Milgrom, C., Giladi, M., Chisin, R., & Dizian, R. (1985c). The long term follow-up of soldiers with stress fractures. *The American Journal of Sports Medicine, 13*(6), 398-400.

Milgrom, C., Giladi, M., Stein, M., Kashtan, H., Margulies, J. Y., Chisin, R., . . . Aharonson, Z. (1985a). Stress fractures in military recruits- a prospective study showing an unusually high incidence. *Journal of Bone and Joint Surgery, 67b*(5), 732-735.

Milgrom, C., Simkin, A., Eldad, A., Nyska, M., & Finestone, A. (2000). Using bone's adaptation ability to lower the incidence of stress fractures. *The American Journal of Sports Medicine, 28*(2), 245-251.

Milgrom, C. M. D., Chisin, R. M. D., Giladi, M. M. D., Stein, M. M. D., Kashtan, H. M. D., Margulies, J. M. D., & Atlan, H. M. D. (1985b). Multiple stress fractures - A Longitudinal Study of a Soldier with 13 Lesions. *Clinical Orthopaedics & Related Research, 192*, 174-179.

Miller, T., Kaeding, C. C., & Flanigan, D. (2011). The classification system of stress fractures: a systematic review. *The Physician and Sports Medicine, 39*(1), 93-100.

Moen, M. H., Tol, J. L., Weir, A., Steunbrink, M., & De Winter, T. C. (2009). Medial tibial stress syndrome – A critical review. *Sports Medicine, 39*(7), 523-546.

Moran, C. G., Evans, R., Arbel, Y., Luria, O., Hadid, A., Yanovich, R., . . . Finestone, A. S. (2013). Physical and psychological stressors linked with stress fractures in recruit training. *Scandinavian Journal of Medicine and Science in Sports 23*, 443–450.

Moran, C. G., Fairclough, J. A., & Evans, R. C. (1987). Stress fracture of the tarsal navicular. *British Journal of Radiology, 21*(1), 51.

Moran, D. S., Evans, R. K., & Hadad, E. (2008). Imaging of lower extremity stress fracture injuries. *Sports Medicine, 38*(4), 345-356.

Moran, D. S., Finestone, A. S., Arbel, Y., Shabshin, N., & Laor, A. (2012). A simplified model to predict stress fracture in young elite combat recruits. *Journal of Strength and Conditioning Research, 26*(9), 2585-2592.

Morris, J. M. (1968). Fatigue fractures. *California Medicine, 108*(4), 268-274.

Morrow, B. (2010). An overview of cohort study design and their advatges and disadvatges. *International Journal of Therapy and Rehabilition, 17*(10), 518-523.

Moss, A., & Mowat, A. G. (1983). Ultrasonic assessment of stress fractures. *BMJ, 286*, 1479-1480.

Mulrow, C. D. (1994). Systematic reviews: Rationale for systematic reviews. *BMJ, 309*, 597-599.

Murray, S. R., Reeder, M. T., Udermann, B. E., & Pettitt, R. W. (2006). High-risk stress fractures pathogenesis, evaluation, and treatment. *Comprehensive Therapy, 32*(1), 20-25.

Nattiv, A. (2000). Stress fractures and bone health in track and field athletes. *Journal of Scince and Medicine in Sport, 3*(3), 268-279.

Nielsen, M. B., Hansen, K., Holmer, P., & Dyrbye, M. (1991). Tibial periosteal reactions in soldiers - A scintigraphic study of 29 cases of lower leg pain. *ACTA Orthopaedica Scandinavica, 62*(6), 531-534.

Nikpoor, N. (2009). Scintigraphy of the musculoskeletal system In B. N. W. Weissman (Ed.), *Imaging of arthritis and metabolic bone disease.* (p. 17-33). Philidelphia: MosbyElsevier.

Niva, M., Kiuru, M. J., Haataja, R., & Pihlajamaki, H. K. (2005). Fatigue injuries of the femur. *The Journal of Bone and Joint Surgery, 87*(10), 1385-1390.

Niva, M., Mattila, V. M., Kiuru, M. J., & Pihlajamaki, H. K. (2009). Bone stress injuires are common in female military trainnes - a preliminary study. *Clinical Orthopaedics and Related Research, 11*(467), 2962-2969.

Nussbaum, A. R., Treves, S. T., & Micheli, L. (1988). Bone stress lesions in ballet dancers: scintigraphic assessment. *American Journal of Roentgenology, 150*(4), 851-855.

Orava, S., & Hulkko, A. (1988). Delayed unions and nonunions of stress fractures in athletes. *The American Journal of Sports Medicine, 16*(4), 378-382.

Orava, S., Puranen, J., & Ala-Ketola, L. (1978). Stress fractures caused by physical exercise. *Acta orthopaedica Scandinavica, 49*(1), 19-27.

Otis, C. L., Drinkwater, B., Johnson, M., Loucks, A., & Wilmore, J. (1997). The female athlete triad. *Medicine & Science in Sports & Exercise, 29*(5), i-ix.

Papalada, A., Malliaropoulos, N., Tsitas, K., Kiritsi, O., Padhiar, N., Buono, A. D., & Maffulli, N. (2012). Ultrasound as a primary evaluation tool of bone stress injuries in elitetrack and field athletes. *The American Journal for Sports Medicine, 40*(4), 915-919.

Pearce, A. I., Richards, R. G., Milz, S., Schneider, E., & Pearce, S. G. (2007). Animal models for implant biomaterial research in bone: A review. *European Cells and Materials 13*(1), 1-10.

Pegrum, J., Crisp, T., & Padhiar, N. (2012). Diagnosis and management of bone stress injuries of the lower limb in athletes. *BMJ,* 344(7854), 35-40.

Pester, S., & Smith, P. C. (1992). Stress fractures in the lower extermities of soliders in basic training *Orthopaedic Review 21*(3), 297-303.

Philipson, M. R., & Parker, P. J. (2009). Stress fractures. *Orthopedics and Trauma, 23*(2), 137-143.

Pihlajamäki, H. K., Ruohola, J.-P., Weckström, M., Kiuru, M. J., & Visuri, T. I. (2006b). Long-term outcome of undisplaced fatigue fractures of the femoral neck in young male adults. *Journal of Bone and Joint Surgery British Volume, 88*(12), 1574-1579.

Pihlajamäki, H. K., Ruohola, J. P., Kiuru, M. J., & Visuri, T. I. (2006a). Displaced femoral neck fatigue fractures in military recruits. *The Journal of Bone & Joint Surgery, 88*(9), 1989-1997.

Popovich, R. M., Gardner, J. W., Potter, R., Knapik, J. J., & Jones, B. H. (2000). The effect of rest from running on overuse injuries in Army basic training. *American Journal of Preventative Medicine, 18*(3), 147-155.

Pouilles, J. M., Bernard, J., Tremollieres, F., Louvet, J. P., & Ribot, C. (1989). Femoral bone density in young male adults with stress fractures. *Bone, 10*(2), 105-108.

Prather, J. L., Nusynowitz, M. L., Snowdy, H. A., Hughes, A. D., McCartney, W. H., & Bagg, R. J. (1977). Scintigraphic findings in stress fractures. *The Journal of Bone and Joint Surgery, 59-A*(7), 869-874.

Protzman, R. R., & Griffis, C. G. (1977). Stress fractures in men and women undergoing military training. *Journal of Bone & Joint Surgery 59*(6), 825-825.

Provost, R. A., & Morris, J. M. (1969). Fatigue fracture of the femoral shaft. *The Journal of Bone & Joint Surgery, 51*(3), 487-560.

Ranson, C. A., Burnett, A. F., & Kerslake, R. W. (2010). Injuries of the lower back in elite fast bowlers - Acute stress changes on MRI predict stress fracture. *The Journal of Bone and Joint Surgery, British Volume 92*(12), 1664-1668.

Rauh, M. J., Macera, C. A., Trone, D. W., Shaffer, R. A., & Brodine, S. K. (2006). Epidemiology of stress fracture and lower extremity overuse injury in female recruits *Medicine & Science in Sports & Exercise, 38*(9), 1571-1577.

Reeder, M. T., Dick, B. H., Atkins, J. K., Pribis, A. B., & Martinez, J. M. (1996). Stress fractures. Current concepts of diagnosis and treatment. *Sports Medicine, 22*(3), 198-212.

Reis, J. P., Trone, D. W., Macera, C. W., & Rauh, M. J. (2007). Factors associated with discharge during marine corps basic training. *Military Medicine, 172*(9), 936-941.

Rome, K., Handoll, H. H., & Ashford, R. L. (2005). Interventions for preventing and treating stress fractures and stress reactions of bone of the lower limbs in young adults. *Cochrane Database Systematic Review, 2*, 1-49.

Roub, L. W., Gumerman, L. W., Hanley, E. N., Jr., Clark, M. W., Goodman, M., & Herbert, D. L. (1979). Bone stress: a radionuclide imaging perspective. *Radiology, 132*(2), 431-438.

Ruohola, J. P., Kiuru, M. J., & Pihlajamaki, H. K. (2006). Fatigue bone injuries causing anterior lower leg pain. *Clinical Orthopaedics And Related Research, 444*, 216-223.

Rupani, H. D., Holder, L. E., Espinola, D. A., & Engin, S. I. (1985). Three-phase radionuclide bone imaging in sports medicine. *Radiology, 56*(1), 187-196.

Saladin, K. S., & Porth, C. M. (1998). Bone tissue. In K. S. Saladin (Ed.), *Anatomy and physiology - The unity of function and form* p. 225-251. Massachusetts: McGraw-Hill.

Salter, R. B. (1970). *Textbook of disorders and injuries of the musculoskeletal system*. Baltimore: Williams & wilkins.

Savoca, C. J. (1971). Stress fractures: A classification of the earliest radiographic signs. *Radiology, 100*(3), 519-524.

Schaffler, M. B., Radin, L., & Burr, D. B. (1989). Mechanical and morphological effects of strain rate on fatigue of compact bone. *Bone, 10*(3), 207-214.

Schmid, L., Pfirrmann, C. W. A., Hess, T., & Schlumpf, U. (1999). Bilateral fracture of the sacrum associated with pregnancy: A case report. *Osteoporos International, 10*(1), 91-93.

Schweitzer, M. E., & White, L. M. (1996). Does altered biomechanics cause marrow edema? *Radiology, 198*(3), 851-853.

Schwellnus, M. P., & Jordaan, G. (1992). Does calcium supplimentation prevent bone stress injuries? A clinical trial. *International Journal of Sports Nutrition 2*(2), 165-174.

Scott, S. J., Feltwell, D. N., Knapik, J. J., Barkley, C. B., Hauret, K. G., Bullock, S. H., & Evans, R. K. (2012). A multiple intervention strategy for reducing femoral neck stress injuries and other serious overuse injuries in U.S. Army Basic Combat Training. *Military Medicine, 177*(9), 1081-1089.

Scully, T. J., & Besterman, G. (1982). Stress fracture-a preventable training injury. *Military Medicine, 147*(4), 285-287.

Seeley, R. R., Stephens, T. D., & Tate, P. (2000). Skeletal system, bones and bone tissue. In R. R. Seeley, T. D. Stephens & P. Tate (Eds.), *Anatomy and Physiology* (6th ed.). New York: McGraw Hill.

Shaffer, R. A., Brodine, S. K., Almeida, S. A., Williams, K. M., & Ronagh, S. (1999). Use of simple measures of physical activity to predict stress fractures in young men undergoing a rigorous physical training program. *American Journal of Epidemiology, 149*(3), 236-242.

Shellock, F. (2010). *Reference Manual for Magnetic Resonance Safety, Implants, and Devices.* Los Angeles: Biomedical Research Publishing Company.

Shin, A. Y., Morin, W. D., Gorman, J. D., Jones, S. B., & Lapinsky, A. S. (1996). The superiority of magnetic resonance imaging in differentiating the cause of hip pain in endurance athletes. *The American Journal of Sports Medicine, 24*(2), 168-176.

Sirbu, A. B., & Palmer, A. M. (1942). March fractures: a report of fifteen cases. *California and Western Medicine, 57*(2), 123-127.

Slocum, K., Gorman, J. D., Puckett, M., & Jones, S. B. (1997). Resolution of abnormal MR signal intensity in patients with stress fractures of the femoral neck. *American Journal of Roentgenology, 168*(5), 1295-1299.

Smith, P. T. (2011). Discrepancies in clinical definitions of stress fractures: Implications for the United States Army. *Military Medicine, 176*(1), 60-66.

Sofka, C. (2006). Imaging of stress fractures. *Clinical Journal of Sport Medicine, 25*(1), 53-62.

Sopov, V., Liberson, A., & Groshar, D. (2000). Bone scintigraphic findings of os trigonum: a prospective study of 100 soldiers on active duty. *Foot & ankle international / American Orthopaedic Foot and Ankle Society [and] Swiss Foot and Ankle Society, 21*(10), 822-824.

Sormaala, M. J., Niva, M., Kiuru, M. J., Mattila, V. M., & Pihlajamaki, H. K. (2006). Outcomes of stress fractures of the talus. *The American Journal for Sports Medicine, 34*(11), 1809-1814.

Sormaala, M. J., Ruohola, J., Mattila, V. M., & Koskinen, S. K. (2011). Comparison of 1.5T and 3T MRI scanners in evaluation of acute bone stress in the foot. *BMC Musculoskeletal Disorders 12*(1), 128-134.

Stafford, S. A., Rosenthal, D. L., Gebhardt, M. C., Brady, T. J., & Scott, J. A. (1986). MRI in stress fracture - case report. *American Journal of Roentgenology, 147*(3), 553-556.

Steele, J. R., & Milburn, P. D. (1988). Effect of different synthetic sport surfaces on ground reaction forces at landing in netball. *International Journal of Sport Biomechanics, 4*(2), 130-145.

Stone, M. H., O'Bryant, H. S., Schilling, B. K., Johnson, R. L., Pierce, K. C., Haff, G. G., & Koch, A. J. (1999). Periodization: effects of manipulating volume and intensity. Part 1. *Strength & Conditioning Journal, 21*(2), 56.

Stoneham, M. D., Chir, M. B., & Morgan, N. V. (1991). Stress fractures of the hip in Royal Marine recruits under training: a retrospective analysis. *British Journal of Sports Medicine, 25*(4), 190-194.

Subcommittee on Body Composition, Nutrition and Health of Military Women, Committee on Military Nutrition Research, Institute of Medicine. (1998). *Reducing Stress Fracture in Physically Active Military Women* (p. 110).

Subramanian, G., & McAfee, J. G. (1971). A new complex of 99mtc for skeletal imaging. *Radiology, 99*(1), 192-196.

Sullivan, D., Warren, R. F., Pavlov, H., & Kelman, G. (1984). Stress fractures in 51 runners. *Clinical orthopaedics and related research, 187*, 188-192.

Sur, R. L., & Dahm, P. (2011). History of evidence-based medicine. *Indian Journal of Urology, 27*(4), 487–489.

Sweet, D. E., & Allman, R. M. (1971). Stress fracture RPC of the month from the AFIP. *Radiology, 99(*3), 687- 693.

Swissa, A., Milgrom, C., Giladi, M., Kashtan, H., Stein, M., Margulies, J., . . . Aharonson, Z. (1989). The effect of pretraining sports activity on the incidence of stress fractures among military recruits. A prospective study. *Clinical Orthopaedics and Related Research, 245*, 256-260.

Tappeniers, L., De Maeseneer, M., De Ridder, F., Machials, F., Shahabpour, M., Tebache, C., . . . Osteaux, M. (2003). Can bone marrow oedema be seen on STIR images of ankle and foot after 1 week of running? *European Journal of Radiology, 47*(1), 25-28.

Torg, J. S., Pavlov, H., Cooley, L. H., Bryant, M. H., Arnoczky, S. P., Bergfeld, J. A., & Hunter, L. Y. (1982). Stress fractures of the tarsal navicular. A retrospective review of twenty-one cases. *Journal of Bone & Joint Surgery, American Volume, 64*(5), 700-712.

Van der Wall, H., Lee, A., Magee, M., Frater, C., Wijesinghe, H., & Kannangara, S. (2010). Radionuclide bone scintigraphy in sports injuries. *Seminars in Nuclear Medicine, Skeletal Scintigraphy Update (Part II), 40*(1), 16–30.

Van Holsbeeck, M. T., & Introcaso, J. H. (2001). *Musculoskeletal Ultrasound* (2nd ed.). St. Louis: Mosby.

Vogler, J. B. r., & Murphy, W. A. (1988). Bone marrow imaging. *Radiology, 168*(3), 679-693.

Warren, M. P., & Shantha, S. (2000). The female athlete. *Best Practice & Research: Clinical Endocrinology & Metabolism, 14*(1), 37-53.

Weaver, J. B., & Franciso, C. B. (1940). Pseudofractures - A manifestation of non-suppurative osteomyelitis. *Journal of Bone and Joint Surgery, 22*(3), 610-615.

Weiss Kelly, A. K., & Hame, S. L. (2010). Managing stress fractures in athletes - The goal of diagnosis and treatment is speedy return to play. *The Journal of Musculoskeletal Medicine, 27*(12), 480-486.

Wen, D. Y., Propeck, T., & Singh, A. (2003). Femoral neck stress injury with negative bone scan. *The Journal of the American Board of Family Medicine, 16(2)*, 170-174.

Wilcox, J. R., Moniot, A. L., & Green, J. P. (1977). Bone scanning in the evaluation of exercise - related stress injuries. *Radiology, 123*(3), 699-703.

Wilson, E. S., & Katz, F. N. (1969). Stress Fracture - An analysis of 250 consecutive cases. *Radiology, 92*, 481-486.

Yanovich, R., Friedman, E., Milgrom, R., Oberman, B., Freedman, L., & Moran, D. S. (2012). Candidate gene analysis in Israeli soldiers with stress fractures. *Journal of Sports Science and Medicine 11*(1), 147-155.

Yao, L., Johnson, C., Gentili, A., Lee, J. K., & Seeger, L. L. (1998). Stress injuries of bone: analysis of mri imaging staging criteria. *Academic Radiology, 5*(1), 34-40.

Yildirim, M., Gursoy, R., Varoglu, E., Oztasyonar, Y., & Cogalgil, S. (2004). 99mTc-MDP bone SPECT in evaluation of the kneww in asymptomatic soccer players. *British Journal of Sports Medicine, 38*(1), 15-18.

Yoon, P. W., Yoo, J. J., Yoon, K. S., & Kim, H. J. (2012). Case report - multifocal subchondral stress fractures of the femoral heads and tibial condyles in a young military recruit. *Clinical Orthopaedics & Related Research, 470*(3), 944–949.

Zadpoor, A. A., & Nikooyan, A. A. (2011). The relationship between lower-extremity stress fractures and the ground reaction force: A systematic review. *Clinical Biomechanics 26*(1), 23-28.

Zubler, V., Mengiardi, B., Pfirrmann, C. W. A., Duc, S. R., Schmid, M. R., Hodler, J., & Zanetti, M. (2007). Bone marrow changes on stir mr images of asymptomatic feet and ankles. *European Journal of Radiology, 17*(12), 3066-3072.

Zwas, S. T., Elkanovitch, R., & Frank, G. (1987). Interpretation and classification of bone scintigraphic findings in stress fractures. *The Journal of Nuclear Medicine, 28*(4), 452-457.

Appendix One

Questions that should be included during a clinical examination

Question	Response
Was there an acute onset of pain?	Fractures and tendon ruptures are usually acute traumatic events. In athletes, the acute onset of pain may be preceded by low grade chronic pain of a stress fracture or tendinosis.
Is the pain chronic but stable?	Pain that is getting worse over time should raise concerns of a tumor.
Do you have a history of injury or prior leg pains?	Old fractures or injuries can lead to scar tissue, stiffness and pain.
Is the pain worse with impact?	Stress fractures are classically exacerbated with impact. Medial tibial periostitis and muscle strains may also be made worse with loading and resistance.
Is the pain worse with exertion?	Pain that is absent at rest but presents with exertion is classic for exertional compartment syndrome. However, popliteal artery entrapment can have a similar presentation, but with posterior rather than anterior/lateral pain.
Does the pain improve with warm-up and stretching?	Medial tibial periostitis and muscle strains will frequently improve with pre-exercise stretching, whereas stress fractures and exertional compartment syndrome will not.
Does the pain get worse with stretching or resistance?	Resistance given to the muscle tendon units, including their origins and insertions, should exacerbate the symptoms related to medial tibial periostitis and muscle tendon strains and tendinopathy.
Where is the pain? Is the pain focal? Is the pain diffuse?	The anatomical site of pain is the best physical clue to diagnosis. Focal pain over bone should raise suspicion of a stress fracture, focal pain over the muscle–tendon is likely to be a muscle strain or tendinopathy, diffuse pain over the posteromedial border of the tibia is likely to be medial tibial periostitis.
Do you have swelling with the pain? Is it diffuse? Is it focal?	Localized swelling is possible with a contusion, a stress fracture or muscle herniation. Diffuse swelling may indicate more significant injury, vascular problems such as deep venous thrombosis, or diffuse inflammatory problems such as medial tibial periostitis.
Do you feel electric shooting pain? Do you have weakness with the pain? Do you get numbness with the pain?	Electric shooting pain, dermatomal loss of sensation, and sclerotomal loss of motor power usually indicate nerve injury, entrapment or radiculopathy. Always check the lumbar spine.
Does the pain get better with ice or NSAIDs?	Pathologies associated with inflammation should improve with cryotherapy and anti-inflammatories. Osteoid osteomas (benign bone tumors) are known to have a significant response to aspirin (ASA).
Do you have pain at night?	Pain that wakes a patient up at night should raise concern about tumors.

(Bradshaw et al., 2006, p. 559).

Appendix Two

Paper Number	Study type		Author	Country	Year	Subjects	Different groups	Data for group	Age				Sample Size		
									Mean	SD	Min	Max	Total	Men	Women
1	Prospective	Cohort	Bergman et al	USA	2004	Endurance Athlete	NO		ND	ND	18	19	21	11	10
2	Retrospective	Case Study	Butler et al	USA	1982	Track & Field Athletes	NO		ND	ND	18	22	7	4	3
3	Prospective	Cohort	Giladi et al	Israel	1985	Military	NO		19	ND	18	23	86	86	0
4	Retrospective	Reviewed	Gofrit & Livneh	Israel	1994	Military	NO		ND	ND	18	19	1118	1118	0
5	Retrospective	Reviewed	Groshar	Israel	1985	Military	NO		19	ND	18	21	64	ND	ND
6	Prospective	Cohort	Hadid et al	Israel	2008	Military	NO		18.5	0.4	ND	ND	201	41	160
7	Retrospective	Reviewed	Harolds	USA	1981	Military	NO		ND	ND	ND	ND	ND	ND	0
8	Retrospective	Reviewed	Hod et al	Israel	2006	Military	NO		ND	ND	19	20.6	146	0	146
9	Retrospective	Reviewed	Kiuru	Finland	2003	Military	NO		20.7	ND	18	29	340	295	45
10	Prospective	Cohort	Kiuru	Finland	2005	Military	NO		19.6	ND	19	22	21	21	0
11	Prospective	Cohort	Lohman	Finland	2001	Marathon Runners	YES	CONTROL	45.9	ND	ND	ND	19	10	9
								EXPERIMENTAL	45	ND	27	58	19	10	9
12	Prospective	Cohort	Major & Helms	USA	2002	Basketball Players	NO		ND	ND	18+	ND	17	12	5
13	Prospective	Cohort	Major	USA	2006	Basketball Players	NO		20	ND	18	22	26	26	0
14	Retrospective	Reviewed	Matheson et al (a)	Canada	1987	Athlete	NO		ND	ND	ND	ND	320	145	175
15	Retrospective	Reviewed	Meurman & Elfving	Finland	1980	Military	NO		20.6	ND	ND	ND	42	ND	ND
16	Prospective	Cohort	Milgrom	Israel	1985	Military	NO		ND	ND	18	20	295	295	0
17	Retrospective	Reviewed	Niva et al	Finland	2005	Military	NO		20.4	ND	18	29	170	147	23
18	Prospective	Cohort	Niva et al	Finland	2009	Military	YES	FIRST SCAN	20.2	ND	19	28	10	0	10
								SECOND SCAN	20.9	ND	19	25	9	0	9
								THIRD SCAN	20.9	ND	19	25	9	0	9
19	Prospective	Cohort	Nielsen et al	Denmark	1991	Military	NO		ND	ND	ND	ND	22	22	0
20	Prospective	Cohort	Roub	USA	1979	Athlete	YES	EXPERIMENTAL	ND	ND	18	28	35	ND	ND
								CONTROL	ND	ND	ND	ND	13	ND	ND
21	Prospective	Cohort	Schweitzer	USA	1996	Civilians	YES	FIRST SCAN	30	ND	19	41	12	6	6
								SECOND SCAN	ND	ND	ND	ND	3	ND	ND
22	Prospective	Cohort	Shin	USA	1996	Military	NO		19.66	ND	18	30	19	19	0
23	Prospective	Cohort	Sopov	Israel	2000	Military	NO		20	0.5	ND	ND	100	98	2
24	Prospective	Cohort	Trappeniers	Belgium	2003	Civilians	YES	BEFORE	25.7	ND	22	30	10	8	2
								AFTER	25.7	ND	22	30	10	8	2
25	Prospective	Cohort	Yildirim	Turkey	2004	Athlete	NO		22.3	ND	19	31	42	21	21
26	Prospective	Cohort	Zubler	Switzerland	2007	Civilians	NO		ND	ND	22	83	78	37	41
27	Retrospective	Reviewed	Zwas	Israel	1987	Military	NO		20	ND	19	22	310	310	0

Paper Number	BSI Bone Scintography																						
	Number of subjects with Symptomatic BSI	Number of subjects with Asymptomatic BSI	Number of Subjects	Total number of BSI	Symptomatic										Asymptomatic									
					Number of BSI	Location									Number of BSI	Location								
						Tibia	Fibula	Femur	Tarsal	Metatarsal	Sesamoid	Patella	not stated	Other		Tibia	Fibula	Femur	Tarsal	Metatarsal	Sesamoid	Patella	not stated	Other
1																							
2	7	1	7	10	9			8		1					1			1					
3				0	0										0								
4	ND	ND	1118	196	ND			7							ND			28					
5	64	ND	64	124	92	69	3	15	2	3					32	14		17		1			
6	11	0	146	ND	ND	11									0								
7	ND	ND	18	30	ND										ND								
8	ND	ND	93	247	ND										ND								
9				0	0										0								
10				0	0										0								
11				0	0										0								
				0	0										0								
12				0	0										0								
13				0	0										0								
14	320	145	320	ND	0										289	146	22	22	73	26				
15	ND	19	42	109	73								73		36								36	
16				0	0										0								
17				0	0										0								
18				0	0										0								
19	17	4	22	29	24	24									5	5							
20	30	0	35	44	44	44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	1	13	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
21				0	0										0								
				0	0										0								
22	19	0	19	22	22			22							0								
23	ND	ND	100	31	10									10	21									21
24				0	0										0								
25	0	28	42	56	0										56	52		4					
26				0	0										0								
27	235		310	391	233								233		158								158	

Paper Number	BSI MRI																						
	Number of subjects with Symptomatic BSI	Number of subjects with Asymptomatic BSI	Number of Subjects	Total number of BSI	Symptomatic										Asymptomatic									
					Number of BSI	Location									Number of BSI	Location								
						Tibia	Fibula	Femur	Tarsal	Metatarsal	Sesamoid	Patella	not stated	Other		Tibia	Fibula	Femur	Tarsal	Metatarsal	Sesamoid	Patella	not stated	Other
1	0	10	21	14	0										14	14								
2					0										0									
3				0	0										0									
4				0	0										0									
5				0	0										0									
6	0	7	55	7	0										7	7								
7				0	0										0									
8																								
9	137	ND	340	174	ND										31			19						12
10	ND	ND	21	75	30	13		1	2	12				2	45	9		14	13	7				2
11	0	3	19	3	0										3								3	
	0	3	19	4	0										4		1						3	
12	0	ND	17	14	0										14								14	
13	0	ND	26	6	0										6					6				
14				0	0										0									
15				0	0										0									
16				0	0										0									
17	170	1	170	185	184			184							1			1						
18	7	8	10	30	16	6	1	7						2	14	1		13						
	3	8	9	22	3	1		2							19	6		13						
	3	9	9	38	5	2		2						1	33	16		17						
19				0	0										0									
20				0	0										0									
				0	0										0									
21	0	11	12	21	0										21	3		3	3	4				8
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22	13	1	19	15	14			14							1			1						
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24	0	3	10	3	0										3				2	1				
	0	5	10	13	0										13				12	1				
25				0	0										0									
26	0	28	78	ND	0										ND									
27				0	0										0									

Paper Number	BSI X Ray																						
	Number of subjects with Symptomatic BSI	Number of subjects with Asymptomatic BSI	Number of Subjects	Total number of BSI	Symptomatic										Asymptomatic									
					Number of BSI	Location									Number of BSI	Location								
						Tibia	Fibula	Femur	Tarsal	Metatarsal	Sesamoid	Patella	not stated	Other		Tibia	Fibula	Femur	Tarsal	Metatarsal	Sesamoid	Patella	not stated	Other
1				0	0										0									
2	7	0	7	7	7			7							0									
3	ND	ND	86	35	ND										ND									
4				0	0										0									
5				0	0										0									
6				0	0										0									
7	ND	ND	ND	101	ND										ND									
8			22	1	ND										ND									
9	ND	ND	215	36	ND										ND									
10				0	0										0									
11				0	0										0									
				0	0										0									
12				0	0										0									
13				0	0										0									
14			139	14	0										0									
15	ND	ND	42	54	41								41		13								13	
16				0	0										0									
17				0	0										0									
18				0	0										0									
				0	0										0									
				0	0										0									
19			22	13	13	13									0									
20	14	0	35	14	14	14									0									
	0	0	13	0	0										0									
21				0	0										0									
22			19	15	15			15							0									
23	ND	ND	22	ND	ND										ND									
24				0	0										0									
25				0	0										0									
26				0	0										0									
27				0	0										0									

Paper Number	Total	Total																				
	Total Number of subjects with BSI	Total number of fracture sites	Symptomatic										Asymptomatic									
			Number of fracture sites	Location									Number of fracture sites	Location								
				Tibia	Fibula	Femur	Tarsal	Metatarsal	Sesamoid	Patella	Not Stated	Other		Tibia	Fibula	Femur	Tarsal	Metatarsal	Sesamoid	Patella	Not Stated	Other
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2	7	10	9			8		1					1			1						
3	64	94	85	66	1	16		2					9	1		8						
4	95	196	ND			7							ND			28						
5	ND	124	92	69	3	15	2	3					32	14		17		1				
6	18	ND	ND										7								7	
7	9	30	ND										ND									
8	93	247	ND										ND									
9	137	174	ND										31			19						12
10	16	75	30	13		1	2	12				2	45	9		14	13	7				2
11	3	3	0										3								3	
	3	4	0										4		1						3	
12	ND	14	0										14								14	
13	ND	6	0										6					6				
14	320	ND	0										289	146	22	22	73	26				
15	39	109	73								73		36								36	
16	91	184	123	86		19					17		61	8		43					11	
17	170	185	184			184							1			1						
18	10	30	16	6	1	7						2	14	1		13						
	9	22	3	1		2							19	6		13						
	9	38	5	2		2						1	33	16		17						
19	ND	29	24	24									5	5								
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	1	1	0	0	0	0	0	0	0	0	0	0	1	1								
21	11	12	24	21									21	3		3	3	4				8
	1	3	1	1									1					1				
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23	22	27	10									10	17									17
24	3	3	0										3				2	1				
	5	13	0										13				12	1				
25	28	56	0										56	52		4						
26	28	ND	0										ND									
27	235	391	233								233		158								158	

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Figure 1: A graph depicting the 'bone strain continuum' and its relationship to pain and diagnostic findings (Bennell & Brunker, 2005, p. 175).

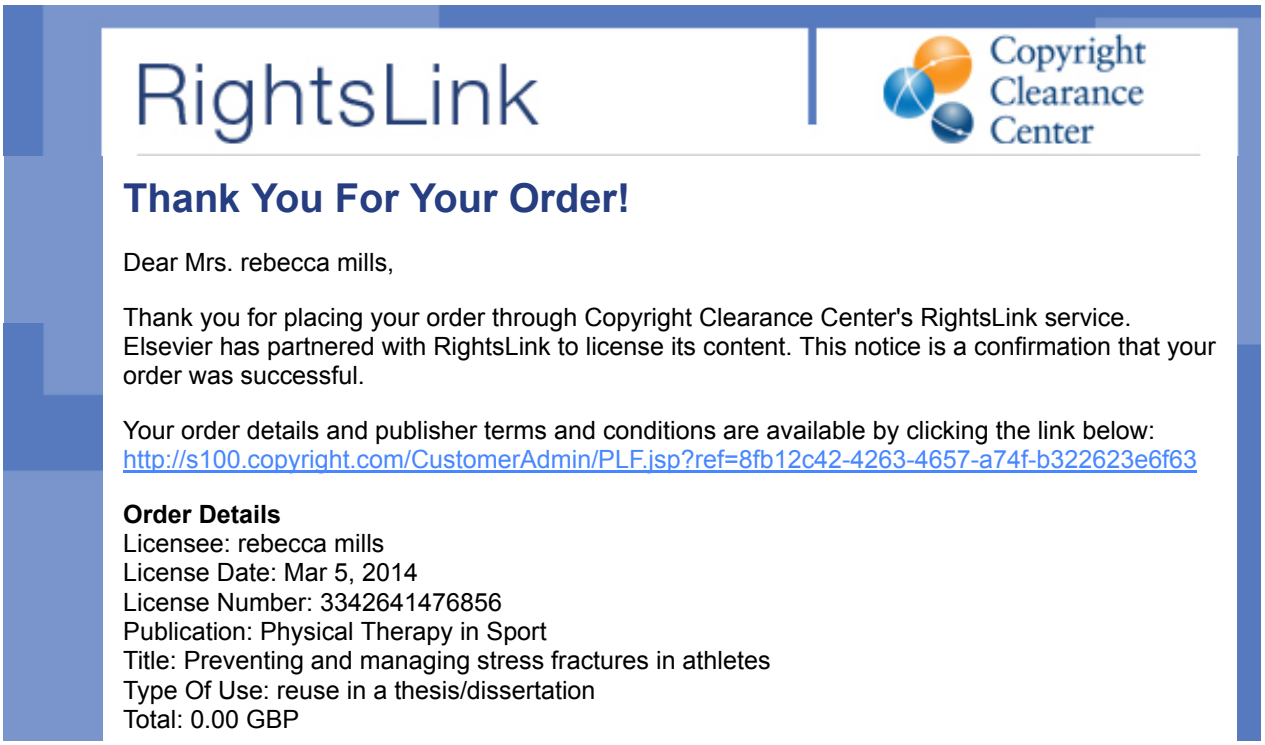

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Figure 2: An axial MRI T2 FS sequence illustrating a grade 2 asymptomatic BSI of a tibia.

(Bergman, Fredericson, Ho, & Matheson, 2004, p. 637).

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Figure 3: A diagram depicting the continuum of bone in response to varying levels of stress and its relation to pain and radionuclide images and radiographs

(Roub et al., 1979, p. 436).

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Figure 6
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Figure 4: A radiograph of stress fractures to the second and third metatarsal in a runner.

(Boden, Osbahr, & Jimenez, 2001, p. 109).

SAGE

Title: Low-Risk Stress Fractures:
Author: Barry P. Boden, Daryl C. Osbahr, Carlos Jimenez
Publication: American Journal of Sports Medicine
Publisher: SAGE Publications
Date: 01/01/2001
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Figure 5: An illustration of Osteogenic, Osteoblast and Osteocyte cells

(Saladin & Porth, 1998, p. 232).

Figure 6: A three dimensional illustration of the structure of compact bone

(Saladin & Porth, 1998, p. 235).

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Figure 7: An image depicting the composition of mature bone.

(Pegrum, Crisp, & Padhiar, 2012, p. 7).

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Figure 8: An illustration demonstrating the distribution of red and yellow bone marrow

(Vogler & Murphy, 1988, p. 680).

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Figure 9: A dynamic representation of two possible mechanisms for BSI development.

(Bennell et al., 1996b, p. 203).

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Figure 10: A schematic diagram to illustrate how cracks in bone arise and propagate with repetitive cyclical loading.

(Pegrum et al., 2012, p. 7).

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Figure 11: A photomicrograph of micro-damage to bone.

(Schaffler, Radin, & Burr, 1989, p. 12).

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Figure 12: A diagram demonstrating the continuum of BSI.

(Blackman, 2010, p. 25).

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Figure 13: A cross sectional sample of a tibial cortex with the characteristic appearance of a periosteal reaction.

(Sweet & Allman, 1971, p. 690).

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Figure 14: An x-ray taken from a cross sectional sample of a tibial cortex with multiple holes merging into a confluent lytic defect in the cortex.

(Sweet & Allman, 1971, p. 690).

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Figure 15: A microscopic image illustrating the radial streamers of periosteal new bone in contrast to circumferential lamellar of undisturbed bone cortex

(Sweet & Allman, 1971, p. 690).

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Figure 16: A graph demonstrating the fatigue curve in association to bone stress.

(Reeder et al., 1996, p. 201).

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Figure 17: A flowchart to illustrate the contribution of risk factors to BSI pathogenesis.

(Bennell et al., 1999, p.96).

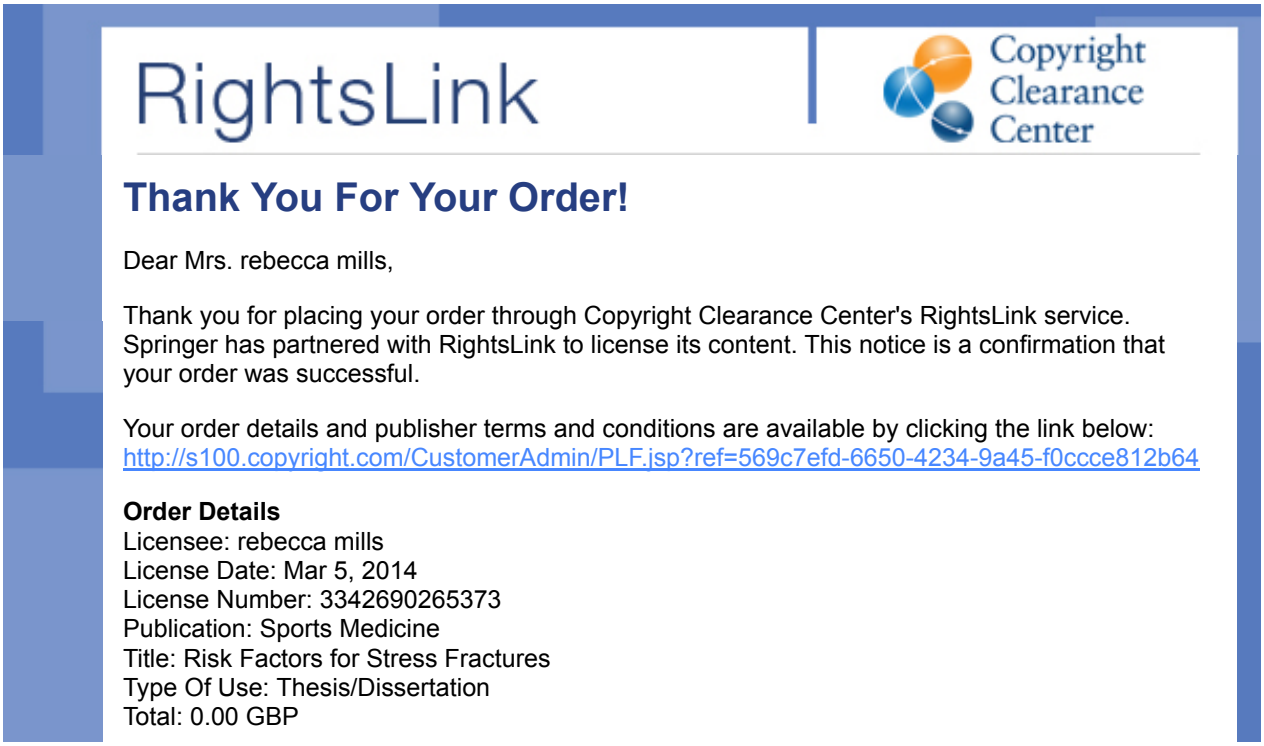

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Figure 18: A plain radiograph illustrating bilateral non-displaced BSI of the tibia.

(Yoon et al., 2012, p. 946).

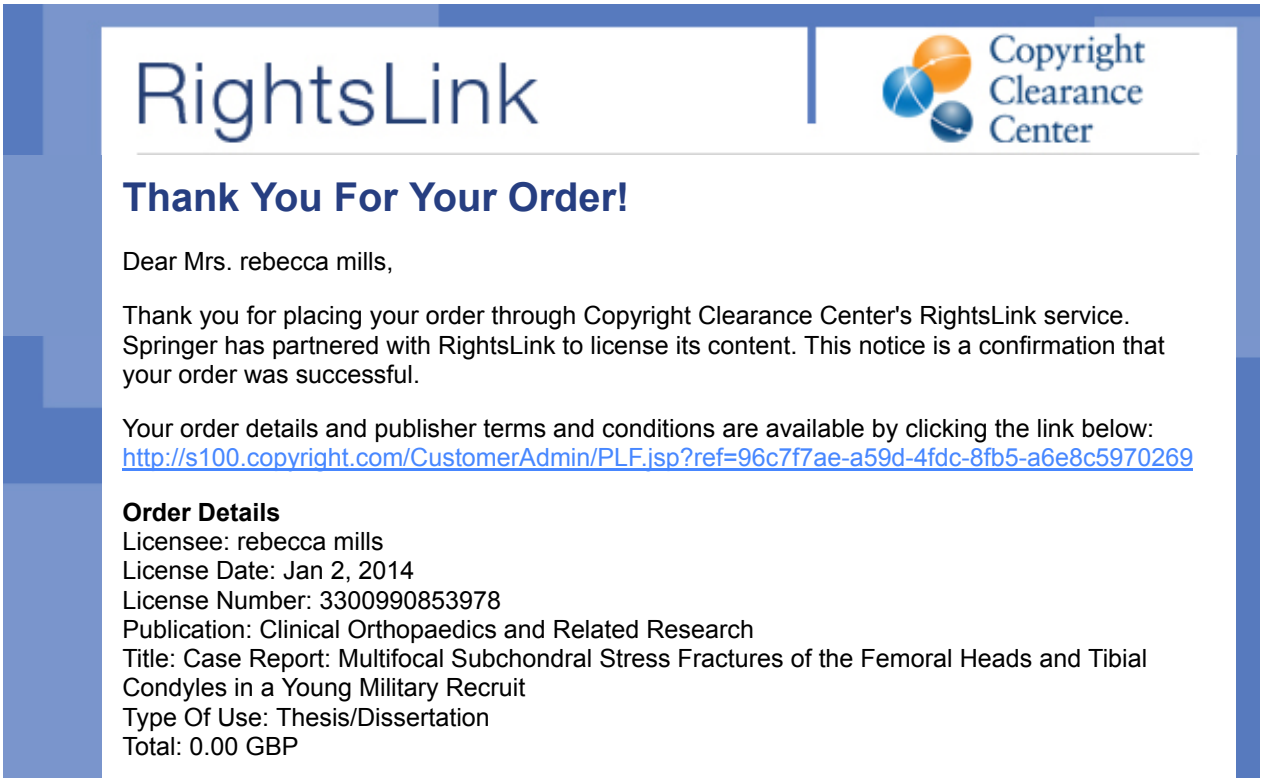

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Figure 19: A displaced fracture to neck of femur.

(Fullerton & Snowdy, 1988, p. 368).

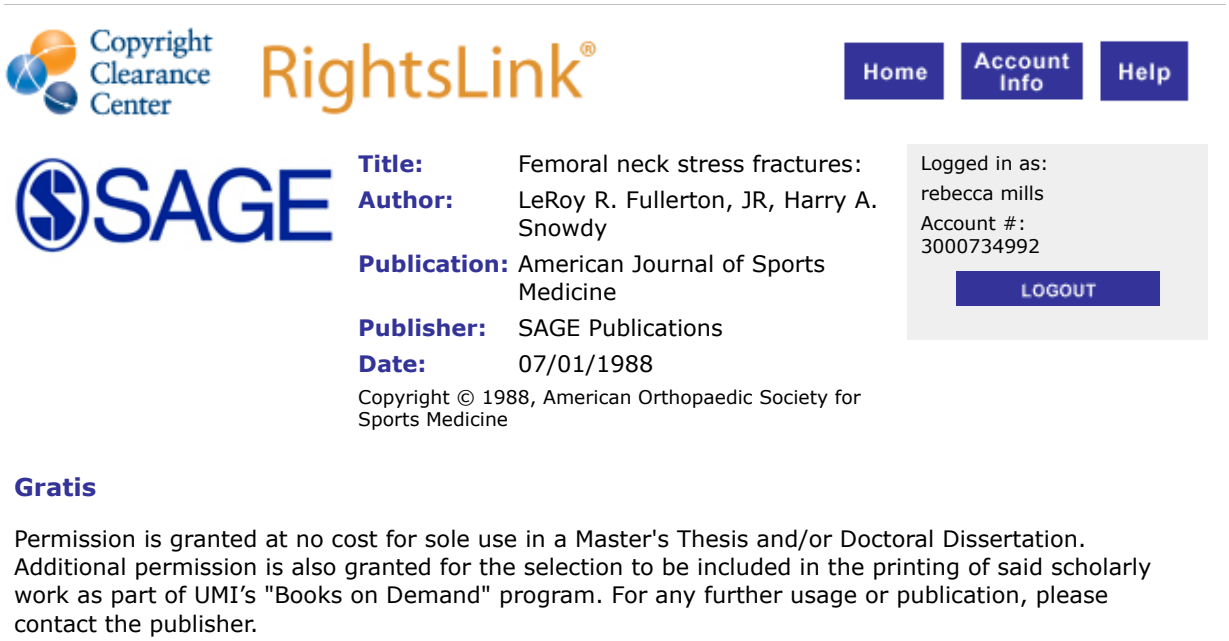

Figure 20: A diagram illustrating the spectrum of BSIs against imaging and clinical symptoms.

(Anderson & Greenspan, 1996, p. 3).

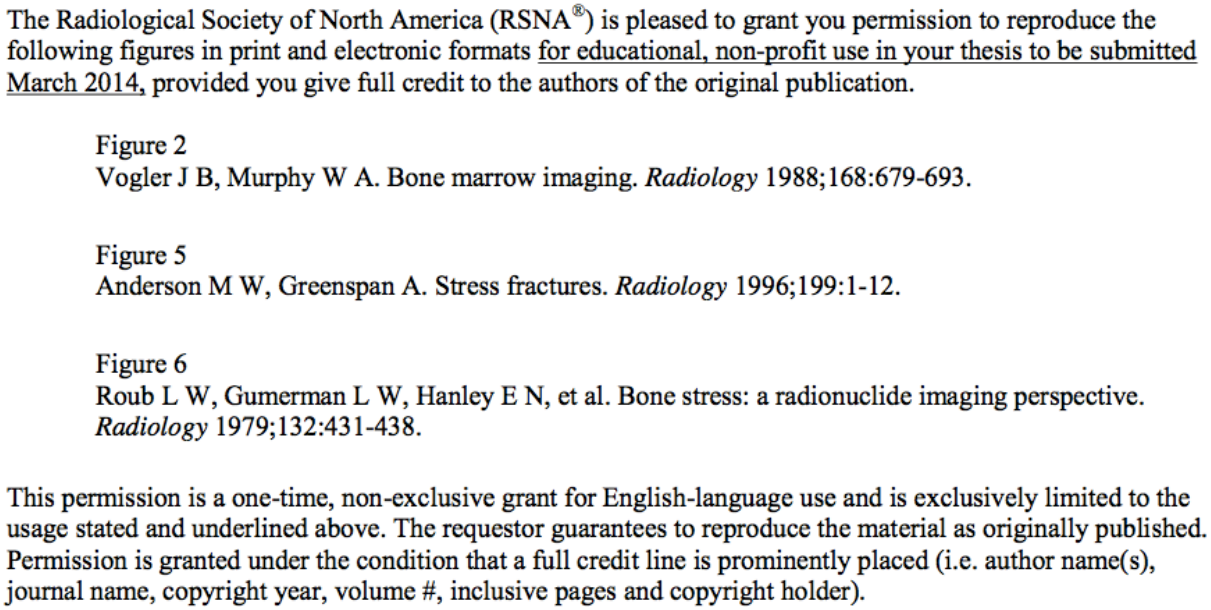

Figure 21: A lower leg bone scintigram of a symptomatic runner at initial examination.

(Rupani et al., 1985, p. 195).

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Figure 22: A follow up lower leg bone scintigram of a runner 7 weeks later.

(Rupani et al., 1985, p. 195).

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Figure 23: (A) A schematic representation of the four grades of BSI (B) Bone scintigraphy images transposed on to this grading system.

(Zwas et al., 1987, p. 453).

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Figure 24: An axial CT slice of a right tibia illustrating a BSI.

(Feydy et al., 1998, p. 600).

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Figure 25: An axial T1 weighted MRI slice of a right tibia illustrating a BSI.

(Feydy et al., 1998, p. 600).

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Figure 26: Three different weighted coronal MRI sequences of a female runner's tibia.

(Arendt et al., 2003, p. 964).

Figure 27: An ultrasound image of a BSI to a 5th Metatarsal head.

(Jones & Philips, 2010, p. 4).

Early Identification of Foot and Lower Limb Stress Fractures using Diagnostic Ultrasonography: A review of three cases

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Figure 28: A power Doppler ultrasound image of a 5th metatarsal BSI.

(Jones & Philips, 2010, p. 4).

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Figure 29: A clinical decision tree for BSI.

(Lappe et al., 2001, p. 37).

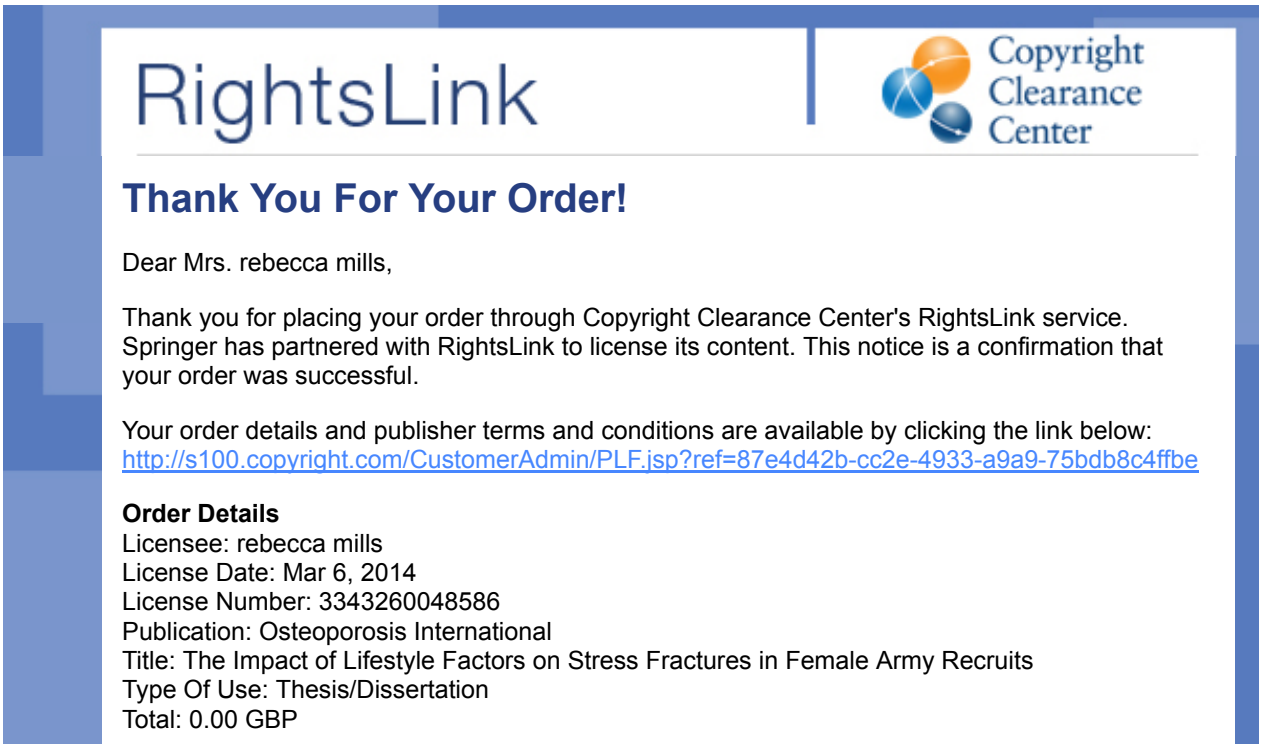

Figure 30: A photograph depicting the clinical presentation of a BSI to the foot.

(Jones & Philips, 2010, p. 4).

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Figure 31: A simplified BSI management algorithm

(Pegrum et al., 2012, p. 7).

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Figure 32: A post-operative radiograph demonstrating a restored femoral head and a fibular allograft.

(Yoon et al., 2012, p. 947).

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Figure 33: A flow diagram illustrating the process of pooling the data: synthesizing the evidence.

(Biggam, 2011, p. 109).

Figure 38: A T1 weighted MRI sequence of a pelvis with bilateral BSI.

(Yoon et al., 2012, p. 947).

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Figure 39: A T1-weighted MRI image of bilateral BSI to the tibial plateau.

(Yoon et al., 2012, p. 947).

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Figure 40: A radiograph demonstrating the initial appearance of a displaced transverse fracture in the mid portion of the femur.

(Luchini et al., 1980, p. 690).

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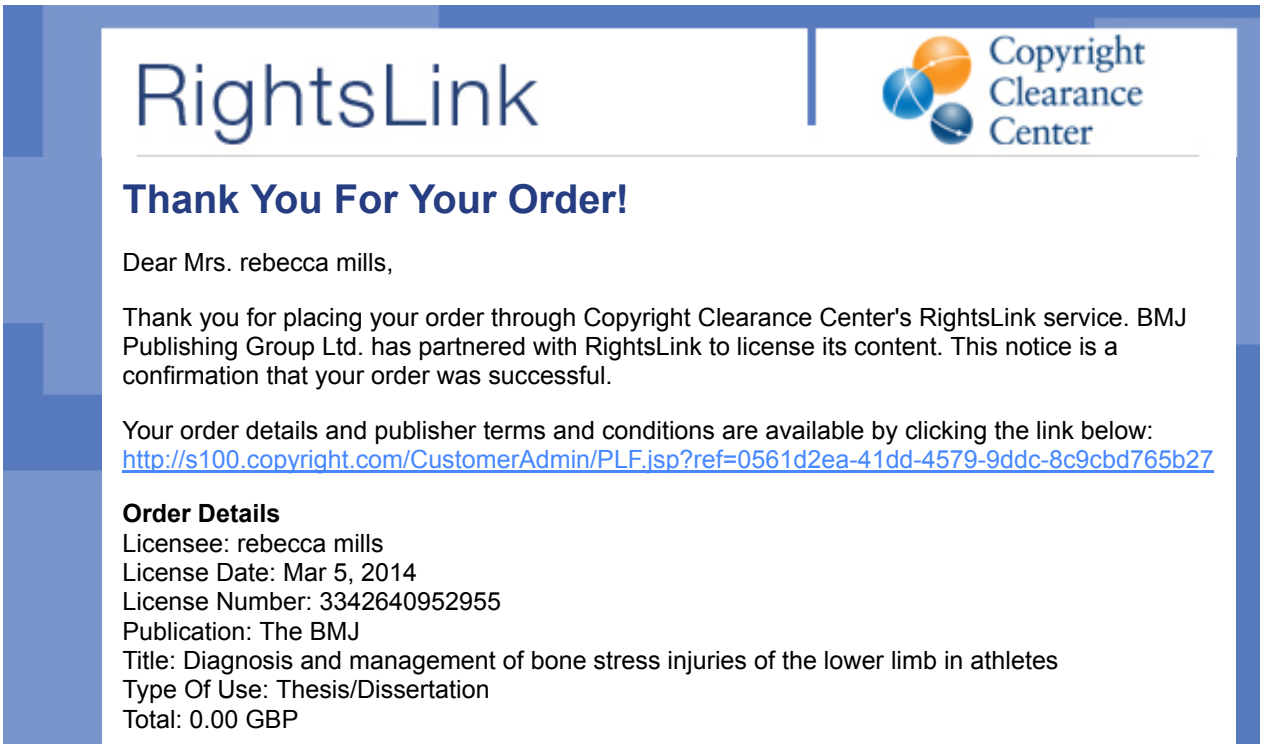

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