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FATIGUE FRACTURES IN MILITARY CONSCRIPTS A STUDY ON RISK FACTORS, DIAGNOSTICS AND LONG-TERM CONSEQUENCES

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Academic Dissertation

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*To my buffers against the world,
Tiina-Mari, Laura and Saku-Petteri*

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ABSTRACT

Fatigue fracture is an overuse injury commonly encountered in military and sports medicine, and known to relate to intensive or recently intensified physical activity. Bone responds to increased stress by enhanced remodeling. If physical stress exceeds bone's capability to remodel, accumulation of microfractures can lead to bone fatigue and stress fracture. Clinical diagnosis of stress fractures is complex and based on patient's anamnesis and radiological imaging. Bone stress fractures are mostly low-risk injuries, healing well after non-operative management, yet, occurring in high-risk areas, stress fractures can progress to displacement, often necessitating surgical treatment and resulting in prolonged morbidity.

In the current study, the role of vitamin D as a predisposing factor for fatigue fractures was assessed using serum 25OHD level as the index. The average serum 25OHD concentration was significantly lower in conscripts with fatigue fracture than in controls. Evaluating TRACP-5b bone resorption marker as indicator of fatigue fractures, patients with elevated serum TRACP-5b levels had eight times higher probability of sustaining a stress fracture than controls. Among the 154 patients with exercise induced anterior lower leg pain and no previous findings on plain radiography, MRI revealed a total of 143 bone stress injuries in 86 patients. In 99% of the cases, injuries were in the tibia, 57% in the distal third of the tibial shaft. In patients with injury, forty-nine (57%) patients exhibited bilateral stress injuries. In a 20-year follow-up, the incidence of femoral neck fatigue fractures prior to the Finnish Defence Forces new regimen in 1986 addressing prevention of these fractures was 20.8/100,000, but rose to 53.2/100,000 afterwards, a significant 2.6-fold increase. In nineteen subjects with displaced femoral neck fatigue fractures, ten early local complications (in first postoperative year) were evident, and after the first postoperative year, osteonecrosis of the femoral head in six and osteoarthritis of the hip in thirteen patients were found.

It seems likely that low vitamin D levels are related to fatigue fractures, and that an increasing trend exists between TRACP-5b bone resorption marker elevation and fatigue fracture incidence. Though seldom detected by plain radiography, fatigue fractures often underlie unclear lower leg stress-related pain occurring in the distal parts of the tibia. Femoral neck fatigue fractures, when displaced, lead to long-term morbidity in a high percentage of patients, whereas, when non-displaced, they do not predispose patients to subsequent adverse complications. Importantly, an educational intervention can diminish the incidence of fracture displacement by enhancing awareness and providing instructions for earlier diagnosis of fatigue fractures.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

- I Ruohola J-PS, Laaksi IT, Ylikomi TJ, Haataja RI, Mattila VM, Sahi T, Tuohimaa PJ, Pihlajamäki HK. An Association between Serum 25OHD₃ Concentrations and Bone Stress Fractures in Finnish Young Men. *J Bone Miner Res* 21:1483-1488, 2006.
- II Ruohola J-PS, Mulari M, Haataja RI, Ettala O, Väänänen HK, Pihlajamäki HK. Elevated Serum Levels of TRACP-5b Predict Bone Stress Injuries: A Prospective cohort study, submitted.
- III Ruohola J-PS, Kiuru MJ, Pihlajamäki HK. Fatigue Bone Injuries Causing Anterior Lower Leg Pain. *Clin Orthop Relat Res* 444:216-223, 2006.
- IV Pihlajamäki HK, Ruohola J-PS, Kiuru MJ, Visuri T. Displaced Femoral Neck Fatigue Fractures in Military Recruits. *J Bone Joint Surg (Am)* 88A:1989-1997, 2006.
- V Pihlajamäki HK, Ruohola J-PS, Weckström M, Kiuru MJ, Visuri TI. Long-term prognosis of non-displaced fatigue fractures of the femoral neck in young male adults. *J Bone Joint Surg (Br)* 88:1574-1579, 2006.

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ABBREVIATIONS

25OHD	25-hydroxyvitamin D
99mTc	technetium-99m
BMC	bone mineral content
BMI	body mass index = a person's weight in kilograms divided by height in meters squared
CECS	chronic exertional compartment syndrome
CT	computerized tomography
HHS	Harris hip score
LSD	least significant difference
MR	magnetic resonance
MRI	magnetic resonance imaging
NSAID	nonsteroidal anti-inflammatory drug
P	probability
PTH	parathyroid hormone
TRACP5b	tartrate-resistant acid phosphatase 5b
VAS	visual analogue scale

1. INTRODUCTION

Bone stress fractures are overuse injuries associated with intensive or recently intensified physical activity. Consequently, they are common among athletes and military conscripts involved in strenuous training programmes (Pentecost et al. 1964, Milgrom et al. 1986, Matheson et al 1987b, Jones et al. 1989, Sterling et al. 1992, Clanton and Solcher 1994). Plenty of research has been conducted investigating factors predisposing to stress fractures, and although the results have been inconsistent, several proposals have been published (Jones et al. 2002, Välimäki et al.2005). That the bone stress injuries detected with radiographic imaging methods (e.g. scintigraphy, MRI) are often not only multiple and simultaneous but also symptomless (Ha et al. 1991, Giladi et al. 1991, Kiuru et al. 2002, Niva et al. 2005) suggests, however, a greater susceptibility to stress fractures among certain persons compared to others. Furthermore, considering the wide evidence regarding the association of vitamin D with bone health (Compston 1998, Utiger 1998, Lips 2001, Holick 2003a), a possible association of vitamin D status with stress fractures would seem well worth intensified research.

When bone is subject to elevated stress levels, it accelerates its remodeling process in which the damaged bone cells dissolve and new matrix is laid down to permit formation of new cells. Should the physical stress exceed bone's remodeling capacity, the repair process may remain incomplete, thus making way to microfractures in the bone and bone fatigue. These changes in the bone structure increase proneness to stress fractures (Li et al. 1985, Jones et al.1989, Boden and Osbahr 2000).

A clinical diagnosis of a fatigue bone stress injury, as well as a differential diagnosis distinguishing it from other imitating conditions can be complicated (Mubarak et al. 1982, McBryde 1985, Michael and Holder 1985, Milgrom et al. 1986, Rosfors et al. 1992, Hutchinson and Ireland 1994). Stress related anterior lower leg pain, which is very common among military recruits and certain athletes (Milgrom et al. 1986, Clanton and Solcher 1994), is often referred to under categories like shin splints or medial tibial stress syndrome that cover a wide spectrum of conditions behind the pain (Mills et al. 1980, Dettmer 1986). Radiographic imaging in its various forms has been widely exploited to confirm the diagnosis. Since many stress injuries are not detectable even by plain radiography, magnetic resonance imaging (MRI) has been increasingly preferred as offering superior sensitivity for detecting these injuries even at an early stage (Lee and Yao 1988, Anderson and Greenspan 1996, Kiuru et al. 2002). Unfortunately MRI is not widely available, which can delay the diagnosis and treatment of stress injury, thus

possibly contributing to severe consequences and prolonged morbidity (Salminen et al. 2003). Partly because of this, development of a new useful instrument is attracting wide interest to permit more accurate detection of bone stress fractures already in primary health care units with limited imaging facilities. Here, the knowledge regarding biochemical markers of bone resorption, such as TRACP5b, which mirror the body's rate of bone loss (Stepan 2000), should encourage research about their potential in stress fracture prediction.

Generally classified as benign low-risk injuries, bone stress injuries have mainly been treated non-operatively with reduced exercise and non-weight-bearing. Occurring in high-risk areas e.g. the femoral neck, these injuries can, nonetheless, progress to displacement and other severe consequences and prolonged morbidity (Salminen et al. 2003, Boden and Oshbar 2000, Visuri et al. 1988). However, previous reports on the long-term consequences of femoral neck fatigue fractures have mainly been case reports. Thus, systematically collected data on the long-term outcome of both displaced and non-displaced femoral neck fatigue fractures are lacking.

2. REVIEW OF THE LITERATURE

2.1. Fatigue fractures

A German military surgeon J. Breithaupt was the first doctor in history (Breithaupt 1855) to describe fatigue fracture in literature. However, he failed to recognize the main reason for painful and swollen feet associated with marching in Prussian soldiers, mistaking a fatigue fracture for a traumatic inflammatory reaction. Since the year 1855, the majority of publications describing stress reactions of bone have been based on studies among military recruits until, in the last four decades, an increasing number of studies concerning stress injuries of bone among athlete populations have appeared in the medical literature (Jones et al. 1989). The fact that military publications are so well presented in medical literature with respect to bone fatigue fractures is due to military populations having been in the past the only populations large enough, with their type and level of physical activity, to provide sufficient amounts of stress reactions of bone to raise general interest among medical researchers. Only later, with the ever-growing number of people participating in fitness and sports training programs, have stress fractures become increasingly common in civilian athlete populations as well.

Once the condition behind the “painful foot” was detected using X-rays invented by Wilhelm Röntgen in 1895, and actually identified as bone fractures (Stechow 1897), also other bones of the lower extremities exhibiting symptoms of stress-related pain were subjected to observation. During the first half of the 19th century, along with more widely available native radiography, it became clear that sites like tibial and femoral shaft as well as femoral neck could be affected by fatigue fracture more often than previously thought. Another obvious finding was that the majority of these fractures typically occurred during the first weeks or months of military training when physical activity intensified. For the fatigue fracture itself, several names were used, including march fracture, stress fracture, exhaustion fracture, spontaneous fracture, and others, some of which have remained in use until today (Branch 1944, Jones et al. 1989, Ha et. al 1991, Anderson and Greenspan 1996).

Clinically it was, and still is, difficult to make differential diagnosis between stress fracture and other pathological conditions simulating it. Consequently, radiographs played a remarkable role in the diagnosis until the

1970s, when scintigraphy and MRI, offering a much better sensitivity and specificity, became valuable tools for the purpose. Interestingly, at same time when these improved imaging methods with higher accuracy were adopted for diagnosis of stress fractures, the most diagnosed fracture location in the lower extremities moved from the metatarsal bones to the tibia in military populations. Owing to its lower costs and good availability in primary health care units, however, plain radiography has stayed long as the first line tool for fracture imaging. Only recently are there signs that MRI is becoming common in medical practice (Lee and Yao 1988, Shin et al. 1996, Deutsch et al. 1997, Boden and Osbahr 2000, Spitz and Newberg 2002, Kiuru et al. 2004, Niva et al. 2005, Niva et al. 2006a and 2006b, Sormaala et al. 2006a and 2006b).

Today, stress-related fractures have been described for nearly every bone of our body. The most common sites for stress fractures are the weight-bearing bones of the lower extremities and the pelvis. Both sites have been typically noted among military recruits due to the type of physical training they undergo, and among athletes, of whom runners in particular have emerged as the main subgroup suffering from these injuries (Hallel et al. 1976, Rupani et al. 1985, Hulkko and Orava 1987, Matheson et al. 1987b, Boden and Oshbar 2000, Jones et al. 2002, Kiuru et al. 2004, Kiuru et al. 2002).

2.2. Terminology of bone stress injuries

Stress fracture as a term in itself can be potentially misleading, because stress injuries of the bone, although diagnosed and classified under the rubric of stress fractures, do not necessarily result in a fracture line or a break in bone continuity (Jones et al. 1989). Pathophysiology of these injuries covers a wide spectrum of events, from accelerated remodeling to stress fracture (Anderson and Greenspan 1996).

Stress reaction is the first phase indication that a stress injury is developing to a bone. This reaction starts, when adaptability of the bone to increased repetitive stress is overloaded. In these early phases, native radiography often shows normal findings, whereas on MRI, marrow edema can be seen (Lee and Yao 1988, Kiuru et al. 2002).

Stress fracture occurs when the abnormal stress continues without the needed recovery periods for the bone, and the bone responds by incomplete remodeling. Callus or fracture line can then be visualized with plain radiography, and more certainly with MRI (Lee and Yao 1988, Anderson and Greenspan 1996). Bone stress fractures can be classified into two main types, fatigue fractures and insufficiency fractures (Pentecost 1964, Daffner and Pavlov 1992).

Fatigue fractures occur when normal bone, with normal elastic resistance, is exposed to abnormal repetitive stress (Pentecost 1964, Daffner and Pavlov 1992).

Insufficiency fractures occur when abnormal bone, with deficient elastic resistance, is exposed to normal stress (Pentecost 1964, Daffner and Pavlov 1992).

Pathological fractures occur in bone which is affected and weakened by another pathological lesion, such as infection or neoplasm (Daffner and Pavlov 1992).

Compressive fractures may occur when bone is exposed to compressive forces along the concave margin of the bone. Stress fractures of the femoral neck located at the inferior surface of the neck are typical compression-side fractures (Fullerton et al. 1988, Flinn et al. 2002).

Tension fractures may occur when bone is exposed to tensile forces along the convex margin of the bone. Stress fractures of the femoral neck located at the superior surface of the neck are typical tension-side fractures (Fullerton et al. 1988, Flinn et al. 2002).

Low-risk stress injuries can usually be diagnosed on the basis of careful anamnesis, physical examination, and radiographs. Moreover, they can be treated with rest periods without a fear of problematic consequences (Boden et al. 2001). According to Boden et al. (2001), the low-risk sites are, with some exceptions, the upper extremities, the ribs, the pelvis, the femoral shaft, the tibial shaft, the fibula, the calcaneus, and the metatarsal shaft.

High-risk stress injuries can, unfortunately, progress to complete fracture, displacement, delayed union, or nonunion, and they therefore require a more aggressive approach. They commonly occur on the tensile side of bone, or in bone areas with critical blood supply. The problematic sites are the femoral neck (tension side, Fig 1), the patella, the anterior cortex of the tibia, the medial malleolus, the talus, the tarsal navicular, the fifth metatarsal, the second metatarsal base, and the first digit sesamoids (Boden and Oshbar 2000, Lassus et al 2002).

Risk factor is an attribute or circumstance associated with enhanced risk of developing a specific disease. Identification and understanding of a risk factor can provide an opportunity to create preventive strategies against the disease related to that particular risk factor.

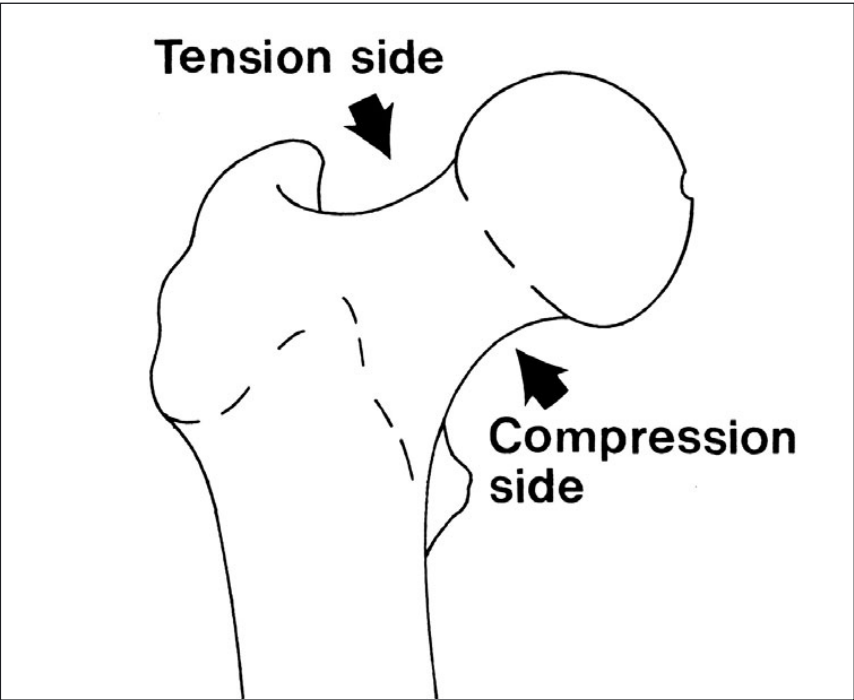


Figure 1. Tension and compression sides of the femoral neck.

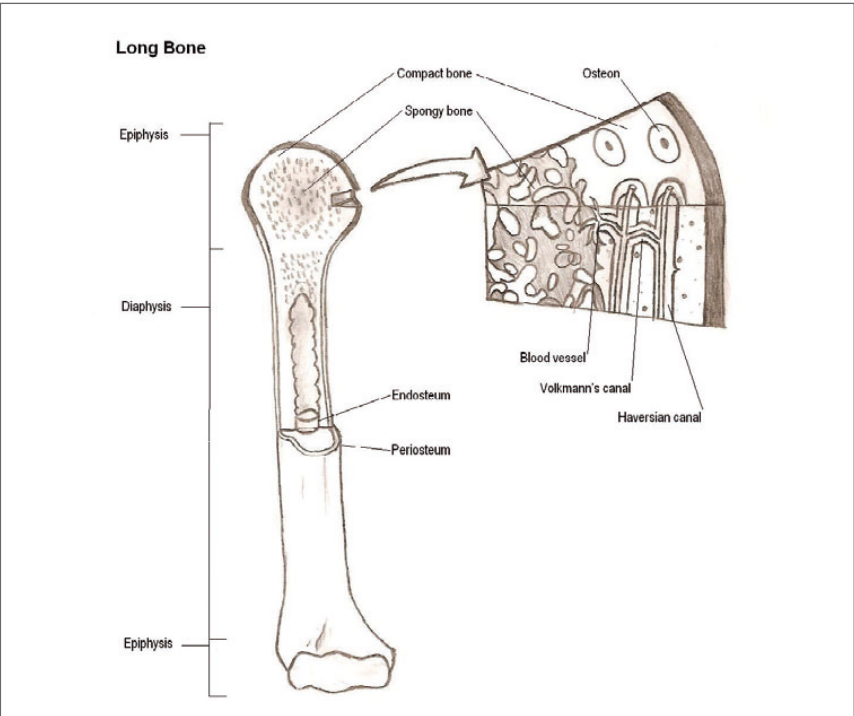


Figure 2. The macroscopic and microscopic structure of bone

2.3. Bone anatomy, remodeling and reaction to stress

Bone consists of two different components characterizing the widely varying gross arrangement of this connective tissue. The gross anatomy is greatly influenced by the position and function of the bone within the body. Cortical bone is typically present along the outer margin of long bones. Cancellous (trabecular or spongy) bone is usually found at the end of long bones and internal to cortical bone, or it can compose some bones, e.g. the calcaneus, almost alone (Fig 2). The basic histological structure of these bone types is equal to both, but differences exist. Cortical (compact or dense) bone has, as justly indicated by its name, a solid architecture, which only the narrow canals of the Haversian systems interrupt. Cortical bone has a low surface-to-volume ratio, with the cells completely surrounded by bone matrix. Cancellous bone is a meshwork of longitudinal (primary) and transverse (secondary) trabeculae separated by hematopoietically active red marrow or hematopoietically inactive, yellow (fatty) marrow. Cancellous bone has a high surface-to-volume ratio, with the cells directly influenced by bone marrow cells, ensuring that the bone is under a better metabolism control when compared to cortical bone. The extracellular matrix of bone tissue, with its chemical composition of both organic and inorganic elements, enables bone to withstand physical stresses better than other tissues.

Through a microscope, bone is composed mainly of extracellular matrix and cells that represent the lesser amount of organic matter in bone. Osteoblasts, osteoclasts, osteocytes and osteoprogenitor cells are the four active matrix cell types found in bone. Bone metabolism is regulated by bone cells and the regulation depends on the cell activity. Since osteoblasts' main function is to synthesize and mineralize bone matrix, they are regarded as bone forming cells. If the osteoblast becomes surrounded by the matrix it has been producing, it can become an osteocyte with metabolically inactive appearance. Osteocytes are numerous in the mineralized bone matrix of both cancellous and cortical bone. Their function is not completely understood, but they are assumed to play a role in the mechanical regulation and regeneration of bone (Cowin et al. 1991, Lanyon 1993, Mullender and Huiskes 1995 and 1997). Osteoclasts are cells that function in the resorption process of calcified bone matrix. Osteoprogenitor cells are found throughout the bones, and, under relevant stimulation, they can differentiate into functional osteoblasts (Buckwalter et al. 1995).

Bone is a dynamic connective tissue that requires stress for normal development and health (Sterling et al. 1992). Metabolically, bone is never at rest. In a continual formation, resorption and remodeling process taking place throughout the bone, the osteoblasts form and the osteoclasts remove bone matrix without remarkably affecting the shape or density of the bone. In healthy bone, under a constant load, normal bone remodeling occurs

through osteoclast resorption and osteoblast reconstruction of the bone tissue, meaning that these two are in balance with each other. One component both contributing to osteoclast activity and enhancing the differentiation of osteoclast and osteoblast precursors is vitamin D (Riggs 1997, Utiger 1998, Holick 2003b), which also lowers intact parathyroid hormone (iPTH) secretion and controls both calcium absorption and reabsorption (Utiger 1998). With the calcium and phosphate homeostasis having a major effect on bone mineralization, in the event of dietary calcium inadequacy, vitamin D causes osteoclasts to mature and resorb calcium from the bone (Compston 1998, Lips 2001, Välimäki et al. 2004). A possible relationship between calcium intake and stress fracture has been investigated in some studies, but the evidence is still lacking (Lips et al. 1991, McKane et al. 1996).

Under an increasing load, with the bone subject to prolonged, recurrent or excessive stress, the remodeling process accelerates through stimulated bone resorption, resulting in incomplete remodeling response (Li et al. 1985, Burr et al. 1990). Dominant osteoclastic activity at bone stress sites may cause local weakening of the bone, thus predisposing it to microdamage (Werntz and Lane 1993). With continuing abnormal loading, these microdamages, also called microfractures, can gradually progress to complete fractures (Knapp and Garrett 1997). On the other hand, if the load is reduced, diminishing stress to the bone and giving the remodeling process time to normalize, the development of bone fracture can be avoided.

2.4. Incidence of bone stress injuries

Stress fracture is a commonly seen injury type in sports clinics as well as the primary health care units of military health services (Table 1) (Morris and Blickenstaff 1967, Mills et al. 1980, Milgrom et al. 1985, Hulkko and Orava 1987, Matheson et al. 1987b, Beck et al. 1996). The overall incidence of stress fractures in military recruits has varied between 0.9% and 12.3%, but incidences as high as 31% have been reported (Brudvig et al. 1983, Sahi 1984, Milgrom et al. 1985, Jones et al. 1993, Macleod et al. 1999, Givon et al. 2000, Armstrong et al. 2004, Lappe et al. 2005). In the Finnish Defence Forces, the current published incidences of bone stress injuries have stayed within these values (Sahi et al. 1996, Välimäki et al. 2005). However, with most of the stress fractures in the Finnish Defence Forces occurring during the first two or three months of military service, the military conscripts represent a homogenous exposure group regarding physical stress during the 8-week basic training period equal for all. In contrast, there is considerable variation internationally between armed forces, and even military branches, with respect to training procedures, physical fitness of trainees and methodology of diagnosis (Kiuru et al. 2004).

Table 1. Previous studies of bone stress injuries of the lower extremities

Author and year	Participants	Number of participants, male/female	Method	Incidence of bone stress injuries, male/female (%)
Hallel et al. 1976	military	not reported	prospective	5/-
Protzman and Griffis, 1977	military	1228/102	prospective	1.0/9.8
Brudvig et al. 1983	military	20442 overall	retrospective	0.9/3.4
Milgrom et al. 1985	military	295/-	prospective	31/-
Taimela et al. 1990	military	108/-	prospective	7.4/-
Finestone et al. 1991	military	392/-	prospective	24/-
Jones et al. 1993	military	124/186	prospective	2.4/12.3
Goldberg and Pecora, 1994	athletes	approx. 1000 overall	retrospective	1.9 overall
Johnson et al. 1994	athletes	914 overall	prospective	2.6 overall
Beck et al. 1996	military	626/-	prospective	3.7/-
Bennell et al. 1996	athletes	49/46	prospective	20.4/21.7
Macleod et al. 1999	military	3367/855	retrospective	2.8/10.8
Armstrong et al. 2004	military	1021/203	prospective	2.3/8.4
Lappe et al. 2005	military	-/4139	prospective	-/4.7
Välimäki et al. 2005	military	179/-	prospective	8.4/-

In the general athletic population, the incidence has remained below 3.7% (Matheson et al. 1987b, Jones et al. 1989, Goldberg and Pecora 1994). In runners and some other groups of athletes, the occurrence of bone stress injuries might be somewhat higher, from 10% to 31% (Matheson et al. 1987b, Boden and Oshbar 2000, Jones et al. 2002, Kiuru et al. 2004).

Almost all stress fractures among military trainees and athletes are found in the lower extremities or the pelvis (Milgrom et al. 1985, Matheson et al. 1987a, Jones et al. 1989, Ha et al. 1991, Jones et al. 2002, Kiuru et al. 2002, Kiuru et al. 2004, Tuan et al. 2004). Although the variation reported in different studies concerning the distribution of stress injuries in the lower extremities is remarkable, these injuries have been encountered in nearly every bone of the foot and leg, as well as around the hip joint (Visuri et al. 1988, Visuri 1997, Williams et al. 2002, Lee et al. 2003, Song et al. 2004, Niva et al. 2005). However, the most common sites for bone stress injuries are the tibia and the metatarsal bones. (Milgrom et al. 1985, Jones et al. 1989, Bennell et al. 1996).

2.5. Risk factors for bone stress injuries

Numerous reports have documented that the main cause predisposing bone to stress injuries is repeated or recently started mechanical loading (Lassus et al. 2002, Tuan et al. 2004). In addition, various potential risk factors have been proposed to explain, more or less, why some sustain a stress fracture while others do not. These etiological risk factors can be categorized as extrinsic (external) or intrinsic (internal) (Table 2). Extrinsic factors are characteristics of the environment in whose activities the individual participates. Extrinsic causes include training conditions, methods and equipment, and training errors, such as excessive intensity or volume, duration and change of each strain cycle, excessive muscle fatigue, and faulty or wrong technique. Intrinsic factors, e.g. mechanical, muscular, nutritional or hormonal factors, are characteristics of the individuals themselves. Intrinsic causes include muscle fatigue leading to transmission of excessive forces to underlying bone (Blickenstaff and Morris 1966, Boden and Osbahr 2000), muscle imbalance, insufficient flexibility due to generalized muscle tightness, focal muscle thickening, limited range of joint motion, lack of bone strength due to decreased bone mineral density (Pouilles et al 1989), and psychological factors like nutritional intake and eating disorders (Matheson et al 1987b, Bennell et al. 1999)

Table 2. Possible risk factors for bone stress injuries according to Bennell et al. 1999

Intrinsic risk factors	Extrinsic risk factors
Bone mineral density	Volume of training
Bone geometry	Pace of training
Skeletal alignment.	Intensity of training
Body size and composition.	Recovery periods
Bone turnover	Faulty training technique
Muscle flexibility and joint range of motion	Training surface
Muscular strength and endurance.	Footwear/insoles/orthotics
Calcium intake	External loading
Caloric intake/eating disorders	
Nutrient deficiencies	
Sex hormones	
Menarcheal age	
Other hormones	
Physical fitness	
Age	
Gender	

Several publications have studied risk factors contributing to a predisposition to stress fractures, and quite often the results have been, in whole or in part, conflicting with each other. Moreover, there exists a possibility that risk factors have the potential to predispose bone to developing stress fractures alone or through the joint effect of various factors. Of the risk factors for stress fractures, female gender, age, body composition, bone characteristics, low bone density and bone strength, low aerobic fitness, low past physical activity level, smoking, and excessive running have been identified in an epidemiologic review (Bennell et al. 1999, Jones et al. 2002).

Several studies based on bone scintigraphy or MRI regarding the lower extremities or the pelvis, have reported occurrence of multiple simultaneous bone stress injuries in the same individual (Ha et al. 1991, Giladi et al. 1991, Nielsens et al. 1994, Kiuru et al. 2002, Niva et al. 2005). Multiple fractures may imply that the subject's overall bone composition is defective, and thus some general factor be present for predisposing bone to stress fractures (Fig 3AB).

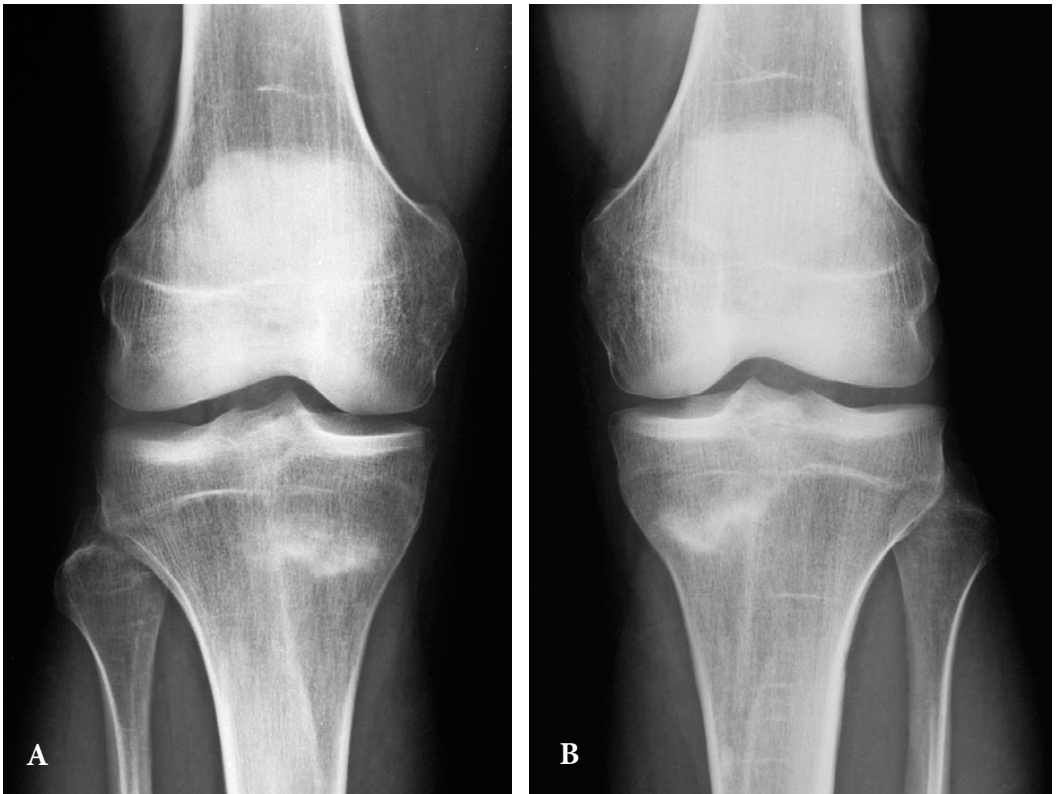


Figure 3AB. A 19-year-old male conscript suffering from knee pain. Plain radiography reveals bone stress injuries in both the right (A) and the left (B) knee.

2.6. Diagnosis of bone stress injuries

2.6.1. Clinical diagnosis of bone stress injuries

Clinical diagnosis of bone stress injuries with no specific signs or findings is a difficult task. However, the complexity should not deter the physician from action, since an early suspicion and diagnosis of a possible stress injury is essential for adequate treatment (Fig 4AB). The clinical diagnosis of bone stress injury is based on the patient history of physical activity, duration and type of symptoms, and a number of uncertain clinical findings needing confirmation by radiological imaging methods.



Figure 4AB. An 18-year-old male conscript suffering from foot pain. The stress fracture in the third metatarsal bone is hardly detectable on the primary radiographic image (A), yet despite a rest period, displacement of fracture is observed a week later (B).

The symptoms of a developing stress injury often appear 2 to 3 weeks after the beginning or remarkable intensification of training. However, duration of the evolution of injury may vary from days to months (Greaney et al. 1983, Jones et al. 1989, Ha et al. 1991). At the early stages of stress injury,

the patient may be symptomless on clinical examination. Stress-related pain with no previous trauma can occur suddenly or gradually, and may vary from radiating to very unspecific. Furthermore, at least among military recruits, the motivation for duty and service combined with personal characteristics can produce very diverse reactions to exercise-induced pain (Halle et al. 1976). At the onset, pain can be exercise-induced only, generally disappearing with rest. However, even then, and more probably so if loading continues non-reduced, pain will be present also at rest and during nights. The location of pain and suspected fracture can be clinically very important, affecting decision making concerning appropriate treatment. Some high-risk stress fractures, e.g. displaced femoral neck fracture, can cause severe complications and prolonged recovery, leading all the way to avascular necrosis and joint replacement surgery (Blickenstaff and Morris 1966, Fullerton and Snowdy 1988, Visuri et al. 1988, Johansson et al. 1990, Mendez and Eyster 1992). In these specific locations of suspected fracture, early suspicion and accurate diagnosis are even more important to avoid fracture displacement and surgical treatment.

Swelling and discolouration with local warmth (Anderson and Greenspan 1996) may be seen, and localized pain and possible periosteal thickening indicating new bone formation, callus, may be palpable (Sterling et al. 1992). Pain at a distant site produced by the percussion of bone, e.g. in the tibia, can signal a stress injury. A few special tests exist, the fulcrum test for example, for diagnosing a stress injury (Johnson et al. 1994) in the femoral bone, which is otherwise difficult to palpate due to strong muscles covering it (Fig 5).

No appropriate laboratory tests exist to assist the diagnosis of stress fractures in primary health care units with no advanced imaging modalities. However, biochemical markers of bone resorption reflecting the rate of bone loss (Stepan 2000) have been the focus of recent research, aimed at developing an adequate diagnostic test. These markers are relatively inexpensive, widely available and, expressing both bone quantity and quality, they would be conceivable as possible fracture predictors. One of these potential bone turnover markers, TRACP5b is secreted into circulation during osteoclast resorption, mirroring this osteoclastic activity in enzyme secretion and bone degradation (Nesbitt and Horton 1997, Salo et al. 1997, Vääräniemi et al. 2004). TRACP5b has been suggested to be an independent, specific, and sensitive serum marker of bone resorption (Halleen et al., 2000, Halleen 2003, Nenonen et al. 2005). It has so far been successfully used in monitoring response to the treatment of bone metastases in cancer patients (Wada et al. 1999, Terpos et al. 2003).

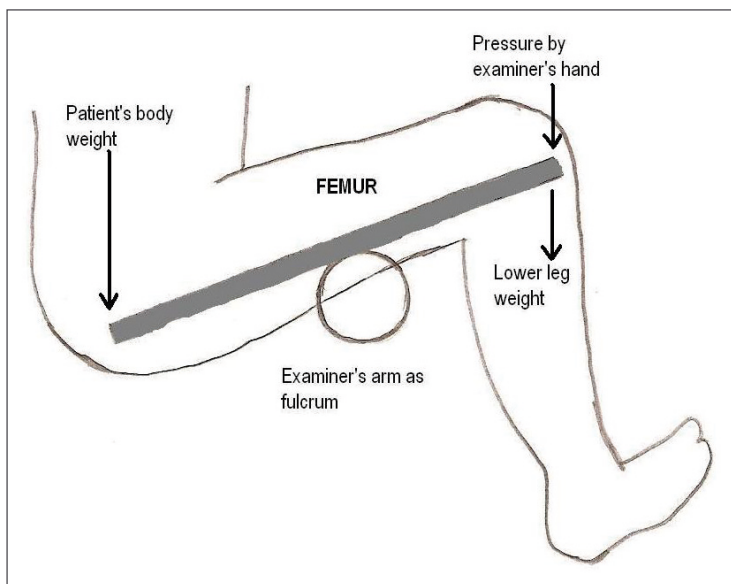


Figure 5. Fulcrum test: Patient is seated with the lower legs dangling. Examiner's arm is used as fulcrum under the patient's distal thigh moving the arm towards the proximal thigh, while applying gentle pressure to the dorsum of the patient's knee with the opposite hand. Pain occurs when the arm as fulcrum is located under the stress fracture.

2.6.2. Radiological imaging in diagnosis of bone stress injuries

Imaging studies are needed to confirm the diagnosis of stress injuries (McBryde 1985, Michael and Holder 1985, Milgrom et al. 1986, Clanton and Solcher 1994, Anderson and Greenspan 1996). Plain radiography has generally been used as the primary imaging tool since the end of the 19th century. Only two years after Wilhelm Röntgen discovered X-rays was the technology already used to detect stress fractures in the metatarsals (Stechow 1897), and it has maintained its position as the first-line imaging tool owing to its common availability and cost effectiveness. However, in imaging of stress injuries, the sensitivity of radiography at the early stages of injury may be as low as 10%, although in the follow-up of these injuries, it rises to 30% and up to 70% (Prather et al. 1977, Orava 1980, Greaney et al. 1983, Rupani et al. 1985, Matheson et al 1987a, Nielsen et al. 1991). Because of the somewhat low sensitivity, diagnosis has often been based on bone scintigraphy or MRI in patients with stress related pain and no visible stress injury on radiographs.

Bone scintigraphy was considered the gold standard for detecting early stages of bone stress injuries from the 1970s until the early 2000s, when it began to give way to MRI (Kiuru et al. 2002). Acceleration in bone metabolism related to stress injuries is visible on scintigraphy long before changes are seen on radiography. Bone scintigraphy is substantially more sensitive (nearly 100% sensitivity) than radiography, but its specificity is inferior,

so that identification of pathological conditions in particular, such as tumors, infections and traction periostitis, remains deficient (Anderson and Greenspan 1996, Kanstrup 1997). The radiation dose received at a scintigraphic examination is equal to a dose of two years of background radiation (Kanstrup 1997). Today, MRI is overriding scintigraphy in terms of availability as well.

Magnetic resonance imaging (MRI) offers not only a high sensitivity but also a superior specificity in detecting the early changes related to bone stress injury, yet without exposing the body to ionizing radiation (Lee and Yao 1988, Anderson and Greenspan 1996, Kiuru et al 2002). It is therefore fully understandable that MRI is currently considered the gold standard in stress injury imaging. Moreover, its high contrast and spatial resolution permit visualization of associated soft tissue involvement (Anderson et al 1997, Deutsch et al. 1997). On MRI, a developing bone stress fracture can be detected already at its earliest stages, with the initial signs of bone stress injury being displayed as periosteal or endosteal marrow edema. However, as such endosteal edema may signal other pathological conditions as well, the finding should be considered non-specific (Schweitzer and White 1996, Lazzarini et al. 1997). Endosteal bone marrow edema has also been documented in healthy, physically active asymptomatic patients, and because these asymptomatic low grade injuries do not seem to possess a tendency to progress to higher grade injuries, MR imaging of asymptomatic military trainees or athletes is not recommended (Kiuru et al. 2005). Evolution of a stress-related bone injury comprises several varying stages, characterized by an equally large variety of MRI signs. For the purpose of assessment of these signs, several stress reaction or fracture grading scales have been published (Lee and Yao 1988, Kiuru et al. 2001). According to the scaling system by Kiuru et al. bone stress injuries are classified on the basis of MRI findings as: Grade I, endosteal marrow edema; Grade II, periosteal edema and endosteal marrow edema; Grade III, muscle edema, periosteal edema, and endosteal marrow edema; Grade IV, fracture line; and Grade V, callus in cortical bone. A disadvantage of MR imaging is still today the general unavailability of the technology. Moreover, its costs might be considered as another limitation to its use.

2.7. Differential diagnosis of bone stress injuries

Stress-related pain in the lower extremities is common in military recruits and athletes (Milgrom et al. 1986, Clanton and Solcher 1994). It is difficult, or even impossible, to differentiate a bone stress injury from other pathological conditions mimicking it based on clinical examination alone, even though a patient history in terms of physical activity level and symptoms is usually quite typical when concerning stress injuries to bone (Table 3). Thus, in the majority of cases, the history combined with characteristic radiographic findings suffices to reach the diagnosis. Diagnosis can, however, be further confused by imitating conditions, including exertional conditions like the compartment syndrome, and nonexertional inflammatory, infectious, vascular, neurological and tumorous conditions in soft tissues and bones (D'Ambrosia 1977, Mubarak et al. 1982, McBryde 1985, Michael and Holder 1985, Milgrom et al. 1986, Rosfors et al. 1992, Hutchinson and Ireland 1994). This again emphasizes the importance of sensitivity and specificity of the imaging method used in unclear cases to ensure rapid and adequate diagnosis and treatment, usually meaning the MRI. Stress-related pain in the lower extremities is most commonly located in the anterior lower leg. Although a stress-related bone injury is by no means an unusual cause of lower leg pain, yet with no findings suggestive of bone injury, the pain is often referred to as shin splints (traction periostitis), or the medial tibial stress syndrome (Mills et al 1980, Detmer 1986). However, the terms lack accuracy covering so broad a spectrum of possible conditions behind the pain (Johnell et al 1982, Mubarak et al. 1982, Michael and Holder 1985, Gerow et al. 1993, Beck 1998). The differential diagnosis can be even more demanding, because conditions like traction periostitis, chronic exertional compartment syndrome and bone stress injury can occur separately or combined, and furthermore, because stress injuries often affect several bones simultaneously. Such cases of simultaneous and combined symptoms, difficult for both the patient and the physician to pinpoint, can greatly disturb the diagnosis (Giladi et al. 1991, Ha et al. 1991, Kiuru et al. 2002, Niva et al. 2005). In patients with lower grade injuries, treated by reducing load with rest period, there exists already a suspicion of a possible stress fracture. Nonetheless, the final diagnosis may remain open, because, with decreased stress, the bone can heal a developing stress injury before it becomes visible on radiographs, and later, with less or no symptoms, a patient is likely never to undergo repeated plain radiography or MRI scan to confirm the diagnosis (Devas 1958, Li et al. 1998, Kiuru et al. 2005).

Table 3. Differential diagnosis of bone stress injuries

Conditions imitating bone stress injuries
Exertional compartment syndrome
Bone tumors and metastase
Inflammatory disease
Infectious condition
Transient bone marrow edema
Traction periostitis
Osteonecrosis
Vascular pathological condition
Neurological pathological condition
Osteomyelitis
Osteomalacia
Bursitis
Iliotibial band syndrome
Distal femoral cortical defect
Femoral cortical excavation
Internal derangement of the knee
Morton's neuroma
Osteochondral fracture

2.8. Treatment and long-term consequences of bone stress injuries

The anatomic location of the injury carries mentionable prognostic importance for the possible long-term consequences of bone stress injury, since some injuries involving bones like the femoral neck are more prone to displacement and severe complications than those found at other bones and sites (Table 4). The majority of low-risk stress fractures seen in clinics are managed conservatively with reduced exercise, and heal with no fear of complications (Fig 6AB). In more severe cases, use of crutches, splints, or casts may be necessary. In displacements or other fractures where non-operative treatment is insufficient, surgical treatment, mainly internal fixation, is warranted (Hulkko and Orava 1987). Regarding the nature and extent of reduced exercise as a treatment method, these depend on the site and grade of injury, varying from a period of cutting down daily physical exercise to a half to a period of complete inactivity including a possible non-weight-bearing period for up to 8 weeks. In military service, this of-

ten also means a temporary exemption from military service due to the lengthy recovery time. In all injury management, the return to normal physical activity level should be gradual.

Table 4. Low- and high-risk stress fractures by Boden et al. 2001

Low-risk areas	High-risk areas
Upper extremity.....	Femoral neck
Ribs.....	Patella
Pars interarticularis.....	Anterior cortex tibia
Pelvis.....	Medial malleolus
Femoral shaft.....	Talus
Tibial shaft.....	Tarsal navicular
Fibula.....	Fifth metatarsal
Calcaneus.....	Second metatarsal base
Metatarsal shaft.....	Great toe sesamoids

Some stress fractures, e.g. fractures of the femoral neck, are classified as high-risk stress fractures, because they possess a potential for adverse consequences and prolonged morbidity (Boden and Oshbar 2000, Kaeding et al. 2004). Femoral neck stress fractures can progress to a complete fracture and fracture displacement complicated by delayed union, nonunion, malunion, or avascular necrosis of the femoral head, which in turn may result in devastating problems or even permanent disability (Ernst 1964, Visuri 1988, Weistroffer 2003). After discovery of five cases of displaced fatigue fractures of the femoral neck within one year, the military institution in Finland prepared permanent orders effective nationwide as of 1986 with detailed instructions for the diagnosis and treatment of fatigue fractures. The information was designed to increase awareness of the symptoms of femoral neck fatigue fracture among both military physicians and medical officers as well as conscripts, and to ensure the most effective injury management by providing centralized diagnostic services at the main military hospital.

For athletic young people and military trainees, extra care must be taken to avoid delayed diagnosis, and efforts should be made to treat fractures without surgical procedures. Of particular importance is the detection of non-displaced femoral neck fatigue fractures as well as injuries in other high-risk bones at an early stage, when it is usually possible to use non-operative fracture management and avoid severe consequences and prolonged morbidity frequently associated with these injuries.



Figure 6AB. A stress fracture in the third metatarsal bone of a 20-year-old male conscript (A) was treated conservatively with rest periods and reduced exercise. The healed fracture shown six months later (B).

3 AIMS OF THE PRESENT STUDY

I. To assess the effect of serum 25OHD concentration as a predisposing factor on fatigue bone stress injuries, and to evaluate the incidence and anatomic distribution of these injuries and their relationship with age, weight, height, BMI, muscle strength, and result of running test.

II. To determine if TRACP-5b bone resorption marker indicates enhanced bone remodeling in military conscripts with stress fractures, and to evaluate the incidence and anatomic distribution of these bone stress injuries.

III. Based on MR imaging, to determine the incidence of fatigue bone stress injuries causing stress related anterior lower leg pain, and to assess their anatomic distribution, grade of injury with respect to location, and duration of symptoms before diagnosis.

IV/V. To evaluate the incidence, symptomatology, morphologic characteristics, clinical course, risk factors and long-term outcomes of displaced and non-displaced fatigue fractures of the femoral neck, and to assess the effects of instructions by the Finnish Defence Forces, Department of Medical Services in 1986 for the prevention of femoral neck fatigue fractures in military service.

4 MATERIALS AND METHODS

The two prospective cohort studies (I, II) were conducted at the Pori Brigade, Säkylä, at the Research Institute of Military Medicine, Central Military Hospital, Helsinki, at the University of Tampere (I), Tampere, and at the University of Turku (II), Turku. The third, retrospective study (III) was conducted at the Department of Radiology and at the Research Institute of Military Medicine, Central Military Hospital, Helsinki. The studies IV and V were conducted at the Departments of Radiology and Surgery, and the Research Institute of Military Medicine, Central Military Hospital, Helsinki. All the studies (I-V) were approved by the appropriate Ethics Committees. All study designs (I-V) were approved by the Defence Staff of the Finnish Defence Forces.

4.1. Patients

All the participants included in Studies I-V were or had been conscripts performing their military service in the Finnish Defence Forces. All male citizens of Finland become liable for a mandatory military service at the age of 18, whereas female citizens have had the opportunity to volunteer for the service since year 1995. Annually, on average 26,500 male conscripts and 500 female conscripts underwent military training within the time periods of studies I-III, and the annual number of male conscripts was between 34,723 and 36,606 during studies IV and V.

Study I

In July 2002, eight hundred young men (aged 18-28 years, mean 19.8 years) entering into military training as conscripts of the same infantry unit (Pori Brigade) of the Finnish Defence Forces were randomly selected for the study. They had no known diseases or medications and they all had passed the entrance medical examinations as healthy. The subjects represented the common conscript population of the Finnish Defence Forces with no specific features. During their military service, the conditions were homogenous in that physical activity, nutrition, clothing, accommodation, and exposure to sunlight were the same for all participants. From the original sample, we excluded patients whose follow-up data was incomplete as a result of failed blood samples drawn during the study, and patients who were compelled to interrupt their military service, which left the total of 756 patients for the follow-up.

Study II

Eight hundred and twenty Finnish young men and women (aged 18-28 years, mean 19.8 years; mean BMI 23.4) entering military training in July 2002 as conscripts of the same infantry unit (Pori Brigade) of the Finnish Defence Forces were randomly selected for the study. They had no previous medication or diseases and they all passed their entry medical examination as healthy. The subjects represented the general conscript population of the Finnish Defence Forces without specific features. During the military service, the conditions related to physical activity, nutrition, clothing, and accommodation were homogenous for all subjects.

Study III

Material for Study III covered a study period of five years, from March 1, 1997 to February 28, 2002. A total of 154 patients, seven female and 147 male (age range, 17–25 years; mean, 19.6 years) meeting the inclusion criteria were identified from the MRI archives of the Central Military Hospital. The inclusion criteria for the present study were exercise-induced anterior lower leg pain during military service, at least one negative plain radiograph taken at a primary health care unit, physical examination by an orthopaedic surgeon, diagnosis of injury still unclear, and one MR image taken at the Central Military Hospital. Patients with a recent trauma or presenting symptoms on arrival at their military service were excluded from the study. The patients came from different units and represented the general conscript population of the Finnish Defense Forces with no specific features. The mean population at risk per year during the study period consisted of 14,640 conscripts within the service area of the hospital.

Studies IV and V

During the study periods of twenty years, from January 1, 1975 to December 31, 1994 (IV) and twenty-one years, from January 1, 1970 to December 31, 1990 (V), a total of twenty-one consecutive displaced (IV) and 106 non-displaced (V) femoral neck fatigue fractures were treated in military conscripts within the catchment area of concern in the present study. Identification of the fractures was performed by running a computer search on the National Hospital Discharge Register, using the appropriate diagnostic codes of the 8th (1969-86) and the 9th (1987-1995) editions of the International Classification of Disease (ICD), and by linking them with the codes of the military hospitals nationwide. During the study periods, in Study IV, on average 34,723 males, and in Study V, on average 36,606 males started their military service annually, constituting the populations at risk for sustaining a stress fracture of the femoral neck. At the beginning of the military service, the majority of the conscripts were 19 to 20 years old in both studies.

4.2. Methods

4.2.1. Study description

Study I

In this study, the effect of serum 25OHD concentration on fatigue bone stress injuries was evaluated. For this purpose, serum samples were gathered from all participants of the study at the beginning of their military service. The samples were frozen for later analysis performed with OCTEIA[®] enzyme immunoassay by IDS (Immunodiagnostic Systems Inc, Fountain Hills, AZ, USA). Computer-based data on conscript height, weight and physical fitness obtained during the first weeks of their service were collected. Physical fitness was assessed using a 12-min running test and five measures of muscle strength. The conscripts were followed for three months to identify possible stress injuries to bone. All the patients who by clinical examination and anamnesis were suspected to have developed a bone stress injury during the said period underwent plain radiographic imaging, and those whose symptoms continued and radiographs remained negative further underwent MR imaging. The subjects without stress fractures under observance constituted controls for the stress fracture cases.

Study II

In this study, serum TRACP-5b concentrations were measured to determine whether they can be used to identify enhanced bone remodeling related to bone stress fractures. The baseline blood samples for determining TRACP-5b levels were drawn from all subjects of the study at their arrival to military service. These subjects were then followed for three months to identify possible occurrence of stress fractures. The subjects with symptoms suggestive of bone stress injury were clinically examined, and, later, the diagnosis was confirmed by plain radiography, subsequently repeated if necessary. From the patients with diagnosed or strongly suspected stress fracture, four additional blood samples were drawn at 3-4-day intervals to measure TRACP-5b activity. Blood was also drawn from two non-symptomatic controls with matching BMIs for each fracture case. The analysis of serum samples from patients with a confirmed stress fracture together with corresponding samples from controls was subcontracted to Suomen Bioanalytiikka Oy (SBA sciences, Oulu, Finland), and conducted by using an immunoassay protocol described by Alatalo et al. (Alatalo et al. 2000)

Study III

In this study, the original medical records and MR images of the conscripts who underwent MRI for unclear stress-related anterior lower leg pain were retrospectively obtained and evaluated. The MR images were interpreted

with the aim to determine the incidence, anatomic location and grade of the possible stress injury involved. The normal procedure among the orthopaedic surgeons at the Central Military Hospital was to prescribe MRI for cases with prolonged stress-related lower leg pain when no other, clear diagnosis was known.

Studies IV and V

Information retrieved from the medical records and imaging examinations concerning the military service period of the subjects was evaluated, and the long-term outcome data of the subjects was collected by asking all the patients in the studies (IV, V) to participate in a follow-up examination. Time from the initial injury to follow-up examination varied between eight and thirty-two years. In Study IV, of the 21 patients with a diagnosed displaced femoral neck fatigue fracture, long-term follow-up data was available on 19 patients. In Study V, 66 of 106 patients invited agreed to participate in the follow-up. Moreover, in connection with the long-term follow-up visit, information regarding possible examinations and treatments performed in other hospitals after patient's previous visits to the military hospital were asked, and the medical records and radiographs from those hospitals were retrieved for review and analysis. Fracture patterns were determined according to Garden and Orthopaedic Trauma Association classifications (Garden 1961, Muller et al. 1990, Orthopaedic Trauma Association Committee for Coding and Classification 1996). The body mass index (BMI) at the time the fracture was detected was computed (World Health Organization 1995) and classified according to Llwellyn-Jones and Abraham classification (Llwellyn-Jones and Abraham 1984). The BMIs of the patients in the study were compared with those of 223 conscripts born in 1958 and serving their time of compulsory military service in 1978 (Dahlström 1981).

The impact of the new instructions implemented in the army nationwide in 1986, designed to increase awareness of the diagnosis and treatment of fatigue fractures, was assessed by calculating the incidence of all fatigue fractures of the femoral neck as well as the incidences of displaced and non-displaced femoral neck fatigue fractures before and after 1986 within the time periods of the studies.

The follow-up visit consisted of a physical examination, including estimation of the functional status of the hip joint using the Harris Hip Score (Harris 1969), conventional anteroposterior radiography, and MRI of the pelvic area. A ten-point (0 to 100 mm) visual analogue scale (VAS), with zero denoting none, from 10 to 30 light, from 40 to 60 moderate, from 60 to 90 hard, and 100 denoting the worst imaginable pain, was used to assess the degree of subjective pain experienced by the patients one week before the follow-up examination.

4.2.2. Clinical diagnosis and treatment

In Studies I-III, the physical examinations conducted at patients' primary health care units adhered to identical care policies, including careful history taking, inspection of skin changes, and palpation. In addition, the orthopaedic examination (III-V) included observation of joint movements and ligamentous stability of the lower extremities as well as checking for distal pulse and sensation. Each unit participating in the studies followed identical procedures for diagnosis, treatment, and patient referral for additional examinations. Before orthopaedic evaluation, patients were treated conservatively, as necessitated by pain, with rest periods or reduced exercise, NSAID, and prescribed crutches if walking caused pain.

4.2.3. Imaging methods

In all studies, the same accepted radiological assessment procedure was adhered to during the plain radiographic examinations at both the primary health care units and the Central Military Hospital (Kiuru et al. 2004). The grey cortex sign, periosteal callus, endosteal callus, sclerotic band, and fracture line were accepted as the radiographic signs marking a bone stress injury. In Study III, based on MRI, bone stress injuries were classified as: Grade I, endosteal marrow edema; Grade II, periosteal edema and endosteal marrow edema; Grade III, muscle edema, periosteal edema, and endosteal marrow edema; Grade IV, fracture line; and Grade V, callus in cortical bone (Kiuru et al. 2001). In Study IV, in the radiographic classification of osteonecrosis of the femoral head, the method of Ficat and Arlet (Ficat and Arlet 1980) was used, and in Studies IV and V, the radiographic severity of osteoarthritis was classified according to the criteria of Tönnis (Tönnis 1987). In study V, MRI was used in the detection of osteonecrosis of the femoral head and osteoarthrotic changes of the hip joint. Both hip joint spaces were measured from the original digital MR imaging data and statistically compared with each other in each patient. Moreover, in Studies IV and V, the original diagnoses of the stress fractures were thoroughly checked and verified at the follow-up examination by means of evaluating the whole series of radiographic images for each patient. All the images were evaluated by a musculoskeletal radiologist.

4.2.4. Statistical methods

The data analyses for all studies (I-V) were performed using SPSS for Windows (versions 11.0/11.5/12.0/12.0.1, SPSS Inc, Chicago, Illinois, USA). In Study II, logistic regression analysis was performed using Stata for Windows (version 7.0). The limit for statistical significance was set at a P-value equal to 0.05. Various methods were used for statistical analysis in the different studies.

In Study I, the differences in serum 25OHD levels between the two groups formed by dividing the skew continuous data based on the median were tested by the Pearson chi-square test, and the results were corroborated by the Mann-Whitney's U-test using the original values. The Student's *t*-test was used to test differences in age, BMI, height, weight, muscle strength, and result of 12-min running test between the groups. The association between these variables and stress fracture was studied using logistic regression. Odds ratios were calculated with a 95% confidence interval.

In Study II, the relationship between TRACP-5b activity and an outcome of being a case or a control was estimated using conditional logistic regression. Sensitivity and specificity were investigated using area under the ROC curve with confidence interval and coordinate points of the ROC curve. Because the values were not normally distributed, logarithmic transformations were used to analyze changes in TRACP-5b activity. Tests were performed using analysis of variance for repeated measures.

In study III, the relationship between the locations of tibial stress injuries and their MRI grades was tested using the Fisher's test. Differences between the groups were tested using the Kruskal-Wallis test for skew continuous data.

In Studies IV and V, the Chi-square test was used to determine the significance of differences between two independent groups at the 0.05 P-level. The Student's *t*-test and the Mann-Whitney exact U-test were used for comparing independent means. Incidence rate ratios with 95% confidence intervals were calculated for the fractures occurring in 1975-86 and 1987-1994 in Study IV, and for the fractures occurring in 1970-1985 and 1986-1990 in Study V, correspondingly.

The Least Significant Difference (LSD) test in Study II and the Mann-Whitney U test in Study III were used as post-hoc tests for additional information.

5 RESULTS

5.1. Serum 25OHD concentration as a potential predisposing factor for fatigue bone stress fracture, incidence and anatomic distribution of these fractures, and their relationship with age, weight, height, BMI, muscle strength, and result of running test. (I)

The median serum 25OHD level was 75.8 nmol/l (25.2-259.0) for all the conscripts in Study I, but it was significantly lower in conscripts with stress fracture than in controls ($p = 0.017$). In the multivariate regression model, the conscripts with serum 25OHD levels below the median were at 3.6 (95% CI: 1.2-11.1) times higher risk for stress fracture than conscripts with concentrations above the median level, a difference found statistically significant ($p = 0.002$) (Table 5).

In Study I, conscripts' results in the 12-min running test and in the muscle strength test were significantly poorer compared with controls (mean 2480 m vs. 2670 m, $p = 0.007$; and mean 7 vs. 9, $p = 0.025$, respectively). However, in the multivariate regression model, when all significant variables from the univariate observation were adjusted, a non-significant association emerged with stress fractures. No significant associations between daily smoking, BMI, age, height, and weight and bone stress fracture were found in this study population.

In this study, the incidence of stress fractures was 11.6 (95% confidence interval 6.8-16.5) per 100 person-years (2.9%). A total of thirty stress fractures were diagnosed in the twenty-two patients of this study. Thirteen fractures (43%) were located in the tibia, ten (33%) in the metatarsal bones, three (10%) in the calcaneus, two (7%) in the tarsal navicular bone, one fracture in the inferior ramus, and one in the femur.

Table 5. The characteristics of the study population by stress fracture status.

Variable	Stress fracture group (n=22)	Control group (n=734)	Significance (Test)
<i>Median (Range)</i>			
Concentration of 25OHD, nmol/l	64.3 (40.1-159.0)	76.2 (25.2-259.0)	0.017 (M-W)
<i>Number (Frequency)</i>			
25OHD (nmol/l)			
< median	18 (81.8%)	362 (49.3%)	0.002 (P)
≥ median (75.8 nmol/l)	4 (18.2%)	372 (50.7%)	
Missing N	0	0	
Daily smoking			
Yes	7 (36.8)	93 (34.7)	0.85 (P)
No	12 (63.2)	175 (65.3)	
missing	3	466	
<i>Mean (Range)</i>			
Age (years)	20.0 (18.6-22.3)	19.8 (18.0-28.5)	0.27 (T)
Missing N	0	0	
BMI (kg*m⁻²)	24.0 (15.4-37.4)	23.2 (16.6-39.2)	0.41 (T)
Missing N	1	14	
Height (cm)	177 (168-184)	179 (161-203)	0.15 (T)
Missing N	1	14	
Weight (kg)	75.3 (47.2-121.1)	74.3 (50.3-139.4)	0.70 (T)
Missing N	1	13	
Muscle strength	7 (0-15)	9 (1-15)	0.025 (T)
Missing N	67	67	
Cooper test/12-minute run (m)	2480 (1650-3200)	2670 (1540-3580)	0.007 (T)
Missing N	0	49	

M-W: Mann-Whitney U-test

P: Pearson Chi-square test

T: Student's T-test

5.2. TRACP-5b bone resorption marker as a potential indicator of enhanced bone remodeling in military conscripts with stress fractures, and the incidence and anatomic distribution of these fractures. (II)

The conscripts with elevated serum TRACP-5b activity levels had an eight times higher probability of stress fracture existence than controls when comparing the ratio of sample IV (taken within 10-11 days after detection of stress fracture) to baseline sample in the fracture and control groups (OR 7.95 95% CI 0.41-153.72) (Table 6).

Although an increasing trend in the TRACP-5b levels was found when comparing the baseline samples to samples I-IV in the conscripts of the fracture group, the finding did not show statistical significance ($p = 0.072$). It is noteworthy, however, that the difference between the baseline and sample III was statistically significant ($p = 0.039$) (Fig 7).

Using a cut-off value of 1.09 for the ratio between sample IV and baseline, both the sensitivity (0.62) and the specificity (0.65) of TRACP-5b level as an indicator of stress fracture exceeded 0.6. Sensitivity (0.62-0.54) and specificity (0.55-0.70) were both over 0.5 when the cut-off point varied between 1.05 and 1.14. The area under the ROC-curve, as calculated for the ratio between sample IV and baseline, was 0.60.

Table 6. Results of comparisons of the TRACP-5B activity between fracture and control groups

	Fracture group		Control group		Regression analysis ^a			Area under ROC-curve (AUC) ^b	
	<i>n</i>	mean(sd)	<i>n</i>	mean(sd)	<i>n</i>	<i>P</i>	OR(95%CI)	AUC (95%CI)	<i>P</i> ^c
Baseline	13	3.40(0.77)	20	3.31(0.93)	33	0.780	1.12(0.51, 2.46)	0.54(0.34, 0.74)	0.726
IV	14	3.91(1.13)	28	3.65(1.13)	42	0.471	1.23(0.70, 2.18)	0.55(0.37, 0.73)	0.603
IV/Baseline	13	1.21(0.34)	20	1.09(0.19)	33	0.170	7.95(0.41,153.72)	0.60(0.38, 0.82)	0.338

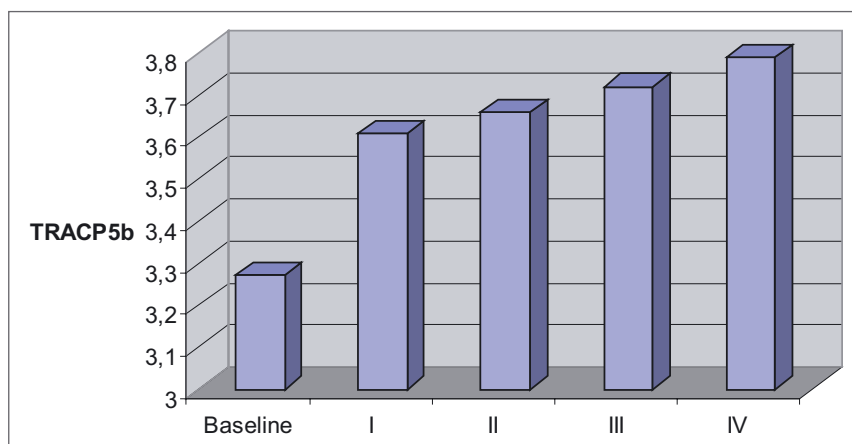
^a Conditional logistic regression analysis

^b The test result variable(s): Baseline and IV has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

^c Null hypothesis: true area = 0.5

In this study, the prevalence of stress fractures was 2.4%. A fatigue fracture was detected in a total of twenty patients. Six patients were lost to final analysis on account of unsuccessful serum samples, incomplete follow-up data, and termination of military service caused by a long recovery time after stress injuries. In the remaining fourteen patients, altogether twenty-one stress fractures were diagnosed. Twelve fractures (57%) were located in the tibia, six (29%) in the metatarsal bones, and three (14%) in the calcaneus.

Figure 7. Changes in TRACP-5b activity of fracture group. Calculations were done using logarithmic transformation and the values were retransferred to original scale (N=14).



5.3. Fatigue bone stress injuries associated with anterior lower leg pain; incidence and distribution, MRI based injury grades depending on injury location and duration of symptoms. (III)

During the 5-year period of this study, the incidence of bone stress injuries requiring orthopaedic consultation and MRI among conscripts was 117 per 100,000 person-years of military service. The findings on MRI revealed 143 bone stress injuries in 86 patients (56%) of the study population of 154 patients. In 141 cases, the injury was located in the tibia and in two cases, in the fibula. Forty-nine patients had stress injuries bilaterally. Four patients had two injuries in the same lower leg, and two patients had three injuries in the same lower leg. One patient had simultaneous bone stress injuries in the tibia and in the fibula. In the tibia, 57% of the injuries were noted in the distal, 30% in the middle, and 10% in the proximal third of the tibial shaft, and 3% in the medial condyle. Moreover, the findings included two legs with symptomatic osteoid osteomas, seven with traction periostitis, and three with soft tissue edemas. Other, clinically irrelevant

findings consisted of two non-ossifying fibromas and one healed cortical defect. In 53 patients, all findings on MRI were normal. Of all the 143 fatigue stress injuries detected by MRI, 17% (24) appeared in legs without any symptoms.

According to the MRI grading system that was used, 50% (71) of the tibial stress injuries represented grade I, 33% (47) grade II, 8% (11) grade III, 7% (9) grade IV, and 2% (3) grade V. The correlation between the locations of tibial stress injuries and the MRI grades I-V was statistically significant ($p < 0.001$) (Table 7). The injuries displayed higher grades in the medial condyle and the proximal third compared to the middle and distal thirds of the tibia. Symptom duration before the stress injury diagnosis was significantly dependent on the MRI grade of the injury ($p = 0.002$). Patients with minor bone lesions (Grade I) on MRI had a greater median of symptom days compared with Grade II ($p < 0.001$) and Grade IV ($p = 0.040$). Statistical significance was also seen in the relationship between patients' symptom duration and MRI based injury location in the tibia ($p = 0.025$) (Table 8). Symptom duration preceding the injury diagnosis was significantly shorter in the medial condyle than in the middle ($p = 0.004$) and distal tibia ($p = 0.006$), whereas in the proximal tibia, the difference bordered significance ($p = 0.053$). No changes were noted in the results after persons with more than one bone stress injury finding were excluded from the data.

Due to a clinical suspicion of a chronic exertional compartment syndrome (CECS), 44 patients (with 74 legs involved) of this study also underwent an intracompartmental pressure measurement, performed using a slit catheter technique (Rorabeck et al. 1981, Moed and Thorderson 1993). Values of 40 mmHg or higher were considered pathological (Whitesides et al. 1975, Hutchinson and Ireland 1994). In these 44 patients, 11 of the 39 legs were confirmed by MRI to suffer from bone injuries with elevated pressure in the anterior tibial compartment.

Table 7. Locations of tibial stress injuries and mri findings classified as grades i-v

Location	MRI grade of bone stress injury					Total
	GI	GII	GIII	GIV	GV	
Medical condyle	0	3	0	2	0	5
Proximal tibia	2	4	2	4	2	14
Middle tibia	20	18	2	2	0	42
Distal tibia	49	22	7	1	1	80

Fisher's test, p value < 0.001

Table 8. Median (range) duration of symptoms in locations of MRI findings

Location of mri finding	N	Duration of symptoms (days)	P value*
medial condyle	5	36(23,59)^"~	0.025
proximal condyle	14	51(30, 105)^	
middle tibia	42	66(16, 210)"	
distal tibia	80	67(2, 224)~	

* Kruskal-Wallis test

Mann-Whitney u-test was used as a post-hoc test, significant or almost significant p-values: ^0.053, "0.004, ~0.006

5.4. Incidence, symptomatology, morphologic characteristics, clinical course, risk factors, and long-term outcomes of displaced and non-displaced fatigue fractures of the femoral neck. (IV, V)

Study IV

Incidence (per service-years) of displaced femoral neck fatigue fractures during 1975-1986, prior to the new regimen of 1986 addressing prevention of fatigue fractures, was 5.3/100,000, decreasing 2.3 fold during 1987-1994 to 2.3/100,000 (95% CI 0.11-1.31). Detection of non-displaced symptomatic femoral neck fatigue fractures increased from 15.5/100,000 to 53.2/100,000 (95% CI 2.27-5.21) service-years, correspondingly. The total incidences of the femoral neck fatigue fractures in the corresponding years were 20.8/100,000 and 53.2/100,000 service-years (in 1987-90 no displacements were observed), respectively, indicating a significant 2.6 fold increase (95% CI 1.7-4.0). Garden-type IV fractures decreased significantly from 3.8 to 0/100,000 (95% CI 0-0.66) service-years between the time-periods concerned.

Nineteen fractures were followed up in the study (Tables 9A and 9B), including eight fractures of Garden-type III and eleven of Garden-type IV. Assessment of the fractures using the system of the Orthopaedic Trauma Association revealed eighteen transcervical (type-31B2) fractures and one subcapital (type-31B1) fracture. During the first postoperative year, ten cases showed early local complications, but in the remaining nine cases, fracture healing was uneventful. Altogether six cases sustained delayed or nonunion of the fracture. In four cases, a repeat operation was necessary during the first postoperative year.

During the subsequent long-term follow-up, starting from the 2nd postoperative year, late, slowly developing complications, such as osteonecrosis of the femoral head in six and osteoarthritis of the hip in thirteen patients,

were detected among the nineteen cases (Fig 8A-E). According to Tönnis classification, we discovered four Grade 1, one Grade 2, and eight Grade 3 cases of osteoarthritis of the hip. The correlation between severe (Tönnis Grade 2 and Grade 3) hip osteoarthritis and osteonecrosis of the femoral head was statistically significant ($p = 0.020$). Revision surgery was necessary in four cases due to these complications. Altogether three patients received total hip prostheses by the final follow-up examination.

In thirteen patients, a mean 32.7% (range 4 to 100%) shortening of the femoral neck compared to the uninjured contralateral side was observed at the latest radiological follow-up examination. Garden-type IV fatigue fracture emerged as a significant risk factor both for osteonecrosis of the femoral head ($p = 0.018$) and for the shortening of the femoral neck ($p = 0.009$). A significant association was also noted between osteonecrosis and shortening of the femoral neck in that the shortening was significantly greater in patients with than without osteonecrosis ($p = 0.001$).

Study V

The incidence (per service-years) of non-displaced femoral neck fatigue fractures was examined separately for the period prior to and the period after the new regimen of 1986 for the prevention of fatigue fractures was introduced. In the former period, 1970-1985, the incidence was 10.2/100,000 and in the latter period, 1986-1990, it was 51.2/100,000, indicating a 5 fold increase ($p < 0.000$). The overall incidence for the 21-year study period was 19.4/100,000 service-years.

None of the non-displaced femoral neck fatigue fractures diagnosed during the study progressed to displacement. With only one exception, all conscripts included in the study returned to normal duty service following recovery after conservative treatment.

The risk factor analysis performed for the two studies (IV, V) failed to reveal any predisposing or risk factors. A significant deviation ($p = 0.013$) was, however, found between the BMIs of the contemporary control conscripts (born in 1958) and the conscripts with displaced femoral neck fatigue fractures (IV) (Table 10). Measurements of the neck-shaft angle from the radiographs (V) did not reveal any angles outside normal limits (125° to 135°). MRI assessments of the average joint spaces in the injured 2.05 mm (SD 0.63) and uninjured 1.97 mm (SD 0.61) hips (V), respectively, showed no significant deviations ($p = 0.297$).

At the final follow-up (V), the intensity of subjective pain and pain experiences was expressed by 62 patients using VAS. The mean score of pain intensity was 5.85 mm (SD 10.48) on a scale of 100 mm. Forty-three patients were completely painless and two patients reported pain levels between 40 mm and 44 mm, correspondingly. The mean HHS was 97 (70 to 100). Thirty-seven (60%) patients did not report any physical disability according to HHS, seven (11%) patients had HHS of 70 to 90 and 19 (31%) had HHS of 91 to 99.

Table 9 A Clinical data of 19 patients with displaced fatigue fracture of the femoral neck, type of primary treatment, early complications and secondary measures

Case no and year of fracture onset	Age (yr)/ affected side	Bmi *	Smoker	Duration of military service at onset of fracture (months)	Activity preceding fracture	Ongoing event leading to onset of fracture	Fracture type**	Primary treatment	Early complications and secondary measures within one year after primary operation
1 / 1975	20 / right	20.2	-	6	Marching	Stumbling	III/ type-31B2	Traction	Malunion (varus angulation)
2 / 1977	18 / left	19.1	+	2	Combat training	None	IV/ type-31B2	Angled plate	Delayed union with broken screws of the plate
3 / 1977	20 / right	19.6	-	7	Marching	None	IV/ type-31B2	DHS	Delayed union with broken screws of DHS plate
4 / 1977	18 / left	17.7	-	5	Marching	Stumbling	IV/ type-31B2	DHS	-
5 / 1978	20 / right	20.6	+	4	Marching	Stumbling	IV/ type-31B2	DHS	Nonunion, removal of hardware and finally malunion
6 / 1979	19 / left	21.0	-	3	Running	Stumbling	IV/ type-31B2	Angled plate	Nonunion, refixation with DHS, and bone grafting (6 mo.)
7 / 1981	20 / right	20.1	-	4	Running	Riding hard on a bicycle	IV/ type-31B2	Angled plate	Deep infection, removal of hardware and bone grafting (3 mo.)
8 / 1983	19 / right	20.8	+	4	Combat training	Stumbling	IV/ type-31B2	DHS	Heterotopic ossification
9 / 1983	20 / right	19.6	-	2	Marching	Slipping	IV/ type-31B2	DHS	Nonunion, intertrochanteric osteotomy, bone grafting (7 mo.)
10 / 1983	20 / left	23.5	-	3	Marching	Stumbling	IV/ type-31B2	DHS	-
11 / 1983	23 / left	18.6	+	5	Marching	None	III/ type-31B2	DHS	-
12 / 1983	19 / right	18.9	+	1	Bicycle march	None	IV/ type-31B1	DHS	Failure of fixation, refixation (1 mo.), delayed union and finally malunion
13 / 1984	20 / right	16.1	+	6	Running	Applying car brakes	III/ type-31B2	DHS	-
14 / 1985	19 / left	20.2	+	4	Marching	Stumbling	III/ type-31B2	DHS	-
15 / 1986	20 / right	26.1	-	2	Marching	Stumbling	IV/ type-31B2	DHS	-
16 / 1991	19 / right	26.2	+	3	Marching	None	III/ type-31B2	DHS	-
17 / 1993	19 / right	19.3	-	2	Running	None	III/ type-31B2	DHS	-
18 / 1993	20 / left	22.2	-	6	Marching	None	III/ type-31B2	DHS	-
19 / 1994	27 / right	24.0	-	6	Marching	None	III/ type-31B2	DHS	Breakage of DHS
Mean:	20 years	20.7		3.9 months					
Range:	18-27 years	16.1-26.2		2-7 months					

*BMI = Body Mass Index, **Garden Classification / Classification System of the Orthopaedic Trauma Association, DHS = Dynamic Hip Screw, OA = Osteoarthritis, OFH = Osteonecrosis of the Femoral Head, - = No Early Complications or Secondary Measures Within One Year After Primary Operation

Table 9 B Final follow-up data on the Patients

Case	Follow-up time (years)	Late complications and reoperations more than one year after primary operation (time of reoperation in months after primary operation)	Radiographic findings		Vas-score	Profession or employment at time of final follow-up
			Shortening of the femoral neck (%)*	Grade of osteoarthritis**		
1	26	OA	10	Gr 3	10	Assistant manager
2	9	-	0	Gr 0	NR	Lawyer
3	25	-	0	Gr 0	0	Projector
4	26	OFH and OA, THA (231 mo.) due to OFH	60	Gr 3 ***	NR	Engineer
5	23	OFH and OA	100	Gr 3	50	Service-man
6	22	OFH and OA	10	Gr 3	13	Chief inspector
7	20	OA, THA (228 mo.) due to OA	10	Gr 3 ***	50	Master builder
8	19	OA	30	Gr 1	36	Plumber
9	18	OFH and OA, THA (172 mo.) due to OFH	100	Gr 3 ***	55	Retired
10	19	OFH and OA	20	Gr 3	NR	Engineer
11	19	OA	0	Gr 1	45	Lawyer
12	20	OFH and OA, 1) vascular bone graft, (25 mo.) due to OFH 2) osteotomy (59 mo.) due to OFH	50	Gr 3	28	Quality supervisor
13	22	-	0	Gr 0	25	Spare parts salesman
14	18	-	10	Gr 0	0	Appraiser
15	16	OA	11	Gr 2	2	Office manager
16	11	OA	4	Gr 1	0	Cook
17	9	-	0	Gr 0	61	Farmer
18	11	-	0	Gr 0	0	Waiter
19	8	OA	10	Gr 1	0	Technical manager
Mean:	20 years		22.4%		23 mm	
Range:	8-26 years		0-100%		0-61 mm	

*As compared with the uninjured hip, ** According to Tönnis Classification, ***Before THA, - = No Late Complications or Reoperations More Than One Year After Primary Operation,

THA = Total Hip Arthroplasty, DHS = Dynamic Hip Screw, NR = Not Reported, OA = Osteoarthritis, OFH = Osteonecrosis of the Femoral Head, VAS-score = Visual Analogue Scale score



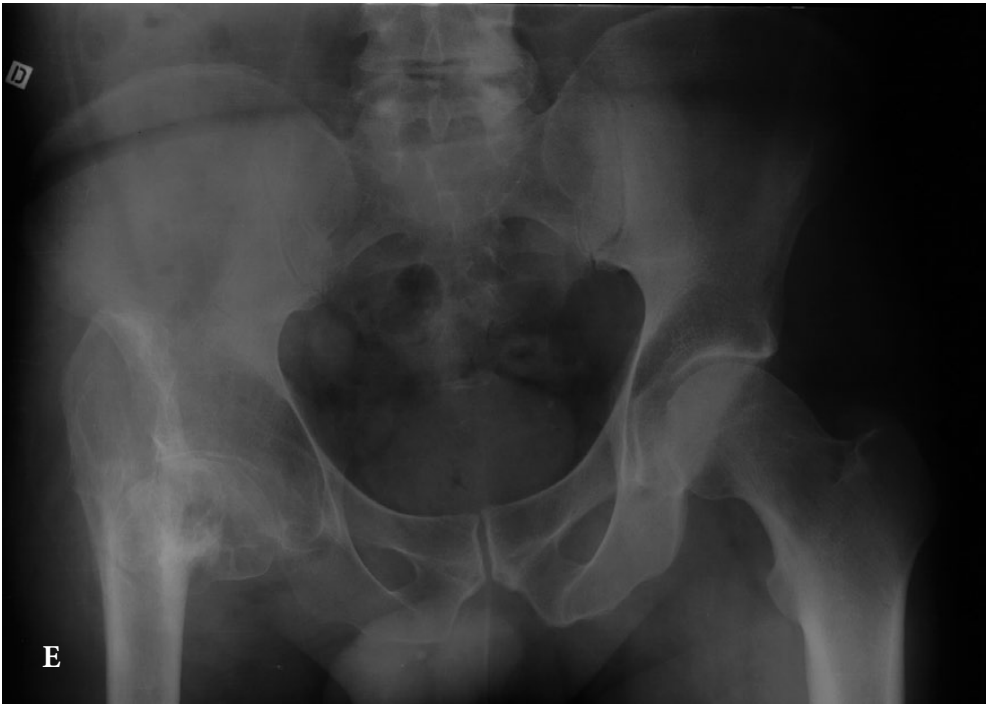


Figure 8A-E.

- A. Case 5. A 20-year-old recruit with Garden-type IV fatigue fracture of the right femoral neck 10 days after a long march.
- B. Acceptable anatomical position after open reduction and fixation of the fracture with dynamic hip screw shows in follow-up radiograph six weeks after the index operation. Minor signs of beginning osteonecrosis in the medial aspect of the femoral neck can be seen.
- C. Advanced resorption of the femoral neck, varus bending, and a still detectable fracture line can be seen three and a half months after the index operation.
- D. Dynamic hip screw has been removed as its supportive and fixative function was lost due to advanced osteonecrosis. Because of the condition, refixation was not possible. Malposition, a still visible fracture line, advanced femoral neck shortening and increased osteonecrosis of the femoral head developed fourteen months after the index operation and six months after removal of the hardware.
- E. At the latest follow-up, twenty-three years after the index operation, the femoral neck is completely resorbed, the head is sclerotic and deformed with distal bony union. The patient has a 5 centimeter shortening of the lower extremity at this time. The patient declined to have a total endoprosthesis of the hip.

Table 10. Characteristics of patients with femoral neck fatigue fractures

FEMORAL NECK FATIGUE FRACTURES	DISPLACED	NON-DISPLACED
Participation in follow-up, cases of all	19 / 21	66 / 106
Mean fracture detection time after patient's arrival to service, months (range)	3.9 (1 to 7)	3.2 (0.7 to 7.9)
Fracture types, compression / tension	-	67 / 3
Harris Hip Score, mean	-	97 (70 to 100)
VAS (of 16 displaced and 62 non-displaced)	23 mm	5.85 mm
Exemption of service, cases of all BMIs of participants	19 / 19	1 / 106
- underweight, 15 to 18.9 kg/m ²	4	6
- normal weight, 19 to 24.9 kg/m ²	13	52
- overweight, 25 to 29 kg/m ²	2	8
Mean BMIs vs 22.4 kg/m ² of 223 controls	20.7 (p = 0.013)	22.3 (p = 0.817)
Affected fracture side		
- right	12	36
- left	7	26
- bilateral	0	4
Dominant lower leg, right / left and correlation to fracture site	-	38 / 28 p = 0.339

6 DISCUSSION

6.1. Prevalence and anatomic distribution of fatigue bone stress injuries

The prevalence of fatigue bone stress injuries as well as the anatomic distribution of the fractures, with areas of high fracture occurrence found in the tibia and the metatarsal bones, as determined for the cohorts of Studies I and II were typical of military recruit populations and corresponded with those documented in previous publications (Brudvig et al. 1983, Jones et al. 1989, Macleod et al. 1999, Devas 1958, Jones et al. 2002, Kiuru et al. 2002, Armstrong et al. 2004, Kiuru et al. 2004). Thus, the current cohorts of the studies seem to reflect well the average military trainee population.

6.2. Diagnosis and characteristics of fatigue bone stress injuries causing stress-related lower leg pain

Not only was the overall occurrence of stress fractures in Study III relatively high, but MRI revealed a striking number of injuries in asymptomatic legs. Almost all bone stress injuries of Study III were located in the tibia, a result consistent with most of the previous studies where tibial fractures have constituted the majority of all stress fractures among athletes and military recruits (Protzman and Griffis 1977, Sullivan et al. 1984, Matheson et al. 1987a, Orava and Hulkko 1988, Courtenay and Bowers 1990, Finestone et al. 1991, Ha et al. 1991). In contrast, studies with diagnosis based on plain radiography have reported notably lower percentages of tibial fractures among all fractures (Hallel et al. 1976, Brudvig et al. 1983, Jones et al. 1989). Furthermore, regarding military populations, diagnoses of stress fractures in the metatarsals have decreased and those in the tibia increased since the 1940s (Darby 1967, Morris and Blickenstaff 1967, Jones et al. 1989). Even if this study is not directly comparable with earlier studies, which used traditional radiography as the sole evaluation method, our findings seem to indicate that the earlier evidence indeed reflects the limitations of plain radiography.

The distal third of the tibia was a noteworthy site among the tibial injuries in Study III. The more distal the tibial injury was, the lower were the grade changes in bone seen on MRI. To explain this finding, first, it

should be remembered that the stress injuries of this study were not detectable on native radiographs, and second, compared with the literature based on plain radiography, the effectiveness of MRI was likely to shift the injury focus toward the distal tibia. The median duration of patient symptoms before MRI was longest in patients with Grade I tibial injuries and in patients with stress injury occurring in the distal third of the tibia. This probably indicates that diagnosis of distal injuries may be the most problematic among stress injuries in primary healthcare units with only plain radiography available.

Bilateral stress fractures were confirmed in 49 of 86 patients of Study III. This prevalence (57%) differs considerably from previous studies, where the percentage of bilateral stress fractures has varied from 6.9 to 17.4% (Matheson et al 1987b, Courtenay and Powers 1990, Ha et al. 1991, Geyer et al. 1993). These results again demonstrate the high sensitivity of MRI examination. Considering the large number of asymptomatic bone stress injuries revealed in Study III, and the fact that the diagnosis of tibial bone stress injuries deserves attention due to their potential complications (Orava and Hulkko 1988, Rettig et al 1988, Orava et al. 1991), our findings support earlier reports recommending that both lower legs be imaged simultaneously in patients with stress-related anterior lower leg pain to avoid diagnostic delay (Kiuru et al. 2003). Moreover, it should be noted that chronic exertional compartment syndrome does not exclude bone stress injuries. Of the legs with pathological pressure, 28% also showed stress-related changes in the bone on MRI.

6.3. Serum 25OHD concentration as a predisposing factor for fatigue bone stress injury

The most remarkable finding of Study I was that the average serum 25OHD concentration reflecting vitamin D status was significantly lower in conscripts with a bone stress fracture than in controls. Even though low levels of vitamin D have been associated with various bone diseases, e.g. rickets or osteomalacia and osteoporosis, an association with bone stress fractures has not been previously shown. However, other associations between low 25OHD levels and bone characteristics have been demonstrated by several investigators, such as with reduced bone mineral density (McKenna 1992, Cheng et al. 2003, Szulc et al. 2003, Zittermann 2003), and between low femoral bone density and stress fractures in military recruits (Pouilles et al. 1989, Taimela et al. 1990, Givon et al. 2000). Interestingly, an association between higher levels of vitamin D and higher bone mineral content (BMC) was also recently found (Välimäki et al. 2004). An increase in bone mineral density has also been described in studies involving vitamin D supplementation (Vieth 1999, Holick 2003).

In Study I, no vitamin D insufficiency, determined as a serum 25OHD concentration level below 40 nmol/l, was evident from the mean serum 25OHD values. Although this is the clinically used limit for indicating vitamin D insufficiency in Finland (Vieth 1999), levels below 50 nmol/l have been found in patients with hip fractures more often than in control subjects of the same age (McKenna 1992, Jacques et al. 1997). Furthermore, a rise in the mean 25OHD level from 53 to 74 nmol/l through vitamin D supplementation seems to reduce fracture risk in elderly people (Trivedi et al. 2003). When combined with calcium, vitamin D is capable of preventing non-vertebral fractures in healthy subjects (Chapuy et al. 1992, Lambert-Allardt et al. 2001).

While a low serum concentration of vitamin D leads to a lower serum calcium concentration, a rise in serum 25OHD increases calcium absorption in the intestine (Heaney et al. 2003). The ensuing increase in PTH secretion leads to secondary hyperparathyroidism followed by accelerated bone turnover (Compston 1998, Lips 2001). With adequate blood levels of vitamin D, an increase in serum intact parathyroid hormone (iPTH) secretion begins to take place when serum 25OHD concentration falls below 78-90 nmol/l (Krall et al. 1989, Chapuy et al 1997, Harkness and Gromer 2005), resulting in increased bone turnover and fragility (Cheng et al. 2003, Szulc et al. 2003). Moreover, in a recent study among young adult male conscripts, a high iPTH level was found to present a risk factor for stress fractures (Välimäki et al. 2005). The serum PTH holds a stable plateau level until serum 25OHD levels drop below a certain threshold level, at which point PTH secretion begins to increase. This 25OHD threshold level has been suggested to be 78 nmol/l (Chapuy et al 1997), but threshold levels as high as 100 nmol/l have been demonstrated among the elderly (McKenna and Freaney 1998). In Study I, the number of stress fractures was significantly higher among conscripts with a serum 25OHD concentration level below 76 nmol/l compared with recruits with higher concentration levels.

The importance of the findings of Study I is twofold. Firstly, in showing that a relationship exists between low levels of vitamin D and bone stress injuries, the study provides reliable evidence that serum 25OHD concentration is a predisposing factor for fatigue bone stress injuries. Secondly, in view of the previous literature, the findings demonstrate that secondary hyperparathyroidism and the ensuing accelerated bone turnover increasing the risk of bone stress fracture can be avoided by ensuring that serum 25OHD levels exceed 78-100 nmol/l throughout the year (Chapuy et al. 1997, Dawson-Hughes et al. 1997, Kinyamu et al. 1998).

In studies conducted by the Israeli Defence Forces, the serum 25OHD levels were assessed in patients with scintigraphically diagnosed high grade stress fractures. According to the findings, the serum 25OHD levels were significantly lower among the patients as compared to controls (Givon et al. 2000). The results of Study I confirmed these findings, as the absolute

levels of 25OHD reflecting vitamin D status were equal to those in Israel. In view of the similar findings from two countries, Israel with a high and Finland with a small number of sunshine hours, and the evidence that inadequate sunlight leads to vitamin D insufficiency even among young people (Lehtonen-Veromaa et al. 1999, Välimäki et al. 2004), there seems to be a strong likelihood of a considerable risk for bone stress fractures in Northern Europe. The risk is emphasized during wintertime when the amount of sunlight fails to initiate sufficient vitamin D production.

6.4. TRACP-5b bone resorption marker as an indicator of fatigue bone stress injuries

The present study (II) showed that the elevation in the serum TRACP-5b activity level indicated increased susceptibility toward the existence of a stress fracture of the lower extremities in military conscripts with symptoms of such a fracture. However, although the TRACP-5b levels in patients with fracture clearly rose over time, the overall rise remained statistically non-significant. To the knowledge of the present authors, no previous reports on the use of TRACP-5b evaluation in relation to bone stress fractures exist in the literature, yet unfortunately the small size of the final fracture group remains a drawback in this study and no firm conclusions can be drawn.

Since the serum levels of TRACP5b correlate with the total bone loss of the body, we hypothesized that this property could be used as an indicator of enhanced bone remodeling associated with bone stress fractures. In Study II, the serum levels of TRACP-5b were measured in patients with diagnosed bone stress fractures. The results were indicative of a bone resorption process consistent with that in elderly osteoporosis patients (Halleen et al. 2000, Halleen 2003). Being a bone metabolic marker, TRACP-5b is useful when information is needed about the dynamic changes taking place in the skeleton. However, elevations of the serum TRACP-5b level in patients with a bone stress injury may indicate either a generally high bone turnover rate characteristic of the individual or a rate specific to the local bone injury.

In discussing the needs to avoid delayed diagnosis and complications involved in bone stress injuries, and the promotion of early appropriate treatment, our findings suggest that serum TRACP-5b may be a useful tool for early diagnosis of these injuries, even though its clinical value can, at present, be considered as relative and needing more investigation. Future research should first of all focus on determining the limits for the TRACP-5b levels related to stress fractures.

6.5. Other risk factors for fatigue bone stress injuries

In previous reports, poor physical fitness has not been clearly related to stress fractures (Giladi et al. 1991, Jones et al. 2002, Lappe et al. 2005, Välimäki et al. 2005). The findings from Study I agreed with these earlier reports, although muscle strength and the results of 12-min running test were independently significant in the univariate analysis. In addition, there was no evidence of a significant association between smoking, BMI, age, height, and weight and bone stress fracture. At large, however, as potential risk factors for stress fractures, all of these factors represent an issue well researched but with conflicting outcomes. For example, investigations among American and Israeli armies found no association between the height, weight, or body mass index and bone stress fracture (Finestone et al. 1991, Giladi et al. 1991, Lappe et al. 2005). In their report, Lappe et al., consistent with many other military studies, did show, however, that older age may increase the risk of stress fracture (Brudvig et al. 1983, Jones et al. 2002, Lappe et al. 2005). This again is in contrast with the current findings (Study I) and those of another recent Finnish study, which in turn implied that tallness might be a risk factor for stress fracture (Välimäki et al. 2005). These examples show how large a variation of findings there exists regarding the predisposing factors for stress injuries, even though this variation might be, at least partly, due to differences in study populations, military branches, training programs, types of activity, equipments, methodology etc.

Earlier studies have paid attention to several risk factors relating to body and bone formation, for example, coxa vara, narrow tibial bone width, high body weight, and small body size, but with contradictory results (Giladi et al. 1987, Pouilles et al. 1989, Giladi et al. 1991, Beck et al. 1996, Bennell et al. 1999, Carpintero et al. 2003, Hohmann et al. 2004). In Study V, various intrinsic factors were analyzed to determine their role as predisposing or risk factors for femoral neck fatigue fractures. No evidence of such an effect was, however, found with respect to neck-shaft angle, BMI (any value), or leg dominance versus fatigue fracture side in this study.

However, in Study IV, an association was found between a low BMI and bone fatigue fractures. Disagreeing and conflicting evidence exists, suggesting on the one hand that the incidence of stress fractures is higher in persons of smaller size (Beck et al. 1996, Givon et al. 2000), and on the other hand that the risk for stress fractures is not related to body size and composition (Taimela et al. 1990, Giladi et al. 1991). In athletes, regarded as homogenous in their somatotype owing to participation in particular sports, neither a low nor a high BMI has emerged as a risk factor for stress fractures when compared to patients with normal BMI (Bennell et al. 1999, Muldoon et al. 2003). Here, it should be noted that Studies IV and V both involved such organizations that incorporate all somatotypes, and further, that all participants were required to perform the same training pro-

grammes. Since body weight is positively related to ground reaction forces, we might assume that a high body weight, especially when linked with low muscle strength and poor overall physical condition, may increase the likelihood of fatigue fractures. Based on existing research evidence, however, it seems that the risk factors related to a thin body structure are not essentially different.

6.6. The long-term outcomes of fatigue fractures of the femoral neck

Without a doubt, the instructions by Finnish Defence Forces in 1986 had a tremendous impact on the awareness among both conscripts and medical personnel in the national military organizations about femoral neck fatigue fractures, notwithstanding the fact that during the long follow-up time of the studies the trends in care modalities tended to show some variation as well. After the year 1986, the total incidence of detected femoral neck fatigue fractures significantly increased, 2.6 fold, with the incidence of non-displaced fractures increasing, and that of displaced fractures decreasing at the same time. Moreover, a significant decrease was noted in the severity of diagnosed fractures. The true calculated incidences of these fractures have been rarely documented, as the earlier literature dealing with these fractures consists mainly of case reports (Branch 1944, Ernst 1964, Walsh 1971, Cady et al. 1975, Erne and Burckhardt 1980, Skinner and Cook 1982, Swiontkowski et al. 1984, Schratz and Fux 1985, Kerr and Johnson 1995, Boden and Speer 1997, Clough 2002, Selzer et al. 2003).

Although uncommon (Erne and Burckhardt 1980, Meurman et al. 1981, Fullerton and Snowdy 1988, Volpin et al. 1990), displaced fatigue fractures of the femoral neck are overuse injuries known for adverse sequelae, including postoperative infection, nonunion, avascular necrosis of the femoral head, severe secondary osteoarthritis, and even hip replacements (Blickenstaff and Morris 1966, Kaltsas 1981, Lombardo and Benson 1982, Swiontkowski et al. 1984, Fullerton and Snowdy 1988, Visuri et al. 1988, Johansson et al. 1990, Volpin et al. 1990, Mendez and Eyster 1992, Egol et al. 1998, Lee et al. 2003). A high percentage of these sequelae were detected in Study IV, in which about 42% of the patients developed a complication. In Study V, we examined the outcomes related to non-displaced fatigue fractures of the femoral neck and found that these fractures are unlikely to predispose patients to avascular necrosis of the femoral head, subsequent development of secondary osteoarthritis of the hip joint, or to other subsequent adverse complications. There is prior evidence, however, indicating that other bony injuries of the hip joint, or even high levels of physical activity, may result in the development of osteoarthritis (Vingard et al. 1993, Kujala et al. 1994, Cheng et al. 2000, Gelber et al. 2000, Lievense et al. 2001,

Lievensse et al. 2003, Shepard et al. 2003, Schmitt et al. 2004).

The follow-up times of Studies IV and V were sufficiently long to enable reliable detection of even gradually progressing complications associated with femoral neck fatigue fractures, e.g. avascular necrosis of the femoral head (Jakob et al. 1999, Kawasaki et al. 2001). The findings of Studies IV and V were also consistent with earlier papers showing that the nature and clinical course of non-displaced versus displaced femoral neck fatigue fractures are quite dissimilar (Visuri et al. 1988, Boden and Oshbar 2000, Lee et al. 2003). High rates of nonunion and avascular necrosis of the femoral head have been documented in association with all types of traumatic displaced femoral neck fractures (Gautam et al. 1998, Bachiller et al. 2002, Haidukewych et al. 2004). Predisposing factors to avascular necrosis have been shown to include the tamponade effect of hemarthrosis related to displaced fractures, the increased intracapsular pressure involved, as well as vascular damage (Gómez-Castresana 1981, Crawford et al. 1988, Maruenda et al. 1997, Bonnaire et al. 1998, Bachiller et al. 2002). Gradually developing non-displaced fatigue fractures obviously do not involve any harmful tamponade effect of hemarthrosis. Extensive destruction to the bony architecture of the femoral neck prior to displacement as a result of a developing fatigue fracture could well be an additional predisposing factor for osteonecrosis of the femoral head. Immediate anatomic reduction and stable internal fixation have been regarded as the most important aspects of fracture management to prevent avascular necrosis in young patients (Kyle 1986), but other, contrasting studies exist, where the delay of more than forty-eight hours before surgery had no unfavourable impact on the outcome (Upadhyay et al. 2004). The two primary operative treatment methods used on displaced femoral neck fatigue fractures are the closed and the open reduction with internal fixation. Closed reduction with internal fixation is underpinned as being less invasive and faster to perform (Parker 2000, Bosch et al 2002), whereas supporters of open reduction with internal fixation argue that surgery under direct vision allows for a more accurate and anatomic reduction of the fracture (Swiontkowski 1994, Gautam et al. 1998). In a previous study with focus on displaced fatigue fractures of the femoral shaft, the bone at the fracture site was evaluated as brittle and more easily prone to shattering during fixation procedures (Salminen et al. 2003). In Study IV, shortening of the femoral neck, assessed as destruction of the bone, was found to be significantly associated with osteonecrosis.

Prodromal local symptoms were reported by the majority of patients with displaced fatigue fracture of the femoral neck (Study IV). The symptoms were located at the hip or groin region, and obviously there had been an opportunity to prevent fracture displacement by early intervention. Our findings gave considerable supportive evidence that detecting femoral neck fatigue fractures while they are still non-displaced should be strongly encouraged. Becoming immediately subject to non-operative treatment,

including non- or reduced weight-bearing, favourable short- and long-term outcomes of these fractures can be expected, without a risk of fracture displacement and its subsequent adverse outcomes.

Arresting fracture development will serve to greatly improve the prognosis, a statement underpinned by the findings of this study for fatigue fractures, and by other investigators (Aro and Dahlström 1986). To achieve this, a correct diagnosis is of outmost importance in order to prevent the initial microfracture from propagating to a complete fracture and eventual displacement. The earlier the diagnosis is made, the more likely are the possibilities that displacement of the fracture can be prevented, along with its operative treatment which, in most of the cases, may result in prolonged morbidity and poor long-term consequences. In previous literature, MRI has been highlighted as a tool of choice for early detection of fatigue fractures (Shin et al. 1996, Spitz and Newberg 2002, Kiuru et al. 2003, Niva et al. 2005).

7. CONCLUSIONS

Recalling the aims of the present study, the following conclusions can be drawn:

I

A lower level of serum 25OHD concentration might be considered as a generally predisposing element for bone stress fractures. The bone stress fracture prevalence of 2.9% as well as the distribution with 77% of the fractures located in the tibia or the metatarsals were typical in the military conscript population. Age, weight, height, BMI, or poor physical fitness were not associated with stress fractures in the multivariate model, although muscle strength and the results of 12-min running test were significant in the univariate analysis.

II

An increasing trend was noted in the group with stress fractures of an elevation of TRACP-5b activity levels from baseline to samples (I-IV).

III

Fatigue bone stress injury was the underlying factor of stress related lower leg pain in 86 of the 154 patients. In addition, MRI revealed 24 asymptomatic bone stress injuries, representing 17% of all 143 bone stress injuries in the study. Ninety-nine percent of lower leg fatigue bone stress injuries were located in the tibia, and the distal shaft was most often affected. In 86 patients with stress injury, 49 (57%) patients exhibited injuries bilaterally. Fatigue bone changes in the distal tibia displayed a lower grade of injury than the more proximal ones, and further on, patients with these lower grade lesions also had longer symptoms before MRI. Bone stress injuries are fairly common cause behind unclear stress-related anterior lower leg pain, and the distal tibial location of these injuries seem to be difficult to diagnose by plain radiography.

IV/V

The overall incidence in conscripts of a displaced fatigue fracture of the femoral neck was 4.3 per 100,000 person-years in military service and 19.4 per 100 000 of a non-displaced femoral neck fatigue fracture. Following the femoral neck fatigue fracture awareness instructions by the Finnish Defence Forces in 1986, there was a significant increase in the detected overall and non-displaced fracture incidences as well as a decrease in the

incidence of displaced femoral neck fatigue fracture, indicating that the new regimen was successful. Non-displaced femoral neck fatigue fractures lack the potential of prolonged morbidity, whereas displaced fatigue fractures of the femoral neck result in long-term morbidity in a high percentage of cases. Most patients with femoral neck fatigue fractures have prodromal symptoms, offering an opportunity to prevent fracture displacement and operative treatment when appropriately diagnosed. If fracture is detected as non-displaced and subjected to immediate non-operative treatment, including non- or reduced weight-bearing, favourable short- and long-term outcomes can be expected.

8. SUMMARY

Using the serum 25OHD level as the index, we assessed the role of vitamin D status as a predisposing factor for bone stress injuries. Serum 25OHD samples of 800 randomly selected military conscripts were collected at the beginning of their military service in homogenous circumstances. Serum 25OHD concentrations were measured with enzyme immunoassay. During a 3-month follow-up, the subjects were monitored for evidence of developing stress fractures. The total number of subjects completing the follow-up was 756 with a total of thirty stress fractures identified in twenty-two conscripts (2.9%). Subjects without fracture constituted the controls. With equal prospective study protocol the relation of TRACP-5b bone resorption marker with enhanced bone remodeling in military conscripts with stress fractures was determined. After gathering the blood samples to measure serum TRACP-5b levels of 820 randomly selected military conscripts at the beginning of their military service in homogenous circumstances, the subjects were prospectively monitored for three months for evidence of developing stress fractures. By the end of the follow-up, fourteen conscripts with a total of twenty-one stress fractures were identified (2.4%). Four subsequent samples (I-IV) were taken at 3-4-day intervals from patients identified with stress fracture, and one sample from two asymptomatic controls for every fracture case on the day of the patient's last sample.

The incidence of fatigue bone stress injury as a cause of unclear stress related anterior lower leg pain was evaluated on the basis of an MRI diagnosis. In addition, the anatomic distribution, injury grades, and symptom durations preceding diagnosis were examined. The MR images and medical records of 154 consecutive military conscripts who underwent magnetic resonance imaging during a 5-year period for unclear stress related anterior lower leg pain were retrospectively reviewed. The incidence of bone stress injuries requiring orthopaedic consultation and magnetic resonance imaging among the recruits during the study period was 117 per 100,000 person-years in military service. In retrospective follow-up studies of twenty and twenty-one years, the incidence, symptomatology, morphologic characteristics, clinical course, risk factors, and long-term outcomes of displaced and non-displaced fatigue fractures of the femoral neck were evaluated. Special attention was paid to the effects of instructions by the Finnish Defence Forces in 1986, addressing prevention of femoral neck fatigue fractures. The incidence (per service-years) of displaced femoral neck fatigue fractures, prior to the new regimen of 1986, was 5.3/100,000 but decreased 2.3 fold after 1986 to 2.3/100,000. The total incidences of all femo-

ral neck fatigue fractures in the corresponding periods were 20.8/100,000 and 53.2/100,000, indicating a 2.6 fold increase. The incidence of non-displaced femoral neck fatigue fractures prior to 1986 was 10.2/100 000 and increased 5 fold to 51.2/100 000 post-1986. During the study periods of twenty (IV) and twenty-one years (V), altogether twenty-one consecutive displaced (IV) and 106 non-displaced (V) femoral neck fatigue fractures were treated in military conscripts within the catchment area. The long-term follow-up data, including medical and imaging examination records, were successfully obtained for 19 patients in Study IV and 66 patients in Study V. In addition, these patients were invited to participate in a long-term follow-up examination.

The average serum 25OHD concentration was statistically significantly lower in the group of conscripts with fatigue fracture, suggesting a relationship between vitamin D and fatigue bone stress fracture. The odds of probability of stress fracture existence was 8-fold in patients with elevated serum TRACP-5b levels, when comparing the last serum sample (taken within 10-11 days after detection of stress fracture) to the baseline sample in the fracture and control groups.

Among the 154 patients with exercise induced anterior lower leg pain and no previous findings on plain radiography, a total of 143 bone stress injuries in 86 patients were diagnosed by MRI. Of the 143 fatigue stress injuries detected on MRI, 17% (24) were asymptomatic. In 99% of the cases, the bone stress injury was located in the tibia, distributed across the distal (57%), middle (30%) and the proximal (10%) thirds of the tibial shaft, while 3% were in the medial condyle. There was a statistically significant relationship between the MRI grades of injury and duration of symptoms and the anatomic location of injuries. The changes in the medial condyle and the proximal tibia due to bone fatigue displayed a higher grade than those in the middle and distal tibia. The duration of symptoms before diagnosis was shorter in the injuries to the medial condyle than in those affecting the middle and distal tibia. The median number of symptomatic days preceding diagnosis was greater in patients with lower MRI injury grades than in patients with higher MRI injury grades.

Among subjects with displaced femoral neck fatigue fractures, ten cases of early local complications (during the first postoperative year) were evident, and osteonecrosis of the femoral head was identified in six and osteoarthritis of the hip in thirteen patients of all nineteen cases after the first postoperative year. The correlation between severe hip osteoarthritis and osteonecrosis of the femoral head was statistically significant. Repeat operations due to these late complications were performed in four cases, and a total of three patients received an implantation of total hip prosthesis by the final follow-up examination. Garden-type IV fatigue fracture emerged as a significant risk factor for osteonecrosis of the femoral head and for shortening of the femoral neck. Osteonecrosis of the femoral head was also

associated with shortening of the femoral neck, since shortening was significantly greater in patients with than without osteonecrosis. None of the non-displaced femoral neck fatigue fractures diagnosed during the study time period progressed to displacement. Moreover, the non-displaced fractures did not predispose patients to avascular necrosis of the femoral head, subsequent development of secondary osteoarthritis of the hip joint, or to other subsequent adverse complications.

No obvious predisposing risk factors for femoral neck fatigue fractures were noted in the risk factor analysis of the studies. However, the majority of the patients experienced prodromal symptoms. Following implementation of the institution's instructions aimed at increasing awareness of femoral neck stress fractures in 1986, there was a statistically significant increase in the detected fracture incidence rates.

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